1. Title Page

Clinical Study Main Report: Fluoxetine Versus Placebo in the Acute Treatment of Major Depressive Disorder in Children and Adolescents

Fluoxetine Hydrochloride (LY110140)
Major Depressive Disorder

A single center, double-blind, randomized, parallel-group study comparing the efficacy and safety of fluoxetine 20 mg/day and placebo for the acute treatment of major depressive disorder in children and adolescents.

Eli Lilly and Company
Protocol B1Y-MC-X065
Phase 3
First patient enrolled (assigned to therapy): 10 April 1991
Last patient completed: 28 February 1995
Date report approved by Lilly Medical: 8 August 2000

Name and affiliation of investigator

[redacted]

[redacted]

Eli Lilly and Company

2. Synopsis

Name of company:	Summary table referring to Part of the dossier,	(For National Authority use only)
Eli Lilly and Company		
Name of finished product:	Volume:	
Prozac®	Page:	
Name of active ingredient:		
Fluoxetine hydrochloride		

Clinical Study Synopsis: Study B1Y-MC-X065

Title:	Fluoxetine Versus Placebo in the Acute Treatment of Major Depressive Disorder in Children and Adolescents
Investigator:	[redacted]
Study Center:	[redacted]
Dates of Study:	10 April 1991 through 28 February 1995
Clinical Phase:	Phase 3
Objectives:	To compare the efficacy and safety of fluoxetine 20 mg/day and placebo for the acute treatment of major depressive disorder (MDD) in children and adolescents.
Methodology:	Single-center, double-blind, randomized, parallel-group, placebo-controlled study.
Number of Subjects:	Fluoxetine: Male 26, Female 22, Total 48; Placebo: Male 26, Female 22, Total 48. Children (8 to <13): Fluoxetine 24, Placebo 24, Total: 48; Adolescents (13 to ≤18): Fluoxetine 24, Placebo 24, Total 48.
Diagnosis and Inclusion Criteria:	Outpatients with non-psychotic, major depressive disorder, single or recurrent episodes according to the Diagnostic and Statistical Manual of Mental Disorders, third edition-revised (DSM-III-R), aged 8 to 18 years, normal intelligence as assessed clinically or by psychomotor testing if evidence of IQ <80, and were willing and able to provide informed consent (parent and patient). Diagnosis of major depressive disorder was also dependent on patients having a Children's Depression Rating Scale-Revised (CDRS-R) total score >40 at study entry. Diagnosis of major depressive disorder and comorbid diagnoses was decided at a consensus meeting of the clinical investigators.

Dosage and Administration:	Test Product, Procured and Prepared by Investigative Site from April 1991 to August 1993 Test Product, Supplied by Lilly from September 1993 to February 1995 Fluoxetine: 20 mg/day, given once daily CT02768 and CT01678: fluoxetine capsules, 20 mg CT02769 and CT01679: placebo capsules All lots of study drug had an expiration date of 1 May 1996.
Duration of Treatment:	Fluoxetine: 8 weeks Placebo: 8 weeks
Criteria for Evaluation:	Efficacy—Primary efficacy analysis was response on the CDRS-R. Secondary analyses included evaluation of CDRS-R, Clinical Global Impressions of Improvement (CGI-Improvement), Clinical Global Impressions of Severity (CGI-Severity), Brief Psychiatric Rating Scale for Children (BPRS-C), Beck Depression Inventory (BDI), and Children's Depression Inventory (CDI) scales. Safety—Safety was evaluated through the reporting and collection of concomitant medications, vital signs, routine laboratory testing, and adverse event data (solicited and non-solicited).
Statistical Methods:	For analyses of continuous data, treatment groups were compared using last-observation-carried-forward (LOCF) in Type III sums of squares from an analysis of variance (ANOVA) with treatment in the model. For analyses of categorical data, Fisher's exact test was used.
Publications:	[redacted]

Summary and Conclusions:

The safety and efficacy of fluoxetine was assessed following 8 weeks of fixed-dose therapy of fluoxetine 20 mg/day versus placebo in 96 pediatric patients diagnosed with major depressive disorder, as defined by the DSM-III-R. This study was conducted as an investigator-initiated trial and was exempt for the Investigational New Drug Application for fluoxetine.

Ninety-six patients were randomized to treatment in this study, with 48 being treated with fluoxetine 20 mg once daily and 48 being treated with placebo. A total of 58 patients (33 fluoxetine, 25 placebo) completed the entire study. Nineteen placebo-treated patients discontinued the study due to lack of efficacy as compared with 6 fluoxetine-treated patients (p=.005). In addition, 13 randomized patients discontinued from the study for other reasons. The treatment groups were balanced with respect to demographic characteristics and psychiatric evaluations at baseline.

Fluoxetine 20 mg/day was effective in the treatment of MDD in this pediatric population as demonstrated by response on the CDRS-R total score, defined as at least a 30% reduction from baseline, when patients were treated for up to 8 weeks (p=.013) and for at least 4 weeks (p=.031). The observed response rates on the CDRS-R total score (58% fluoxetine, 32% placebo) and the CGI-Improvement scores (56% fluoxetine, 34% placebo) are similar to the rates seen in adults with depression.

The clinician's global impressions of improvement and severity also support the effectiveness of fluoxetine 20 mg/day in the treatment of MDD after 8 weeks of therapy. Endpoint (p=.015) and response analyses (p=.040) for CGI-Improvement scores demonstrated the superiority of fluoxetine treatment over placebo treatment. In addition, the mean change in CGI-Severity scores from baseline to endpoint was statistically significant for fluoxetine-treated patients as compared with placebo-treated patients (p=.003).

Analyses of the efficacy variables that demonstrated statistical superiority of fluoxetine treatment over placebo treatment are summarized in the following table.

Efficacy Variable Analyzed	p-Value
Response, at least a 30% reduction in CDRS-R Total score from baseline (at endpoint)	.013
Response, at least a 30% reduction in CDRS-R Total score from baseline (after at least 4 weeks of treatment)	.031
Mean change from baseline to endpoint in CDRS-R Total score	.002
Mean change from baseline to endpoint in CDRS-R Mood Subtotal score	<.001
Mean change from baseline to endpoint in CDRS-R Somatic Subtotal score	.001
Mean change from baseline to endpoint in CDRS-R Behavior Subtotal score	.028
Endpoint analysis of CGI-Improvement score	.015
Response, CGI-Improvement score of 1 or 2 at endpoint	.040
Mean change from baseline to endpoint in CGI-Severity score	.003

Data for this table were taken from RMP.B1YO.X065REP (EFS1EM01), RMP.B1YO.X065REP (EFS1EM06), RMP.B1YO.X065REP (PRCNEM13), RMP.B1YO.X065REP (DES1EM02), RMP.B1YO.X065REP (EFS1EM03), and RMP.B1YO.X065REP (PRCNEM23).

Greater attrition from the placebo treatment group was seen due to failure to respond to treatment as compared with fluoxetine-treated patients. Despite this differential rate of attrition, LOCF analysis of mean CDRS-R total scores over time indicates that fluoxetine treatment was statistically significantly superior to placebo treatment after 3 weeks (Visit 5) of treatment. This treatment effect persisted for the duration of the study.

Of the 96 randomized patients in this study, 92 (96%) reported at least 1 treatment-emergent solicited adverse event, and 85 (89%) reported at least 1 non-solicited adverse event. There were no statistically significant differences in frequencies of adverse events reported in fluoxetine-treated patients as compared with placebo-treated patients.

Two serious adverse events of suicide attempt occurred in patients receiving fluoxetine treatment during the study. Both events were considered to have unknown causality as determined by the principal investigator and occurred early in the study (after 12 and 15 days of therapy, respectively). One patient discontinued from the study as a result. Four additional fluoxetine-treated patients were discontinued from the study due to adverse events. Two patients were discontinued for hypomania, 1 for increased impulsivity, and 1 for rash. Three of the events (increased impulsivity, rash, and 1 event of hypomania) were considered possibly related to fluoxetine treatment. No placebo-treated patients discontinued due to adverse events.

There were no clinically significant findings in the analyses of laboratory analytes or vital signs.

Subgroup analyses of efficacy and safety endpoints indicated that there were no differences in the effectiveness or safety profile for subgroups of age, gender, and study medication type.

The overall efficacy, safety, and tolerability profile of fluoxetine in this depressed pediatric population was consistent with the profile observed in adult studies of depression.

3. Table of Contents for the Clinical Study Main Report

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4. List of Abbreviations and Definitions of Terms

Adverse event	(Used as category; no definition.)
Clinical trial adverse event	An adverse event is any undesirable experience, unanticipated benefit, or pregnancy that occurs after informed consent for the study has been obtained, without regard to the possibility of a causal relationship and without regard to treatment group assignment, even if no study drug has been taken.
Clinical trial serious adverse event	Any adverse event from a clinical study that includes one of the following criteria: • death • initial or prolonged inpatient hospitalization • is life-threatening • severe or permanent disability • cancer (other than cancers diagnosed prior to enrollment in studies involving patients with cancer) • congenital anomaly • drug overdose • is significant for other reason.
Lack of drug effect	Any failure of expected pharmacological action.
Spontaneous adverse event	A spontaneous adverse event is any untoward happening, failure of expected pharmacological action, unanticipated benefit, or pregnancy in a patient after the onset of therapy or upon withdrawal with a Lilly/Dista product, without regard to the possibility of a causal relationship.
Unanticipated benefit	An unanticipated event that may be considered of benefit to the study participant. An event that is considered an unanticipated benefit is reported to Lilly in the same manner as an adverse event.
Affirmation statement	A listing of the study participants by identifier and a statement, signed by the investigator, confirming that all clinical data required by and relevant to the protocol regarding the study participants were submitted to the sponsor, and that the investigator's involvement was in accordance with regulatory requirements.
ANOVA	Analysis of variance.
Audit	A systematic and independent examination to determine whether the conduct of a trial complies with the agreed protocol and applicable guidelines for good clinical practice (GCP), and to determine if the data reported are consistent with the records on site.
Audit report	Reports completed by Lilly Medical Quality Assurance (MQA) or other auditing groups after conducting an audit. These reports are filed separately from the study documentation.
Beck Depression Inventory ***BDI***	The BDI (Beck and Steer 1984) is a patient-rated scale that assesses the major symptom categories associated with depression. Total scores range from 0 to 62. The higher the total score, the more severe the depression. The BDI scale is intended for use in adolescents (patients aged 13 to <18 years).
Blinding, unblinding	(Used as category; no definition.)

Double-blind labels	Labels used in clinical studies to conceal the identity of the drug from the study participant and the investigator.
Double-blind study	A study in which neither the study participant or the investigator is aware of the treatment received. Studies in which Lilly personnel are blinded (in addition to the study participant and the investigator) are also considered double-blind studies (sometimes called triple-blind studies).
Unblinding	The act of providing visual or verbal access to study participant treatment information obtained from secured random number tables, or emergency identification envelopes.
Brief Psychiatric Rating Scale for Children ***BPRS-C***	The BPRS-C is a clinician-rated scale that assess the presence of depressive symptoms in addition to other symptom clusters, such as behavior problems, depression, thinking disturbance, psychomotor excitation, withdrawal retardation, anxiety, and organicity (Overall and Pfefferbaum 1982). The scale consists of 21 items rated on a 7-point scale. Total scores range from 0 to 126. The higher the total score, the more severe the depression.
Children's Depression Inventory ***CDI***	The CDI is a patient-rated scale that assess the major symptom categories associated with depression. The CDI was developed from the BDI (Kovacs 1985). Total scores range from 0 to 54. Like the BDI, the higher the total score, the more severe the depression. The CDI scale is intended for use in children (patients aged 8 to <13 years).
Children's Depression Rating Scale-Revised ***CDRS-R***	The CDRS-R is a clinician-rated instrument designed to measure the presence and severity of depression in children (Poznanski et al. 1983, 1984, 1985). The scale was modeled after the Hamilton Depression Rating Scale for adults and includes questions about school. The scale consists of 17 items scored on a 1 to 5 or 1 to 7 point scale. A rating of 1 indicates normal functioning. Total scores range from 17 to 113. In general, scores below 20 indicate an absence of depression, scores of 20 to 30 indicate borderline depression, and scores of 40 to 60 indicate moderate depression.
Clinical Global Impressions of Improvement ***CGI-Improvement***	The CGI-Improvement scale (Guy 1976) is a clinician-rated instrument that measures the improvement of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "very much improved", a score of 4 indicates that the patient has experienced "no change", and a score of 7 indicates that the patient is "very much worse."
Clinical Global Impressions of Severity ***CGI-Severity***	The CGI-Severity scale (Guy 1976) is a clinician-rated instrument that measures the severity of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "normal" and a score of 7 indicates that the patient has an "extremely severe case of depression."
Clinical report form ***CRF***	The form used for recording study participants' data during a clinical study, as required by the established clinical study protocol. The form operates as a direct report to the sponsor. An electronic version of this form may be used. Sometimes called case card or case report form.
Clinical trial records binder ***CTRB***	A binder furnished to study sites as a suggested tool for organizing and filing all study documents and correspondence (except financial).

Clintrace	Clintrace (previously known as the Drug Experience Network or DEN) is a computerized system of Eli Lilly and Company established in 1998 for the worldwide collection, storage, and reporting of adverse events involving Lilly products since 1983. Clintrace includes clinical trial events described as "serious" according to the US FDA (Food and Drug Administration) regulations as well as serious and nonserious events reported spontaneously from postmarketing experience (including scientific literature and media reports). The coding of events is based on the Coding Symbol and Thesaurus for Adverse Reaction Terms (see **COSTART** below) dictionary.
Coding Symbol and Thesaurus for Adverse Reaction Terms ***COSTART***	A dictionary developed by the US Food and Drug Administration (FDA) that is used to describe, catalog, analyze, and report all adverse events.
Curriculum vitae ***CV***	A document that contains a person's educational and professional background. Clinical research investigators' curriculum vitae (CVs) are collected to ensure that the investigators are qualified and have experience in the appropriate research area.
Declaration of Helsinki	An international standard for the conduct of clinical trials that has been adopted as legally enforceable by many countries and jurisdictions.
Enroll	The act of assigning an individual to a treatment group. Individuals who are *enrolled* in the study are those who have been assigned to a treatment group. A person who has been *entered* into the study is potentially eligible to be *enrolled* in the study, but must meet all criteria for enrollment specified in the protocol before being *enrolled* (assigned to a treatment group). Individuals who are *entered* into the study but fail to meet the criteria for enrollment are not eligible to participate in the study and will not be *enrolled*.
Enter	The act of obtaining informed consent for participation in a clinical study from individuals deemed potentially eligible to participate in the clinical study. Individuals *entered* into a study are those for whom informed consent documents (ICDs) for the study have been signed by the potential study participants or their legal representatives. Adverse events are reported for each individual who has *entered* the study, even if the individual is never assigned to a treatment group (*enrolled*).
Ethical review board ***ERB***	A board or committee (institutional, regional, or national) composed of medical professionals and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects or patients participating in a clinical trial are protected. Sometimes called *institutional review board* (IRB) or *independent ethics committee*.
Expectedness	A term used to indicate whether a particular adverse event (as described by a particular COSTART term) is described or listed in the product information (for marketed products) or the clinical investigator's brochure (CIB) (for adverse events reported from clinical trials). Expectedness is determined for any adverse event report entered into Clintrace. Affiliates outside the US may assign expectedness to other adverse event reports (non-serious) if or when required by local regulatory authorities. Sometimes called *expectancy*.

Informed consent document ***ICD***	An official document that is used to obtain informed consent for a clinical study from potential study participants. See *enter*, *enroll*, *screen*.
Intent-to-treat analysis	An analysis of study participants by the groups to which they were assigned by random allocation, even if the study participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Such an analysis is sometimes stated analyze as randomized.
Investigational new drug application ***IND***	An application to the US Food and Drug Administration (FDA) to allow testing of a new drug in humans.
Major depressive disorder ***MDD***	Criteria according to DSM-III-R (APA 1987): At least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least 1 of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. Symptoms that occur most of the day or nearly every day, as indicated by subjective account or observation by others: (1) depressed mood (can be irritable mood in children and adolescents), (2) markedly diminished interest or pleasure in all, or almost all, activities, (3) significant weight loss or weight gain when not dieting (eg, more than 5% of body weight in a month), or decrease or increase in appetite (in children, consider failure to make expected weight gains), (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation , (6) fatigue or loss of energy, (7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional), (8) diminished ability to think or concentrate, or indecisiveness, and (9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
Medical quality assurance ***MQA***	A part of the corporate quality assurance component that provides corporate and research management with ongoing evaluation of the quality of processes used and data generated to support worldwide registration of drugs.
Monitoring plan	A guide listing the minimum criteria used to monitor a study site. For those persons monitoring the study, the monitoring plan does not replace an understanding of the requirements contained in the approved protocol.
Note to file	A narrative summary that documents significant decisions, rationale, actions, protocol variations, additional instructions provided to a site during the course of a study, and any other issues or situations not adequately documented by other means.
Overdose	For a drug under clinical investigation, any intentional or unintentional consumption of the drug (by any route) that exceeds the dose recommended in the clinical investigator's brochure or in an investigational protocol, whichever dose is larger. For a marketed drug, a drug overdose is any intentional or unintentional consumption of the drug (by any route) that exceeds the dose listed in product labeling, even if the larger dose is prescribed by a physician.
Protocol	A document that states the background, rationale, and objectives of a clinical trial and describes its design, methodology, and organization. This document also includes statistical considerations and conditions under which the study is to be performed and managed.

Protocol violation	Any instance in a clinical trial where the current approved protocol is not followed explicitly.
Quality assurance	The implementation of appropriate planned and systematic actions to provide adequate confidence that the required quality of a function or process will be obtained. In general, quality assurance refers to an independent group or department that oversees a quality control system and establishes confidence that the system is functioning properly. Specific to the clinical study environment, systems, processes, and quality control procedures have been established to ensure that studies are performed and data are generated in compliance with guidelines for good clinical practice (GCP). These include procedures to be followed that apply to ethical and professional conduct, standard operating procedures, reporting, and in the review of professional and personnel qualifications.
Randomization	A two-by-two stratified randomization, based on age (categorized as children, aged 8 to <13, and adolescents, aged 13 to ≤18) and gender, was used in this study. The pharmacist, using a randomization list prepared by the biostatistician, performed assignment to treatment group.
Randomization block size	A specified number of study participants grouped in a block to achieve the desired ratios of study participants in each treatment group.
Randomization codes	The identification of random treatment assignments for study participants in a clinical study.
Randomization table (or random table)	The entire list of randomization codes for a study.
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. *Screening* may involve asking the candidate preliminary questions to determine potential eligibility. In these cases, the screening is not invasive and does not require that *screening* informed consent be obtained. In other cases, *screening* may involve invasive or diagnostic procedures and/or (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for the screening procedures and/or tests shall be obtained.

5. Ethics

5.1. Ethical Review

This study was conducted as an investigator-initiated trial and was exempt from the Investigational New Drug Application for fluoxetine. As such, several sections of this clinical study report present more detail than normal to thoroughly explain how the study was conducted. Section 9.1.1 presents a detailed account of the differences between activities proposed in [redacted] original "protocol" and those performed by Lilly. It should be noted that [redacted] original "protocol" was a National Institute of Mental Health (NIMH) grant proposal and is not structured in the same manner as a traditional protocol (see Appendix 16.1.1). [redacted] NIMH grant proposal will be referred to as his protocol throughout this clinical study report.

The protocol for this study (Appendix 16.1.1) was approved by the [redacted] on 10 September 1990, prior to patient enrollment. The ERB reviewed and approved the protocol as required. Appendix 16.1.9 contains information about the ERB consulted.

5.2. Ethical Conduct of the Study

This study was conducted and informed consent was obtained according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations of the US where the study was conducted, whichever provided the greater protection of the individual.

5.3. Patient Information and Consent

An informed consent document (Appendix 16.1.9) approved by the ERB was signed by the parent or guardian of the patient, the patient, and the investigator on or before Visit 1. Copies of the informed consent were given to each patient/parent or guardian and the original was retained by the investigator.

6. Investigators and Study Administrative Structure

This study was conducted by [redacted] a psychiatrist affiliated with the [redacted] Appendix 16.1.3 contains information on the qualifications of this investigator and information on other key individuals at the study site.

The individuals who were involved in reporting of results for the clinical study report are listed in Table 6.1. All statistical analyses were performed at Eli Lilly and Company.

The sponsor's medical officer responsible for the content of this clinical study report is [redacted] Eli Lilly and Company (see Appendix 16.1.4).

Table 6.1. Study Administrative Structure B1Y-MC-X065

Name/Title/Affiliation	Role
[redacted]	Responsible for clinical review of the clinical/statistical report
[redacted]	Analysis of data and preparation of the clinical/statistical report
[redacted]	Systems lead for database import, development of data entry system, and reporting for the clinical/statistical report
[redacted]	Liaison with the investigators at the study site and Eli Lilly and Company
[redacted]	Liaison with the investigators at the study site and Eli Lilly and Company
[redacted]	Preparation of the clinical/statistical report
[redacted]	Analysis of the clinical blood and urine samples

7. Introduction

Depressive disorders are a leading cause of morbidity and mortality in children and adolescents (Fleming and Offord 1990; Brent 1987; Pfeffer et al. 1991), with prevalence estimates ranging from 0.4% to 8.3% (Burke et al. 1991; Fleming and Offord 1990; Kashani et al. 1987a, b; Lewinsohn et al. 1986, 1993, 1994). Depressive disorders are generally more prevalent in adolescents than in children, with major depressive disorder (MDD) occurring at a 2:1 ratio in adolescent girls as compared with adolescent boys (Emslie et al. 1990). Common outcomes for children and adolescents diagnosed with depression include school failure and dropout (Weinberg and Rehmet 1983; Weinberg and Emslie 1988), with suicide remaining as one of the leading causes of death in adolescents (Brent 1987; Pfeffer et al. 1991; Rao et al. 1993). The age of onset of depression appears to be decreasing (Kovacs and Gatsonis 1994), implying that many individuals will experience their first episodes of depression as children or adolescents.

Depression is difficult to diagnose in children and adolescents because awareness in the general population is low and because the disease has different characteristics in the pediatric population as compared with the adult population. Instead of appearing depressed, children and adolescents may be more irritable than normal, exhibit signs of agitation or hyperkinesia, have an inability to concentrate, and have recurrent thoughts of death according to the Diagnostic and Statistical Manual of Mental Disorders, third edition-revised (DSM-III-R, APA 1987). Although awareness that depression is an organic disease that readily responds to treatment has become more widespread for adults, the awareness of this disease in the pediatric population remains low. As a result, improvements in our capacity to recognize, diagnose, and treat depression in children and adolescents has major public health value. Introduction of effective antidepressant treatments earlier in the progression of the disease state has the potential to effectively treat and control the disease as well as return patients to normal functioning and restore their quality of life.

While much has been written regarding the use of antidepressants in children with various mood and anxiety disorders, there have been few well-powered controlled clinical trials within specific diagnostic areas. Controlled studies of the use of tricyclic antidepressants in children and adolescents with depression have failed to produce a replicable pattern of efficacy (Kramer and Feiguine 1981; Petti and Law 1982; Kashani et al. 1984; Puig-Antich et al. 1987; Geller et al. 1990; Boulos et al. 1992). Possible reasons for differences between the studies may be in part due to methodology, severity of illness, or particular subpopulations of depressives evaluated (Dahl et al. 1990). Problems in design of other antidepressant trials include limited number of placebo-controlled studies, inadequate dosage as compared to blood levels (Geller et al. 1986; Preskorn et al. 1987), and an apparently higher placebo response rate (Puig-Antich et al. 1987).

When evaluating past studies, another primary concern is whether the populations under study were sufficiently homogeneous to allow an evaluation of the effectiveness of the medication. The fundamental questions that arise include (1) are the populations studied abnormally treatment resistant (ie, do the patients have comorbid bipolar disorder, atypical depression, or other substantial comorbidities), (2) are the populations overly treatment responsive, (3) are the samples too heterogeneous to detect treatment effects, or (4) have the wrong medications been evaluated (Emslie et al. 1997).

Fluoxetine was the first selective serotonin reuptake inhibitor antidepressant to receive Food and Drug Administrative (FDA) approval for the treatment of depression in adults. It has been shown to be equally effective to amitriptyline, imipramine, doxepin, trazodone, and mianserin. It is safer, with fewer side effects, less risk of complete suicide, and high cardiovascular safety (Fisch 1985; Halper and Mann 1988; Hendrickse et al. 1994). Open-label studies have been published in adolescents with depression and children with Tourettes and obsessive-compulsive disorder (Riddle et al. 1990), but no double-blind placebo-controlled studies had been published in this age group at the time this study was initiated (April 1991).

Despite the lack of evidence of effectiveness in randomized controlled trials, antidepressant medications have been prescribed in pediatric patients on the basis of adult data. This study was undertaken to evaluate the efficacy, safety, and tolerability of fluoxetine 20 mg/day compared with placebo in child and adolescent outpatients with nonpsychotic MDD and is expected to contribute significantly to raising awareness of depression in this population, advancing diagnostic criteria, and providing guidelines for effective treatment of depression in children and adolescents.

8. Study Objectives

8.1. Primary Objective

The primary objective of this study, based on a responder analysis of the Children's Depression Rating Scale-Revised (CDRS-R), was:

- To test the hypothesis that fluoxetine 20 mg/day is more effective than placebo in the treatment of children (aged 8 to <13 years) and adolescents (aged 13 to ≤18 years) diagnosed with DSM-III-R major depression as measured by response rates on the CDRS-R after up to 8 weeks. Response was defined as a decrease of at least 30% in the CDRS-R total score from baseline to endpoint.

8.2. Secondary Objectives

The secondary objectives of the study included the following:

- To compare the efficacy of fluoxetine 20 mg/day with placebo in the treatment of childhood and adolescent depression as measured by the mean change in CDRS-R total and subtotal scores from baseline to endpoint.
- To evaluate the change in mean CDRS-R total scores over time for fluoxetine 20 mg/day compared with placebo.
- To compare the efficacy of fluoxetine 20 mg/day with placebo in the treatment of childhood and adolescent depression as measured by remission rates on the CDRS-R. Remission was defined as a CDRS-R total endpoint score of ≤28.
- To compare the efficacy of fluoxetine 20 mg/day with placebo in the treatment of childhood and adolescent depression as measured by response rates on the Clinical Global Impressions of Improvement (CGI-Improvement) scale. Response to treatment was defined as a CGI-Improvement score of 1 or 2 at endpoint.
- To compare the efficacy of fluoxetine 20 mg/day with placebo in the treatment of childhood and adolescent depression as measured by recovery rates. Recovery was defined as a CDRS-R total endpoint score ≤28 and a CGI-Improvement score of 1 or 2 at endpoint.
- To compare the efficacy of fluoxetine 20 mg/day with placebo in the treatment of childhood and adolescent depression as measured by mean scores on the Clinical Global Impressions of Severity scale (CGI-Severity), CGI-Improvement scale, Brief Psychiatric Rating Scale for Children (BPRS-C), Beck Depression Inventory (BDI), and Children's Depression Inventory (CDI).

- To compare the efficacy of fluoxetine 20 mg/day with placebo in the treatment of childhood and adolescent depression as measured by response and remission rates on the CDRS-R, for those patients who completed at least 4 weeks of treatment.
- To compare the safety and tolerability of fluoxetine 20 mg/day with placebo in the treatment of childhood and adolescent depression as measured by monitoring of adverse events, vital signs, and laboratory analytes.
- To determine if there were any differences in the efficacy and safety of fluoxetine between subgroups defined by age and gender.

9. Investigational Plan

9.1. Overall Study Design and Plan: Description

9.1.1. Comparison of [redacted] Protocol and Lilly's Analysis of B1Y-MC-X065

9.1.1.1. Study Design

[redacted] original protocol was a NIMH grant proposal and is not structured in the same manner as a traditional protocol (see Appendix 16.1.1). The study described in [redacted] NIMH grant consisted of two study phases (see Figure 9.1). The first phase was a 3-week diagnostic evaluation phase in which patients underwent rigorous evaluation for appropriate diagnosis of depression and secondary comorbid disorders. Some patients also underwent sleep assessments and did not receive any study medication during the diagnostic evaluation phase. The second phase was an acute treatment phase, which consisted of a 1- to 2-week placebo lead-in period followed by an 8-week acute treatment period, during which patients were randomized to fluoxetine 20 mg/day or placebo. An informed consent document was signed for the diagnostic evaluation and acute treatment phases.

In the source documents and some of the electronic records at the study site, week numbers are preceded with letters designating the different phases/periods of the entire study. During the diagnostic evaluation phase, weeks were preceded with an "E," so records are identified as E0, E1, E2, and E3 visits. During the treatment phase of the study, two designations were used. "P" was used to designate visits during the placebo lead-in period (PO, P1, and P2, if needed) and "T" was used to designate visits during the treatment period (TO, T1, T2, T3, T4, T5, T6, T7, T8, and T9). Additionally, "SC" denoted the original screening visit, "CN" denoted the visit at which the consensus diagnosis was reached by the clinical investigators, and "CO" referred to the close-out visit.

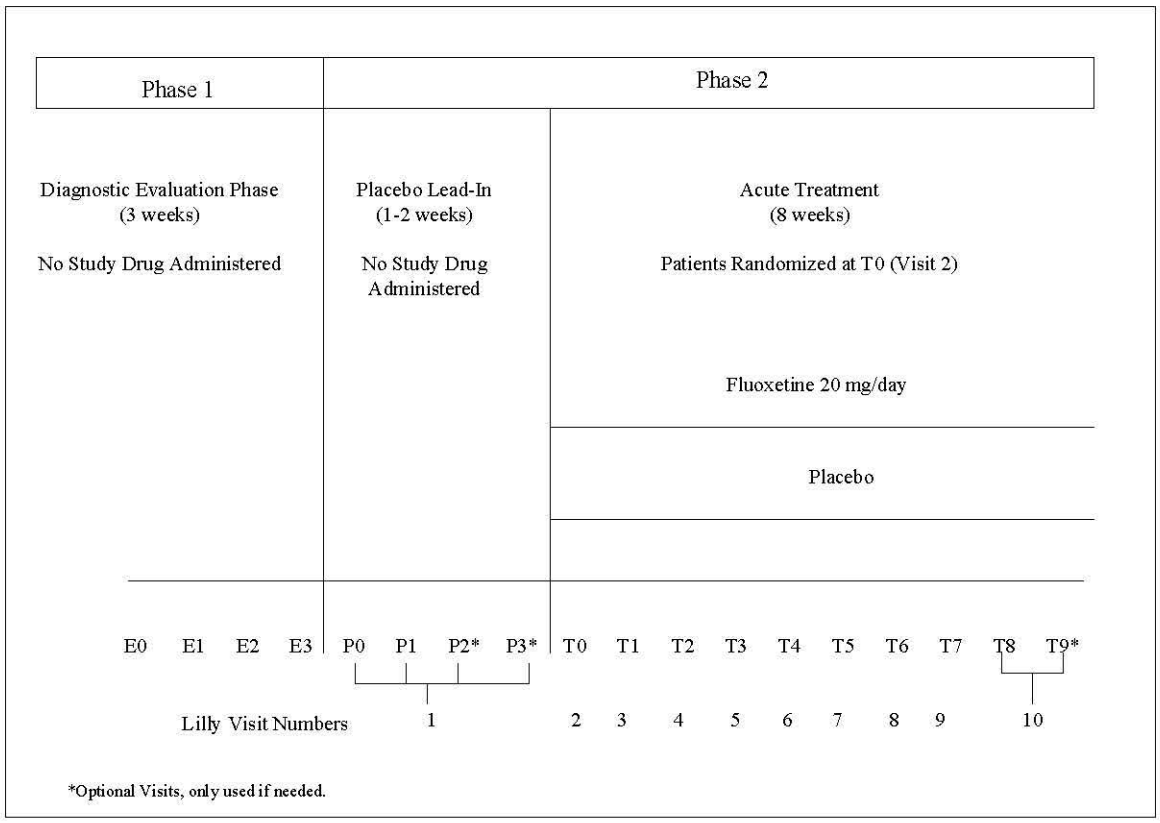


Figure 9.1. Study diagram for protocol as designed by [redacted] and correlation of visits to Lilly's study diagram for B1Y-MC-X065.

When Lilly collected information for the diagnosis of depression (which was performed during the diagnostic evaluation phase), these data were captured at Visit 1 of B1Y-MC-X065. Additionally, all baseline and demographic data for patients that were collected during the placebo lead-in period were captured at Visit 1 of B1Y-MC-X065. Lilly numbered the weekly visits of the acute treatment phase starting with the designation Visit 1 and continued through to Visit 10.

[redacted] also followed patients in a naturalistic setting for approximately 1 year following their participation in the acute phase of his study. Data from this naturalistic follow-up are presented as a manuscript [redacted] in Appendix 16.1.7. Lilly did not audit or collect information from this naturalistic follow-up because it was not controlled and Lilly did not believe that the data from this period would be useful for the intended submission. In addition, Lilly had an ongoing, double-blind, placebo-controlled, long-term study underway to evaluate the safety and efficacy of fluoxetine in depressed children and adolescents [B1Y-MC-HCJE(a)].

9.1.1.2. Study Conduct

Study events according to [redacted] protocol and source documents at the site were completed at the times indicated in Table 9.1.

Table 9.1. Study Events [redacted] Protocol

Study Event	Date
Ethical Review Board approved protocol	10 September 1990
First patient assigned to therapy	10 April 1991
Last patient completed acute treatment	28 February 1995
Publication of [redacted]	Accepted 20 August 1996
Publication of [redacted]	Accepted 17 December 1997

[redacted] protocol stated that informed consent documents would be signed by the parent/guardian and that a separate document, a patient assent form, would be signed by each patient. In actual practice, the site did not use separate consent and assent documents during the study. Rather, parents/guardians and patients signed an informed consent document that was also signed by a clinical investigator. An informed consent document was signed for the diagnostic evaluation and acute treatment phases.

During [redacted] 3-week diagnostic evaluation phase, sleep polysomnography and dexamethasone suppression testing (DST) were performed on some of the patients. [redacted] main objective for this study phase was "to determine whether outpatient children and adolescents with MDD evidence sleep polysomnographic and DST abnormalities like those found in depressed inpatients." Two additional objectives for this phase of the study in relationship to the acute treatment phase of the study were "to determine if pretreatment reduced rapid eye movement latency and/or DST status predicts acute response to medication treatment" and "to determine if clinical, demographic, or family history variables predict acute response to treatment." [redacted] objectives were to evaluate depression in children and adolescents from many different perspectives, covering everything from response to antidepressant treatment to examination of potential predictors for depression in this population. The information collected in the first phase of the study has been presented elsewhere and was not the focus of the study for Lilly.

The second phase (acute treatment) of [redacted] protocol was the focus of Lilly's analysis and is presented in detail throughout Section 9 of this clinical study report.

Study assessments were performed during the study as described in [redacted] protocol. Study assessments were collected by Lilly as presented in the Schedule of Events (see Table 9.2). In addition to the scales presented in the Schedule of Events for B1Y-MC-X065, [redacted] collected information from the patient self-report scales Bellevue Index of Depression (BID) parent and patient versions, Weinberg Screening Affective Scale (WSAS), Children's Global Assessment Scale (CGAS), and Family Global Assessment Scale (FGAS) throughout the treatment study. Lilly's medical audit of the site evaluated the completeness of the data from all scales assessed by the site. These self-report scales were not collected as consistently as the remaining scales. [redacted] stated in his

protocol that these scales were included so that preliminary evaluation of the results from these scales could be performed in an effort to validate them for future use. As the data from these scales were not as complete as the data from other scales and the fact that the data came from relatively unvalidated scales, Lilly decided not to include these data in the analyses for this clinical study report.

Although planned for collection at additional visits beyond baseline of the treatment study (Visit 1), electrocardiograms (ECGs) were only performed at baseline for all patients and at postbaseline visits for some patients.

Fluoxetine/norfluoxetine levels were collected to meet one of [redacted] stated objectives, "to develop preliminary data on blood levels of fluoxetine using a fixed dose." These blood levels were collected at various times throughout the study, but were not collected consistently for all patients. Because of the method in which these samples were collected, it was determined that these data could not be integrated with the data obtained from Lilly-sponsored trials. Lilly had two other controlled studies underway [B1Y-MC-HCIU and B1Y-MC-HCJE(a)] to evaluate the pharmacokinetic behavior of fluoxetine and norfluoxetine in pediatric patients. Consequently, Lilly did not collect data on blood levels from [redacted] study.

Table 9.2. Schedule of Events for B1Y-MC-X065

Visit Number	1	2	3	4	5	6	7	8	9	10	Summary
Demographics	X										
Informed Consent (Parent/Guardian and Patient)	X										
Psychiatric History	X										
CDRS-R	X	X	X	X	X	X	X	X	X	X	X
BPRS-C	X	X	X	X	X	X	X	X	X	X	X
CGI-Severity	X	X	X	X	X	X	X	X	X	X	X
CGI-Improvement			X	X	X	X	X	X	X	X	X
CDI (aged 8 to <13)	X	X	X	X	X	X	X	X	X	X	X
BDI (aged 13 to <18)	X	X	X	X	X	X	X	X	X	X	X
ECG	X										
Laboratories	X					X				X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Side-Effects Checklist	X	X	X	X	X	X	X	X	X	X	X
Non-Solicited Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Fluoxetine Side-Effects Checklist[1]			X	X	X	X	X	X	X	X	X
Study Medication Compliance	X	X	X	X	X	X	X	X	X	X	X
Patient Summary											X

X = performed at this visit.

[1]The Fluoxetine Side-Effects Checklist was used from January 1993 until study completion.

Abbreviations: BDI = Beck Depression Inventory; BPRS-C = Brief Psychiatric Rating Scale - Children; CDI = Children's Depression Inventory; CDRS-R = Childhood Depression Rating Scale - Revised; CGI-Improvement = Clinical Global Impressions of Improvement; CGI-Severity = Clinical Global Impression of Severity; ECG = electrocardiogram.

9.1.1.3. Data Collection and Analysis

When Lilly made the decision to utilize the data from this trial as part of a submission, it was decided that Lilly would only collect data from the second phase of [redacted] study, the acute treatment phase, as the primary focus of Lilly's submission is the treatment of depression in children and adolescents. Lilly did collect information concerning the final consensus diagnosis of patients (recorded at the conclusion of the diagnostic evaluation phase) and confirmed that all of the source documents leading to this final consensus diagnosis were in place at the site (verified at the site audit). The details concerning how the consensus diagnosis was reached during the diagnostic evaluation phase are presented in Section 9.3.4.

Table 9.3 presents a timeline of events for B1Y-MC-X065 following the completion of [redacted] protocol.

Table 9.3. Events Following Completion of [redacted] Protocol B1Y-MC-X065

Study Event	Date
Publication of [redacted]	Accepted 20 August 1996
Publication of [redacted]	Accepted 17 December 1997
Site database delivered to Lilly for consideration of import	November 1997
Study objectives defined	February 1999
Blinding Plan approved	17 March 1999
Site database delivered to Lilly for Lilly's analysis (converted into Lilly-formatted database)	12 May 1999
Development of electronic case report forms at Lilly to collect additional data from the site	1 April 1999 to 30 June 1999
Data Validation Plan initially approved	14 June 1999
Monitoring Plan approved	15 June 1999
Collection of additional data by site personnel using electronic case report forms - added to Lilly database	30 June 1999 to 31 July 1999
Source data verification of all variables in Lilly database against source documents at the site	Completed 18 August 1999
Statistical analysis plan approved	26 August 1999
Data lock and unblinding of the Lilly database	23 November 1999
Creation of clinical study report began	29 November 1999

Lilly defined objectives for analysis of the acute treatment phase prior to reanalyzing any summary statistical data unblinded to treatment group (see Section 8). Although more detailed than [redacted] stated objectives, Lilly's objectives encompass the same overall rationale for the study; namely, determining the effectiveness of fluoxetine 20 mg/day in the treatment of depression in children and adolescents. Lilly selected a different analysis of the primary endpoint than [redacted] based on conversations with the FDA and the appropriateness of the measure. [redacted] primary endpoint was an analysis of

recovery, based on CDRS-R and CGI-Improvement scores at endpoint. Lilly's primary analysis was the number of patients responding to antidepressant therapy after up to 8 weeks of treatment, using a 30% reduction from baseline in CDRS-R total score as the criterion. [redacted] endpoint for recovery was included in Lilly's analysis as a secondary endpoint. The CDRS-R was selected as it is based on the Hamilton Depression Rating Scale, the gold standard for determining efficacy of antidepressants in adult trials, and because it is specific for depression in the pediatric population.

The study site provided Lilly with an electronic database on 12 May 1999. This database was converted into a Lilly-formatted database. Because the site did not enter all variables into their database, Lilly designed electronic case report forms to capture additional information as described in Section 9.6.2. The remaining data were collected by site personnel and entered into Lilly's database. All of the data in the Lilly database were then verified against source documents at the site.

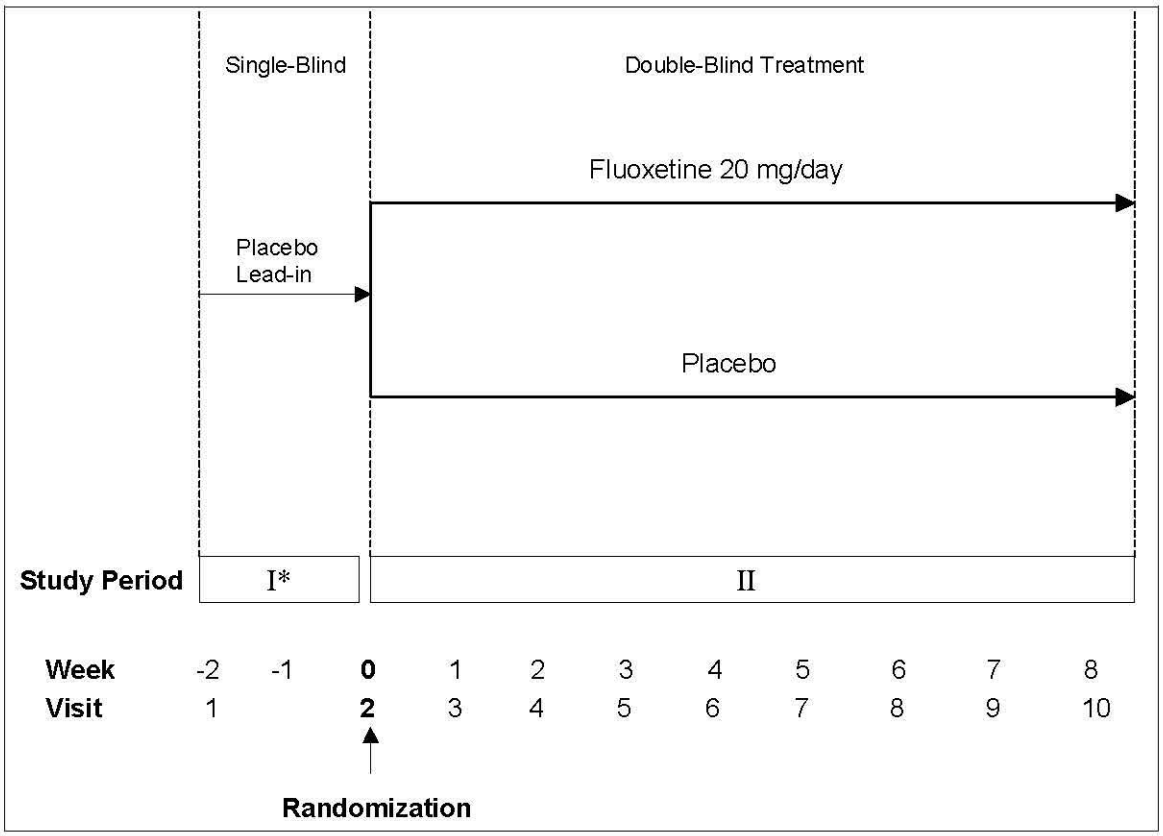
In summary, Lilly collected and analyzed data from the acute treatment phase of an investigator-initiated study conducted at [redacted] from April 1991 to February 1995 (the last patient visit for this study). Separate objectives and statistical analyses were developed prior to unblinding of Lilly personnel at the patient level. The analyses performed within this clinical study report are representative of those typically performed in Lilly-sponsored studies. The results from these analyses are very similar to those found in [redacted] analyses of these data, as presented in Appendix 16.1.7.

9.1.2. Description of B1Y-MC-X065

This was a single-center, double-blind, randomized, parallel-group study comparing the efficacy and safety of fluoxetine 20 mg/day and placebo for the acute treatment (8 weeks) of MDD, as defined by the DSM-III-R, in children and adolescents.

- **Study Period I** was a single-blind, placebo wash-out period that lasted for 1 to 2 weeks. Patients were evaluated at the end of the first (and second) week(s) for placebo response.
- **Study Period II** was a double-blind, acute treatment period during which patients were randomized to receive either fluoxetine 20 mg/day or placebo for 8 weeks. Patients were seen at weekly intervals.

The study design is illustrated in Figure 9.2.



*Study Period I lasted for 1 to 2 weeks.

Figure 9.2. Study design for B1Y-MC-X065.

9.1.2.1. Study Period I

Study Period I was a 1- to 2-week single-blind, placebo lead-in phase. Patients entering this study had previously completed an extensive diagnostic evaluation (described in Section 9.3.4) at the same study center. The data collected during the previous diagnostic evaluation were used to diagnose and establish baseline characteristics for patients entering this acute treatment study. To enter Study Period I, patients were required to have a diagnosis of MDD as confirmed during the diagnostic evaluation and a CDRS-R score >40, which corresponds to a diagnosis of depression.

Informed consent documents for this treatment study were signed by the parent or guardian, patient, and investigator on or before Visit 1. After giving written informed consent, patients underwent psychological and physical screening, including a medical history, psychiatric history, baseline psychiatric evaluations, physical examination (including vital signs), ECG, and laboratory tests.

Patients received placebo during this period. After 1 week of placebo treatment, patients were evaluated for placebo response. If the individual's CDRS-R total score was >40, he/she proceeded to Study Period II. If his/her CDRS-R total score was ≤40, the

individual was allowed to continue receiving placebo treatment for an additional week. If, after 2 weeks of placebo treatment, patients continued to have a CDRS-R total score ≤40, these patients were considered placebo responders and were discontinued from the study.

9.1.2.2. Study Period II

Study Period II was an 8-week, double-blind, acute treatment period. At Visit 2, patients meeting entry criteria (see Sections 9.3.1 and 9.3.2) were randomized to receive either fluoxetine 20 mg/day or placebo. Patients were seen at weekly intervals (Visits 2 through 10). Patients who were unable to tolerate fluoxetine 20 mg/day were allowed to take fluoxetine 20 mg every other day (alternate day dosing). Patients underwent psychiatric evaluations (CDRS-R, BPRS-C, CGI-Severity, CGI-Improvement, and BDI or CDI, as appropriate) and safety assessments (collection of vital signs, concomitant medications, and Side-Effects Checklist) at each visit. In addition, pill counts and comments were recorded at each visit. Laboratory analyses were performed at Visits 1, 6, and 10. The Fluoxetine Side-Effects Checklist, an additional interviewer-elicited checklist designed to evaluate potential side effects of fluoxetine treatment, was administered to patients starting in January 1993. Non-solicited adverse events were recorded at each visit as part of patient comments or in the source notes for that patient. A Patient Summary form was filled out for each patient at the time of discontinuation from the study.

9.2. Discussion of Study Design, Including the Choice of Control Groups

This trial was a placebo-controlled study of fluoxetine 20 mg/day for the acute treatment of MDD in children and adolescents. The study was designed by reviewing the available literature. The majority of available literature reports concerning antidepressant treatment in pediatric patients reported equivocal results and did not show separation of study drug from placebo. These studies had numerous design problems, including lack of placebo control, inadequate dosage, and high placebo response rates.

This study employed a fixed-dose, parallel-group design. The placebo lead-in phase was included in order to minimize the inclusion of placebo responders. The fixed-dose design was selected from evaluation of adult studies of fluoxetine. A dose of fluoxetine 20 mg/day was selected as it is the lowest dose proven to be effective in the treatment of MDD in adults. This dose is high enough to elicit response in most adult patients and is well tolerated. The study was 8 weeks in duration as this is considered an adequate length of time to evaluate acute antidepressant response in adult patients.

9.3. Selection of Study Population

Participation was voluntary. The nature of the study was fully explained to the patients and parents/guardians. A patient was considered entered into the study and a patient

number was assigned once the informed consent document was signed on or before Visit 1. (For definitions of entered and enrolled, see Section 4.)

9.3.1. Inclusion Criteria

Patients included in the study met all of the following criteria:

[1] Were female or male outpatients with nonpsychotic MDD, single or recurrent episodes, according to DSM-III-R.

[2] Were aged 8 to 18 years.

[3] Had normal intelligence as assessed clinically or by psychomotor testing if evidence of Intelligence Quotient (IQ) <80.

[4] Were willing and able to provide informed consent (parent/guardian and patient).

9.3.2. Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

[5] Had a diagnosis of Bipolar I or II disorder.

[6] Had a diagnosis of psychotic depression.

[7] Had a history of Bipolar I disorder in one or more first-degree relatives.

[8] Had a significant previous or concurrent medical illness.

[9] Had prior adequate treatment with fluoxetine.

[10] Had an independent sleep disorder.

[11] Had a history of alcohol or substance abuse.

[12] Had a history of eating disorders, including anorexia and bulimia.

[13] Had known allergies to tricyclic antidepressants.

[14] If sexually active, had inadequate birth control measures.

9.3.3. Removal of Patients From Therapy or Assessment

The criteria for enrollment were followed explicitly. If a patient did not meet the criteria for enrollment and was inadvertently enrolled, the patient was discontinued unless there were ethical reasons to have the patient remain in the study.

If a patient discontinued from the study, the reason for failing to complete the study was recorded (missed appointments, side effects, clinical worsening, etc.).

9.3.4. Disease Diagnostic Criteria

Patients underwent a rigorous 3-week diagnostic evaluation prior to inclusion in the acute treatment study, ie, prior to Visit 1. When Lilly audited the study site, clinical personnel confirmed that the diagnostic evaluations described in the original protocol (see Appendix 16.1.1) were in fact performed. Lilly collected information indicating the final consensus diagnoses for all patients but did not collect the actual scales and evaluations that formed the basis for the final consensus diagnosis. Documentation of these evaluations resides at the study site in [redacted]

Parents were initially screened over the telephone and if the patient met the criteria for the study (see Sections 9.3.1 and 9.3.2), the parent and patient were scheduled for an initiation evaluation. Prior to this initial interview, the study was explained to the patient and parent/guardian, and an informed consent form was signed.

A clinician that was not involved with the treatment phase of this study performed the initial evaluation of patients. During this evaluation, patients underwent a structured psychiatric interview, physical and neurological examinations, and had blood drawn for routine laboratory analysis. Each patient and parent was interviewed separately, using the clinician-rated structured DSM-III-R-based interview schedule, the Diagnostic Inventory for Children (DICA) parent and child versions (Herjanic and Reich 1982; Welner et al. 1987).

Parents were interviewed using a modified family history Research Diagnostic Criteria (RDC) questionnaire (Andreasen et al. 1977). The medical history of each first and second degree relative was reviewed with regards to presence of symptoms consistent with affective disorder, suicide, alcohol and substance abuse, criminal behavior, schizophrenia, anxiety disorders, hysteria, and other psychiatric disorders. Additional information was obtained about functional impairment caused by the disorder, whether treatment was obtained, and what type.

The parent and patient were interviewed together to complete the clinician-rated CDRS-R scale. In addition, several self-report measures were collected. The parents completed the parent version of the BID and the patients completed the WSAS as well as the BDI or CDI, depending on their age. While the patient was interviewed for completion of the DICA, the parent completed the family history using the RDC interview. If the patient met inclusion/exclusion criteria, he/she was scheduled for a repeat interview 1 week later.

At the second interview, the patient and family were interviewed by one of the three primary clinical investigators involved in the treatment phase of this study. The DSM-III-R data collected during the initial evaluation from the parent and child versions of the DICA were reviewed by the clinical investigator. In addition, the clinical investigator scored the patient according to the depressive items of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS), CDRS-R, CGAS, BID, and BPRS-C. A third interview was scheduled for 1 week later. The third interview was conducted by another of the three clinical investigators and was independent from the previous psychiatric

assessment. Again, the DICA DSM-III-R data were reviewed and the K-SADS depressive items and a CDRS-R were completed. At this interview, the parent and patient self-report measures were repeated (CGAS, BID, and BPRS-C). The family history was also reviewed at this visit.

A consensus meeting was held after the three interviews were completed. At this meeting, the clinical investigators systematically reviewed data from interviews, parent and child self-report measures, and additional information (eg, CDRS-R scores indicative of depression). The clinicians first reached consensus for the primary diagnosis of MDD for each patient. They then discussed the presence or absence of any secondary comorbid diagnoses for each patient. Onset dates for each diagnosis were estimated from data obtained from the parents. Although the process for reaching consensus on diagnoses was time consuming, it was considered essential for accurate and definitive diagnosis.

If the patient met inclusion/exclusion criteria at all three interviews and the CDRS-R score was >40, then he/she proceeded to the treatment phase of the study (entering Study Period I).

9.4. Treatments

9.4.1. Treatments Administered

9.4.1.1. Study Period I

Single-blind placebo medication was administered to all patients during this 1- to 2-week lead-in period. Patients were instructed to take one capsule every morning.

9.4.1.2. Study Period II

Double-blind medication was administered during this 8-week acute treatment period. Patients were instructed to take one fluoxetine 20-mg capsule or one matching placebo capsule every morning for 8 weeks starting the day after Visit 2 (randomization). If the dose was not well tolerated, patients were instructed to take one capsule every other day (alternate day dosing).

9.4.2. Identity of Investigational Products

From April 1991 to August 1993, the pharmacy at the [redacted] prepared and provided blinded study drug medication for the patients in this study. The pharmacy used marketed Prozac® capsules, which have an opaque green cap and off-white body. The cap is imprinted with DISTA 3105 and the body is imprinted with Prozac 20 mg. Active study drug was dispensed and appeared as the marketed product (green and white capsules). Placebo medication was prepared by emptying Prozac capsules completely and refilling them with lactose powder. The pharmacy made sure that the printing on the capsules was lined up before dispensing to the patient. Fifty-four

patients (25 fluoxetine-treated, 29 placebo-treated) received study medication prepared in this manner.

From September 1993 to February 1995, Lilly supplied blinded clinical trials material for this study. Active and placebo study medication were identical in appearance as solid white capsules. Fluoxetine 20 mg capsules were provided from lots CT02768 and CT01678. Placebo capsules were provided from lots CT02769 and CT01679. All four lots had an expiration date of 1 May 1995 and an extension expiration date of 1 May 1996. Forty-two patients (23 fluoxetine-treated, 19 placebo-treated) received study medication supplied by Lilly.

No patient received study medication prepared in both ways (site-prepared and Lilly-provided). Lilly does not believe that the change from the site's preparation of study medication to Lilly's supply of medication compromised the blinding or conduct of this study. Patients and study site personnel were blinded to study drug assignment before and after this change occurred. It is possible that the change from the marketed product (green and white capsules) to the clinical trials materials supplied by Lilly (white capsules) may have had an indirect effect on study results; however, this effect would have been consistent for the two treatment groups. To determine if this change was associated with any effect on the study results, subgroup analyses were performed for key efficacy and safety endpoints and are presented in Sections 11.4.3 and 12.7, respectively.

9.4.3. Method of Assigning Patients to Treatment Groups

Qualified patients were randomized to active treatment with fluoxetine 20 mg/day or placebo at the beginning of Study Period II (Visit 2). A two-by-two stratified randomization, based on age (categorized as children, aged 8 to <13, and adolescents, aged 13 to ≤18) and gender, was used in this study. Assignment to treatment group was performed by the pharmacist using a randomization list prepared by the biostatistician. A study site nurse verified that treatment assignment was correct by comparing dispensed medication to the randomization list.

Randomization codes are presented in Appendix 16.1.5.

9.4.4. Selection of Doses in the Study

A dose of fluoxetine 20 mg/day was selected as it is the lowest dose proven to be effective in the treatment of MDD in adults. This dose is high enough to elicit response in most adult patients and was well tolerated.

9.4.5. Selection and Timing of Dose for Each Patient

The Clinical Investigator's Brochure for fluoxetine (Eli Lilly 1990) recommends that fluoxetine 20 mg/day be administered in the morning.

9.4.6. Treatment Blinding

As described in Section 9.3.4, patients underwent a 3-week diagnostic evaluation, during which no medications were administered to patients. Study Period I consisted of a 1- to 2-week single-blind, placebo wash-out period. Study Period II consisted of an 8-week randomized, double-blind, placebo-controlled, fixed-dose acute treatment period. The placebo wash-out period was single-blind, such that the clinician was aware of treatment assignment but the patient was not. At the beginning of Study Period II (Visit 2), patients were randomized and the study continued in a double-blind fashion, with treatment group assigned by the pharmacist.

Clinical management, initial evaluation, and all repeat evaluations were conducted blind to laboratory data. The hospital pharmacy managed the medication and dispensed either placebo or active medication (see Section 9.4.2 for details).

The site has provided written documentation that [redacted] and the clinical study staff were not unblinded to patient therapy codes until Spring 1995, after all patients had completed the study and all databases had been verified (see Appendix 16.1.15).

A study site nurse was involved with rating of patients during the diagnostic evaluation period as described in Section 9.3.4. During this phase, patients did not receive any study medication. This same nurse served as the liaison between the clinical site and the pharmacy during the acute treatment phase of the study. She had access to the randomization list as she was responsible for verifying that study medication was correctly dispensed to patients. She also served as the liaison between the study site and the laboratory. In addition, as a backup to the primary clinical raters, this nurse was involved with the psychiatric ratings for 2 patients during the acute treatment study. She rated patients 2013 (placebo) and 2014 (fluoxetine) at Visits 2 and 3, respectively, as documented in a statement presented in Appendix 16.1.15. As she served as a backup for the blinded clinical investigators and because she was only called in for these 2 patients, Lilly does not believe that her evaluation of these 2 patients compromised their data or that of the other patients in this study. The data for these patients was thoroughly reviewed and it was concluded that the information collected by this individual was comparable to data collected by other raters.

Two patients (2051 and 2163) may have had their treatment assignments revealed to a treating physician, who was separate from personnel involved in this study, because they both attempted to commit suicide. Both patients received fluoxetine 20 mg/day. Patient 2051 was discontinued from the study following hospitalization for the suicide attempt. Patient 2163 completed the protocol.

Lilly personnel performed a thorough review of all patient records to ensure that appropriate blinding practices were maintained throughout the study. Issues identified during this review are noted below. This review indicated that every patient's therapy remained blinded to both themselves and the site throughout their participation and that,

for the most part, the site remained blinded to all patients' treatments until the study was completed and the data validated. Exceptions to this are listed below.

Following a patient's completion in the study, [redacted] believed it was important for patients to continue to be treated and followed; however, the follow-up of patients completing this study was not supported under the NIMH grant for this study. Due to this, the process for referring patients after their completion of the study was not well defined early in the study conduct. In general, patients were referred to other clinical staff at [redacted] who were not involved in the study or to clinicians outside [redacted] However, there were a few instances where patients were referred to physicians involved in this study, including [redacted] for follow-up care. When treating these patients for follow-up care, there were instances (less than ten), where study records indicate these physicians were unblinded to the patient's therapy assignment prior to the completion of all patients in the study. Due to the limited number of occurrences, Lilly does not believe this compromised the overall study results.

It should also be noted that upon Lilly's review of the site records, drug level analysis results listing fluoxetine levels were found in approximately 5 patients' medical charts. In discussion with the site, it was confirmed that these results were filed in the charts following the completion of all patients in the study. In fact, the drug level reports for all patients were held at [redacted] a laboratory familiar with performing research work, until the site notified the laboratory that all patients had completed and all data were completely entered into a database and validated. The laboratory then sent all of the fluoxetine level reports to the site in one batch.

In order to track the patient throughout their entire duration of the evaluation, treatment and follow-up care, a chronology chart called a Psychiatric Rating Scale (PRS) was maintained in the patient's chart. Following completion and publication of the study, [redacted] and his team decided to do some additional follow-up analyses on the patients from this study. To aid in completing these later analyses, the site often wrote that patient's treatment therapy assignment from the study on the PRS. As noted above, this was done well after the data from the study was finalized and presented and in no way compromised the study results.

In reviewing patient charts, it is also important to note that site personnel sometimes referred to study drug as "Prozac," "fluoxetine," or "active treatment" in patient records. Upon communication with the site personnel performing the study, it was confirmed that it was common practice for site personnel to use these terms instead of using the more appropriate term "study drug." Examination of the records revealed that this nomenclature was used for patients assigned to both fluoxetine and placebo treatment. In addition, there were instances in the patient charts where investigators made references that could indicate unblinding of patients at their completion of the study, such as writing "break blind" and "treat openly." In discussion with site personnel, it was explained that it was common practice for site personnel to use the term "break blind" to mean stop

treating the patient with a blinded medication. "Treat openly" then indicated putting the patient on an unblinded drug, often Prozac, prescribed from the pharmacy by the normal route. Following these comments, very rarely did the team see evidence the site did, in fact, unblind the patient's assigned therapy, thereby supporting the site's explanation. The site confirmed that is was not their practice (with the exceptions noted in one of the above paragraphs) to unblind each patient as they completed the study.

Lilly does not believe that any of the specific instances cited above compromised the validity of patients who completed the study nor did any instance of potential unblinding bias future results for this study.

9.4.7. Prior and Concomitant Therapy

[redacted]protocol did not define excluded medications. A record of previous treatments for the current episode of major depression was collected for each patient. Concomitant medications were monitored throughout the study.

9.4.8. Treatment Compliance

Compliance with the treatment regimen was monitored by site personnel through the counting of returned pills. New bottles of study medication were dispensed weekly. Two extra days of pills were given in case emergencies arose and a visit could not be made on schedule.

Because the protocol did not specify parameters of treatment noncompliance, Lilly defined noncompliance prior to unblinding the data at the patient level (see Appendix 16.1.6). A patient was defined to be noncompliant if he/she failed to take study drug on more than 2 days within a visit interval. If the patient received alternate day therapy, noncompliance was defined as failing to take study drug on more than 1 day within a visit interval.

The site maintained a Drug Accountability Log, which was filled out during the study by the study coordinator. This log was compiled from source documents that contained information about drug accountability and/or patient compliance. However, the Drug Accountability Log was the only record that contained all of the relevant information for use of study medication during the trial (see Appendix 16.1.15). Although the information collected on the Drug Accountability Log was intended for compliance with Good Clinical Practices, Lilly used this data as the basis for treatment compliance. As this was not the original intent of this record, there were some gaps in the data regarding patient compliance at every visit during the trial.

9.5. Efficacy and Safety Variables

9.5.1. Efficacy and Safety Measurements Assessed and Schedule of Events

The following efficacy measures were collected at the times shown in Table 9.2 (Schedule of Events), presented in Section 9.1.1.

- **Children's Depression Rating Scale-Revised (CDRS-R):**
  The CDRS-R is a clinician-rated instrument designed to measure the presence and severity of depression in children (Poznanski et al. 1983, 1984, 1985). The scale was modeled after the Hamilton Depression Rating Scale for adults and includes questions about school. The scale consists of 17 items scored on a 1 to 5 or 1 to 7 point scale. A rating of 1 indicates normal functioning. Total scores range from 17 to 113. In general, scores below 20 indicate an absence of depression, scores of 20 to 30 indicate borderline depression, and scores of 40 to 60 indicate moderate depression.

- **Clinical Global Impressions of Severity (CGI-Severity):**
  The CGI-Severity scale (Guy 1976) is a clinician-rated instrument that measures the severity of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "normal" and a score of 7 indicates that the patient has an "extremely severe case of depression."

- **Clinical Global Impressions of Improvement (CGI-Improvement):**
  The CGI-Improvement scale (Guy 1976) is a clinician-rated instrument that measures the improvement of the patient's depression. It is a 7-point scale where a score of 1 indicates that the patient is "very much improved," a score of 4 indicates that the patient has experienced "no change," and a score of 7 indicates that the patients is "very much worse."

- **Brief Psychiatric Rating Scale (BPRS-C):**
  The BPRS-C is a clinician-rated scale that assesses the presence of depressive symptoms in addition to other symptom clusters, such as behavior problems, depression, thinking disturbance, psychomotor excitation, withdrawal retardation, anxiety, and organicity (Overall and Pfefferbaum 1982). The scale consists of 21 items rated on a 7-point scale. Total scores range from 0 to 126. The higher the total score, the more severe the depression.

- **Beck Depression Inventory (BDI):**
  The BDI (Beck and Steer 1984) is a patient-rated scale that assesses the major symptom categories associated with depression. Total scores range from 0 to 62. The higher the total score, the more severe the depression. The BDI scale is intended for use in adolescents (patients aged 13 to <18 years).

- **Children's Depression Inventory (CDI):**
  The CDI is a patient-rated scale that assesses the major symptom categories associated with depression. The CDI was developed from the BDI (Kovacs 1985). Total scores range from 0 to 54. Like the BDI, the higher the total score, the more severe the depression. The CDI scale is intended for use in children (patients aged 8 to <13 years).

The following safety measures were collected at the times shown in Table 9.2 (Schedule of Events), presented in Section 9.1.1.

- **Side-Effects Checklist:**
  The Side-Effects Checklist is a 30-item symptom checklist based on the Subjective Treatment Emergent Symptoms Scale (STESS) developed by the NIMH. The items on the checklist include general symptoms, such as trouble sleeping, diarrhea, headaches, and trouble eating (see Appendix 16.1.2). The patient is asked by the clinician if he/she is having trouble with the symptoms on the checklist. The clinician also records the frequency of these symptoms based on conversation with the patient.

- **Fluoxetine Side-Effects Checklist:**
  The Fluoxetine Side-Effects Checklist is a 30-item checklist developed by Boulos et al. (1992). The items on the checklist include symptoms that are considered possibly associated with fluoxetine treatment. The patient is asked by the clinician if he/she is having trouble with the symptoms on the checklist. The clinician also records the frequency of these symptoms based on conversation with the patient.

- **Non-Solicited Adverse Events:**
  During the study, spontaneous adverse events were not collected systematically, although they were captured during patient visits. Non-solicited adverse events were collected from source documents and progress notes. Adverse events were captured regardless of relationship to study medication. Although these events were captured during the study, the severity of these events was not recorded. These events were captured as actual terms and coded to COSTART terms by blinded Lilly clinical personnel and verified by a blinded Lilly clinical research physician.

- **Concomitant Medications:**
  All concomitant medications taken during the study were recorded.

- **Laboratory Data:**
  Standard laboratory tests included complete blood count, blood chemistry, electrolytes, thyroid panel, and urinalysis.

- **Vital Signs:**
  Vital signs included blood pressure (systolic and diastolic), heart rate, weight, and height.

- **Electrocardiograms (ECG):**
  An ECG was collected at baseline only to determine eligibility of the patient for entry into the study.

The Schedule of Events is provided in Table 9.2, presented in Section 9.1.1.

9.5.2. Appropriateness of Measurements

The CDRS-R, developed by Poznanski et al. (1983, 1984, 1985), is a clinician-rated instrument designed to measure the presence and severity of depression in children. The CDRS-R has good inter-rater reliability and correlates highly with global ratings of depression (Poznanski et al. 1984). The CDRS-R is based on the Hamilton Depression Rating Scale, the gold standard for determining efficacy of antidepressants in adult studies, and is designed for pediatric patients.

The CGI-Severity and CGI-Improvement scales were developed at the NIMH (Guy 1976) and have been used in both adult and pediatric populations. The CGI scales allowed for systematic accumulation of general measures of functioning and improvement.

The BPRS-C includes 21 symptoms that were developed using factor analysis from 63 symptoms found in routine clinical practice (Overall and Pfefferbaum 1982). The BPRS-C was used in this study to assess the presence of other symptom clusters, including behavior problems, thinking disturbance, psychomotor excitation, withdrawal retardation, anxiety, and organicity, in addition to depressive symptoms.

The BDI has been used extensively with both adults and adolescents in research studies (Beck and Steer 1984). The scale has been evaluated psychometrically within a wide variety of psychiatric and normal populations (Beck and Beamesderfer 1974). The instrument has been demonstrated to have high internal consistency and test-retest reliability and validity with adolescents (Reynolds et al. 1985). Ease of administration and strong psychometric properties similar to those demonstrated for adult populations, and validation across clinical and nonclinical populations, make this one of the standards in single point, self-reported depressive state.

The CDI was developed from the BDI and was used as a self-report measure of the severity of depression in children (Kovacs 1985).

A Side-Effects Checklist was used to record adverse events. The checklist had been in use at the site's psychopharmacology clinic for several years prior to this study.

The Fluoxetine Side-Effects Checklist was developed to evaluate adverse events possibly associated with fluoxetine treatment.

9.5.3. Primary Efficacy Variable

The primary efficacy variable for this study was the CDRS-R total score. The primary analysis to support efficacy of fluoxetine 20 mg/day in the acute treatment of MDD was the analysis of response, defined as a decrease of at least 30% in the CDRS-R total score from baseline to endpoint.

A 30% decrease in CDRS-R score is considered to be clinically significant, as it is representative of a change in the patient's condition from active depression to remission (Poznanski et al. 1985). At study entry, patients were required to have a score >40 on the CDRS-R in order to be enrolled (ie, minimum score correlated with active depression). Remission of depressive symptoms is defined as achieving a score of 28 or less on the CDRS-R. This difference between the minimum entry criterion for depression and remission is 30%.

9.6. Data Quality Assurance

9.6.1. During the Study

The study site managed the data collected during the study. The data were managed using a screen and menu-guided automated system. Throughout the study, quality control procedures, such as double-data entry and edit checks, were used to assure the accuracy and completeness of the data.

The data entry system was developed by the study coordinator/systems analyst. Requirements for the data entry system were derived from the study binder, located at the site. After the system was created, test data were entered into all screens to test data input and online editing.

Source data were data entered directly into the automated system by site personnel. The data were initially entered from patient records. The data were spot-checked by comparing the database to source documents. The data were reentered (double-data entry) by a different individual into a second blank copy of the database. The two databases were compared and discrepancies were identified. The discrepancies were resolved by comparing to source documents and the first database was corrected. The efficacy data for randomized patients used in the site's analysis went through a final source data verification process. In addition, the univariate features of the data, such as deviations from symmetry or heteroscedasticity, were checked.

It should be noted that site personnel only entered selected variables into the database. Data were not electronically entered into the site database for non-solicited adverse events, pill counts, laboratory data, concomitant medications, ECGs, vital signs, and some inclusion/exclusion criteria. These data were available in source documents.

9.6.2. During the Data Import by Lilly

As the data from this trial were collected from an investigative site that was not monitored by Lilly while the trial was conducted (1991-1995), the following measures were taken to ensure the integrity of the data:

- a detailed plan to maintain the study blind at the patient level was developed (see Appendix 16.1.14)
- an extensive audit of the source documents and study files was conducted
- affirmation statements from the Investigator and Study Coordinators were obtained (see Appendix 16.1.15)
- an audit trail for the Lilly study database was initiated and maintained
- 100% source data verification of all data points for every patient at every visit (captured in the Lilly database) during the acute treatment phase of the study was conducted (see Appendices 16.1.16 and 16.1.17)
- a 100% data quality review of all data that had been entered into the Lilly database was performed
- a detailed statistical analysis plan was developed prior to reanalyzing any unblinded statistical summary data (see Appendix 16.1.6)
- a data validation plan was developed to document the data collection procedures (see Appendix 16.1.17).

Lilly acknowledges that [redacted] had published a manuscript detailing the results from this study prior to Lilly's decision to import the data from this investigator-initiated trial. This manuscript is presented in Appendix 16.1.7. A timeline of events following completion of the study at the site is presented in Section 9.1.1.3. The project team at Lilly developed a detailed blinding plan, presented in Appendix 16.1.14, to address how personnel would handle data during the data import process. This blinding plan has been followed throughout the preparation of this clinical study report.

Lilly Clinical Research Associates (CRAs) conducted an extensive medical audit of the site to determine the feasibility of importing the data from this study for inclusion in a submission. The purpose of the audit was to assess basic study data and documentation integrity, patient safety, and the qualifications of the investigator and site. As part of this audit, Lilly CRAs began collecting all essential regulatory documents, including copies of the protocol, informed consent documents, and ethical review board approvals. Patient files were reviewed; the information collected from these files was used to enable assessment of site decisions regarding patient safety and study inclusion/exclusion criteria and adherence to the protocol. Using the information obtained during this audit, a risk analysis profile was completed by Lilly area representatives from Regulatory, Medical Quality Assurance, Medical, and Statistics. This group decided to move ahead

with the data importation process as the integrity of the data was sound and the site was found to be compliant with Good Clinical Practice standards.

Some of the data for this study had previously been entered into an electronic database by site personnel (as described in Section 9.6.1). The site database was obtained from the Investigator and converted into a Lilly database. Site personnel captured the following additional data through use of electronic case report forms developed by Lilly: non-solicited adverse events, pill counts, laboratory data, concomitant medications, ECGs, vital signs, and some inclusion/exclusion criteria. These data were collected from study files for each patient, source documents, and also through verbatim transcription of progress notes without interpretation of the data, and were entered into the Lilly database. The study coordinator signed a source affirmation statement indicating that she would not alter source documents as she transcribed the study progress notes written by the physician (see Appendix 16.1.15).

All data points captured in the Lilly database for all visits that occurred during the single-blind placebo phase and the double-blind acute treatment phase (Visits 1 to 10) were verified from source data during subsequent monitoring visits. In addition, all data points from all unscheduled visits that occurred during both the single-blind placebo phase and the double-blind acute treatment phase were source data verified.

Verification and validation of the data were performed by Lilly clinical personnel and an independent contract monitor (see Appendix 16.1.17). Throughout the process, selected Lilly CRAs had access to randomization codes (from source files). These CRAs had a primary role in data validation, including the following: development and approval of edits, assessment of edits, assessment of the completeness of data captured in comparison to medical audit records, and review of the data according to the monitoring plan. However, these CRAs were unable to make changes to the Lilly study database. Data entry, query resolution, and corrections to the Lilly study database were made only by eligible blinded Lilly personnel. An automated audit trail was put into place to track all changes made to the database in response to Lilly queries. All changes were authorized in advance by the investigative site. The Lilly Clinical Research Physician (CRP) remained blinded until data lock. Ascription of COSTART terminology to all adverse events captured during the data collection, source data validation, and verification processes were performed by blinded Lilly personnel and approved by the CRP.

A statistical analysis plan, distinct from the one used by [redacted] and colleagues in publications, was developed by Lilly personnel prior to the final validation and unblinding of the reporting database (see Appendix 16.1.6). Treatment group assignments in the database were masked using a dummy randomization code to maintain blinding during the process of data validation and development of statistical summary tables. Lilly study data were formally unblinded to treatment group assignment at data lock.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

All of the statistical analyses in this study report were performed after the study had been completed. The statistical analysis plan was finalized prior to the final validation and unblinding of the data for this study and is located in Appendix 16.1.6.

General Considerations

All tests of hypotheses were tested at a two-sided, .05 significance level. All total and subtotal scores from rating scales were derived from individual items. If any of the individual items were missing, the total or subtotal was treated as missing.

For analyses of continuous data, treatment groups were compared using Type III sums of squares from an ANOVA with treatment in the model (comparable to a Student's t test). The analyses were performed on the original scale data unless the assumptions of the ANOVA were violated. In these instances, the analyses were performed on the rank-transformed data.

For analyses of categorical efficacy and safety (a response, remission, recovery, or event), Fisher's exact test was used. The analyses of demographic variables were performed using Fisher's exact test.

Supplemental analyses of the data were conducted as deemed appropriate.

Data to be Analyzed

All analyses were performed on an intent-to-treat basis. An intent-to-treat analysis is an analysis of data by treatment group assignment, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol.

Only patients with baseline and postbaseline measurements for the primary efficacy analysis were included in the analyses of all efficacy scales. Patients who were excluded from the efficacy analyses were documented in Appendix 16.2.4. Patients who had their daily dose reduced by switching to alternate day dosing were included in all analyses. The 2 patients who switched to alternate day dosing are discussed in Section 12.1.

Patient Disposition

Reasons for discontinuation for all randomized patients were compared between treatment groups using Fisher's exact test.

Patient Characteristics

Baseline characteristics of origin, age, age category (children and adolescents), gender, height, weight, socioeconomic status, and family structure were compared between

treatment groups. Frequencies were compared using Fisher's exact test and means were compared using an ANOVA with treatment in the model.

Psychiatric History

Psychiatric history, including comorbid Axis I diagnoses, duration of current episode, number of depressive episodes, length of illness, age of illness onset, and positive family history were summarized for each treatment group for all randomized patients. Categorical data were compared across treatment groups using Fisher's exact test and continuous data were compared across groups using an ANOVA with treatment group as the independent variable in the model.

Previous Treatment Current Episode

The use of previous treatments for the current episode of illness was summarized for each treatment group. The frequency of the previous treatments used along with the number of patients using any previous treatment was reported.

Concomitant Medications

Concomitant medications were summarized for each treatment group. Incidence rates of concomitant medications were analyzed by Fisher's exact test.

Compliance

Compliance with study medication was determined post hoc. A patient was considered noncompliant if he/she failed to take study drug for more than 2 days within a visit interval (approximately a week). If the patient's dosage had been reduced to alternate day therapy, noncompliance was defined as failing to take study drug for more than 1 day within a visit interval. The percentage of compliant patients for each treatment group was summarized by visit.

Baseline Psychiatric Evaluation

Baseline scores for the CDRS-R total, CGI-Severity, and BPRS-C total scales were summarized for each treatment group. Baseline was defined as the last available measure for each scale of Visits 1 and 2. Each scale was compared across treatment groups using an ANOVA with treatment in the model.

Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy variable was the CDRS-R total score. The primary analysis was the comparison of the proportion of patients responding between treatment groups. A patient was considered a responder if his/her CDRS-R total score decreased by at least 30% from baseline (last available measure from Visits 1 and 2) to endpoint (last available measure from Visits 3 through 10). Two analyses to augment the primary analyses were also performed: 1) The CDRS-R total response rate using a reduction of at least 50% from

baseline, and 2) CDRS-R total response rate (at 30% and 50% reductions from baseline) for all patients completing at least 4 weeks of treatment. The proportion of patients who responded was compared across treatment groups using Fisher's exact test.

Secondary Efficacy Analysis

Mean change in CDRS-R total score from baseline (last available measure from Visits 1 and 2) to endpoint (last available measure from Visits 3 through 10) was compared across treatment groups using an ANOVA with treatment in the model. The following secondary variables were analyzed in a similar manner:

- CDRS-R Mood Subtotal – sum of Items 8, 11, 14, 15
- CDRS-R Somatic Subtotal – sum of Items 4, 5, 6, 7, 16, 17
- CDRS-R Subjective Subtotal – sum of Items 9, 10, 12, 13
- CDRS-R Behavior Subtotal – sum of Items 1, 2, 3
- CGI-Severity
- BPRS-C Total
- BDI Total
- CDI Total

For the analysis of CGI-Improvement, an ANOVA was performed only on endpoint values, since this scale measures total improvement in direct comparison to the patient's condition at baseline.

Three different longitudinal analyses were conducted to assess the temporal change in the CDRS-R scale data. The first two analyses assessed mean change in CDRS-R total scores from baseline (last available of Visits 1 and 2) to each subsequent visit (Visits 3 through 10) and was compared across treatment groups. Two by-visit analyses were performed: 1) the analysis that included patients active in the study at the visit of interest, and 2) the analysis that included all patients with at least one postbaseline measure using a last-observation-carried-forward (LOCF) approach.

The third analysis to assess the temporal change over time of the CDRS-R total score was a repeated measures ANOVA. The dependent variable was the baseline and postbaseline CDRS-R total score. The model used an unstructured covariance matrix with visit as the within-patient factor, treatment as the between-patient factor, and a treatment-by-visit interaction. The change from baseline to Visit 10 was compared across treatments by assessing this single degree of freedom contrast of the treatment-by-visit interaction. All main effects and interaction tests were made using the approximate F-tests reported by SAS PROC MIXED.

The proportion of patients meeting definitions of response, remission, and recovery was compared between treatment groups as secondary categorical analyses. All frequencies

were analyzed using a Fisher's exact test. The following categorical definitions were analyzed:

- **Remission**: A remitter was defined as a patient who had an endpoint CDRS-R total score ≤28. Endpoint was the last available measurement from Visits 3 through 10. This analysis was also performed on all patients completing at least 4 weeks of treatment (endpoint was be the last measurement from Visits 6 through 10).
- **CGI-Improvement Response**: A patient was defined as a CGI-Improvement responder if his/her last available treatment CGI-Improvement score was 1 or 2, where endpoint was defined as the last available measurement from Visits 3 through 10.
- **Recovery**: Patients with a CDRS-R total endpoint score ≤28 and a CGI-Improvement endpoint score of 1 or 2 were defined as recovered. Endpoint was the last available measurement from Visits 3 through 10.

Safety Analyses

Extent of Exposure

The length of exposure (measured in days) for each patient was summarized by treatment group. Exposure was defined as the last dose date minus the first dose date plus one.

Adverse Events

Adverse events were summarized and analyzed using three sources of data: the Side-Effects Checklist, non-solicited adverse events, and the Fluoxetine Side-Effects Checklist. All randomized patients were included in the analyses and Fisher's exact test was used for comparing incidence of events.

The frequency of treatment-emergent solicited adverse events as defined by the items on the Side-Effects Checklist was analyzed. An event was considered to be treatment-emergent solicited if the Checklist item was present at baseline and worsened as defined by an increase in the score, or if the Checklist item first occurred after baseline. The analysis of the Side-Effects Checklist was considered the primary analysis of safety as it was the most complete source of adverse event reporting in this study.

Non-solicited adverse events that occurred during treatment were also summarized by incidence and frequencies were compared between treatment groups.

All adverse events reported on the Fluoxetine Side-Effects Checklist were summarized and reported. No statistical tests were performed on these data because these data were not considered to be a complete source of information. The Fluoxetine Side-Effects Checklist was administered to only a subset of the patients in the study, starting in January 1993.

Serious adverse events were summarized and discussed in text.

Laboratory Evaluation

The treatment effect on change from baseline (last measurement from Visits 1 and 2) to endpoint (last measurement from Visits 3 through 10) for ranked laboratory values was assessed using an ANOVA with treatment as the independent factor in the model. All patients with a baseline and endpoint score were included in the analysis. The proportion of patients with abnormal laboratory values were summarized and compared across treatment groups by Fisher's exact test.

Vital Signs

Mean change from baseline (last measurement from Visits 1 and 2) to endpoint (last measurement from Visits 3 through 10) in vital signs was compared across treatment groups using ANOVA with treatment in the model. All patients with a baseline and endpoint score were included in the analysis. Vital signs included height, weight, heart rate, and blood pressure.

Subgroup Analyses

The primary efficacy analysis, CDRS-R total response rate, was assessed for differential treatment effects across two subgroups, age category (8 to <13, 13 to ≤18) and gender (male, female). Frequency of response for each subgroup was presented along with the Breslow-Day test for the homogeneity of odds ratio results comparing between-strata differences in the response frequency between treatment groups. A formal subgroup analysis of ethnic origin was not performed because the non-Caucasian population represented approximately 20% of the sample size.

Mean changes in CDRS-R total score from baseline to endpoint were also compared across treatment groups for the subgroups age category and gender. For each subgroup, the statistical evaluation of both the change from baseline while accounting for subgroup effect and the change from baseline within subgroup strata was performed. An analysis of covariance was conducted with treatment, subgroup, and treatment-by-subgroup interaction as the independent factors in the model. The test of the treatment-by-subgroup interaction was the primary assessment of possible differential treatment effects across subgroups. Tests of interactions were performed at a .10 significance level.

Treatment-emergent solicited adverse events from the Side-Effects Checklist were analyzed by the subgroups age category and gender. These adverse events were also analyzed by a Breslow-Day test for homogeneity of odds ratio across subgroups.

9.7.2. Determination of Sample Size

The primary outcome variable specified in the original protocol written by [redacted] (see Appendix 16.1.1) was "the proportion of completing subjects in each group (placebo and drug) who recover, where recovery is defined as below 28 on the CDRS-R and a CGI of 1 or 2." This outcome measure in the protocol, with certain assumptions about recovery rates, was used to calculate a power of 80% based on 40 patients per treatment

group. Lilly believes that response, based on CDRS-R alone, was a more appropriate primary measure than recovery and was a sufficient measure of differentiation between drug and placebo consistent with other depression protocols. This also provided consistency with protocol B1Y-MC-HCJE(a), an ongoing Lilly study of depression in children and adolescents. The original protocol outcome measure was included in this clinical study report as a secondary analysis. Since this study was completed, no recalculation of power based on CDRS-R response rate has been performed.

9.8. Changes in the Conduct of the Study or Planned Analyses

A detailed statistical analysis plan was finalized on 26 August 1999, prior to the final validation and unblinding of the data at the patient level for this study, and is located in Appendix 16.1.6.

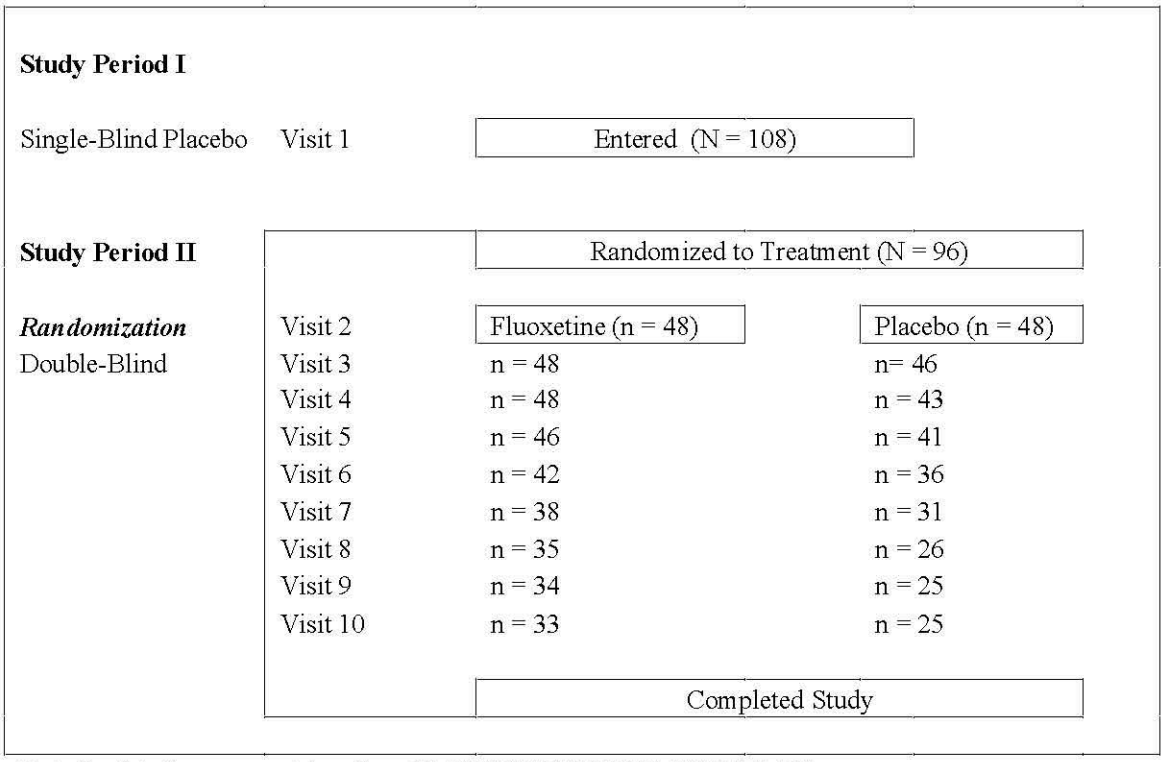
Lilly's original statistical analysis plan indicated that those patients that switched to alternate day dosing would have their exposure calculation adjusted accordingly. Only 2 patients received alternate day dosing. Patient 2162 received alternate day dosing at Visits 6 and 8. Patient 2212 received alternate day dosing from Visits 7 through 10. As a result, this adjustment was not necessary.

Additional post hoc analyses to evaluate the effect of site-prepared versus Lilly-provided study medication were included. These analyses evaluated two subgroups of patients: those who received site-prepared study medication and those who received Lilly-provided study medication. The same subgroup analyses that were performed for age and gender were performed for study medication (site-prepared versus Lilly-provided). These analyses were performed for the CDRS-R total response rate (the primary efficacy analysis), the mean change from baseline to endpoint in CDRS-R total score, and the incidence of treatment-emergent solicited adverse events.

10. Study Patients

10.1. Disposition of Patients

As shown in Figure 10.1, 108 patients were screened for entry into the acute treatment study. Twelve of the 108 patients either failed inclusion/exclusion criteria at Visit 1 and were considered screen failures, or decided not to participate in the study. The remaining 96 patients qualified for the study and were randomized to treatment at Visit 2. Forty-eight patients received fluoxetine and 48 patients received placebo. Fifty-eight patients (60%) completed the entire study, with 33 (69%) fluoxetine-treated patients completing the study as compared with 25 (52%) placebo-treated patients.



Data for this figure were taken from RMP.B1YO.X065REP (RDS2EM01).

Figure 10.1. Overview of patient disposition by visit for B1Y-MC-X065.

The reasons for discontinuation for all 96 randomized patients are summarized by visit and treatment group in Table 10.1.

Table 10.1. Summary of Reasons for Discontinuation by Visit
All Randomized Patients
B1Y-MC-X065

Visit (Week of Treatment)	Number of Patients Continuing	Number of Patients Discontinued	Reason Discontinued	Fluoxetine	Placebo
Visit 2	**96**	**0**	Adverse event	0	0
(Week 0)			Lack of efficacy	0	0
Randomization	↓		Lost to follow-up	0	0
			Patient decision	0	0
			Protocol violation	0	0
Visit 3	**94**	**2**	Adverse event	0	0
(Week 1)			Lack of efficacy	0	0
	↓		Lost to follow-up	0	0
			Patient decision	0	2
			Protocol violation	0	0
Visit 4	**91**	**3**	Adverse event	0	0
(Week 2)			Lack of efficacy	0	2
	↓		Lost to follow-up	0	0
			Patient decision	0	0
			Protocol violation	0	1
Visit 5	**87**	**4**	Adverse event	2	0
(Week 3)			Lack of efficacy	0	1
	↓		Lost to follow-up	0	0
			Patient decision	0	0
			Protocol violation	0	1
Visit 6	**78**	**9**	Adverse event	2	0
(Week 4)			Lack of efficacy	1	5
	↓		Lost to follow-up	0	0
			Patient decision	0	0
			Protocol violation	1	0
Visit 7	**69**	**9**	Adverse event	0	0
(Week 5)			Lack of efficacy	2	5
	↓		Lost to follow-up	0	0
			Patient decision	0	0
			Protocol violation	2	0

(continued)

Table 10.1. Summary of Reasons for Discontinuation by Visit
All Randomized Patients
B1Y-MC-X065 (concluded)

Visit (Week of Treatment)	Number of Patients Continuing	Number of Patients Discontinued	Reason Discontinued	Fluoxetine	Placebo
Visit 8 (Week 6)	**61** ↓	**8**	Adverse event	1	0
			Lack of efficacy	2	5
			Lost to follow-up	0	0
			Patient decision	0	0
			Protocol violation	0	0
Visit 9 (Week 7)	**59** ↓	**2**	Adverse event	0	0
			Lack of efficacy	0	1
			Lost to follow-up	0	0
			Physician decision	1	0
			Protocol violation	0	0
Visit 10 (Week 8)	**58**	**1**	Adverse event	0	0
			Lack of efficacy	1	0
			Lost to follow-up	0	0
			Patient decision	0	0
			Protocol violation	0	0

Data for this table were taken from RMP.B1YO.X065REP (RDS2EM01).

An overall summary of primary reasons for study discontinuation is provided in Table 10.2. Overall, 58 patients (60%) completed the study and 38 patients (40%) discontinued from the study. The most common reason for study discontinuation was lack of efficacy (25 patients), followed by adverse events (5 patients), protocol requirements (5 patients), patient decision (2 patients), and physician decision (1 patient).

There was a statistically significant difference between treatment groups with respect to discontinuation due to lack of efficacy, with 6 (13%) fluoxetine-treated patients discontinuing as compared with 19 (40%) placebo-treated patients (p=.005). There was a trend towards statistical significance between treatment groups with respect to discontinuation due to an adverse event, with 5 (10%) fluoxetine-treated patients discontinuing as compared with zero placebo-treated patients (p=.056).

Table 10.2. Summary of Reasons for Discontinuation
All Randomized Patients
B1Y-MC-X065

Primary Reason for Discontinuation	Flx 20mg (N=48) n (%)	Placebo (N=48) n (%)	Total (N=96) n (%)	p-Value*
PROTOCOL COMPLETE	33 (68.8)	25 (52.1)	58 (60.4)	.144
ADVERSE EVENT	5 (10.4)	0	5 (5.2)	.056
LACK OF EFFICACY	6 (12.5)	19 (39.6)	25 (26.0)	.005
PATIENT DECISION	0	2 (4.2)	2 (2.1)	.495
PROTOCOL REQUIREMENT	3 (6.3)	2 (4.2)	5 (5.2)	1.00
PHYSICIAN DECISION	1 (2.1)	0	1 (1.0)	1.00

RMP.B1YP.JCLLIB2(RDS1EM03)
RMP.B1YO.X065REP(RDS1EM03)
* Frequencies are analyzed using a Fisher's Exact test.
XRDS0001

Patient disposition data for all patients are located in Appendix 16.2.2.

10.2. Significant Protocol Violations

Table 10.3 presents a summary of significant protocol violations that occurred during the study.

Three patients violated inclusion/exclusion criteria and should not have been randomized to treatment in this study. Patients 2185 (fluoxetine) and 2233 (placebo) were both 7 years old when they entered this trial and therefore, violated the minimum entry age requirement of 8 years old. Patient 2185 completed the entire study. Patient 2233 was discontinued at Visit 5, following 20 days of therapy, due to protocol requirement (non-compliance with protocol procedures). Patient 2087 (placebo) reported alcohol abuse as an adverse event with a start date prior to Visit 1. The patient voluntarily discontinued the study at Visit 3, following 6 days of therapy, and was hospitalized for the condition.

Upon Lilly's audit of site records, it was discovered that 2 patients (2014 and 2061) were missing informed consent documents for the acute phase of the study. It is believed that these patients had signed appropriate informed consent documents but these documents were unable to be located at the time of the audit.

The informed consent documents for 2 placebo-treated patients (2052 and 2057) were signed by each patient, but were not signed by each patient's parent/guardian. Site personnel noted these violations in the Comments section of each patient's CRF (see Appendix 16.4.4).

Three patients took concomitant medications that had the potential to interfere with study treatment during the study. Patients 2124 (fluoxetine), 2178 (fluoxetine), and 2220 (placebo) all smoked marijuana during the study. Patient 2124 (fluoxetine) reported smoking marijuana at Visit 7 and 9. This patient discontinued the study at Visit 10, following 51 days of therapy, due to lack of efficacy. Patient 2178 (fluoxetine) reported smoking marijuana at Visit 8. This patient completed the entire protocol. Patient 2220 (placebo) reported smoking marijuana at Visit 3. This patient discontinued the study at Visit 6, following 27 days of therapy, due to lack of efficacy. Because use of marijuana was episodic in all three cases, any effect on study results is considered to be of minimal significance.

A total of 9 patients (4 fluoxetine-treated, 5 placebo-treated) were not compliant with their study medication. Assessment of "non-compliance" was based on the investigator's judgment only. Compliance with study medication, as determined from counting of returned pills, is discussed further in Section 11.3. The degree of non-compliance observed by the investigator was not considered to affect interpretation of study results.

There were 6 patients (4 fluoxetine-treated, 2 placebo-treated) who missed visits during the study. Missing data were taken into account when statistical analyses were performed.

In addition, there were several patients with missing study assessments during the study. Missing data were taken into account when performing statistical analyses and therefore, should not impact the interpretation of results from the study.

Any effect these violations may have on the study results is likely to be of minimal significance in interpreting the findings of this study.

A complete listing of all protocol violations that occurred during the study is located in Appendix 16.2.3. Comments for individual patients (see Appendix 16.4.4) and patient disposition data (see Appendix 16.2.2) were also evaluated in examination of protocol violations.

Table 10.3. Listing of Significant Protocol Violations
All Enrolled Patients
B1Y-MC-X065

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Violation of Inclusion/Exclusion Criteria				
	Flx 20mg	2185	1	Patient was 7 years old at trial entry
	Placebo	2087		Patient diagnosed with alcohol abuse
	Placebo	2233	1	Patient was 7 years old at trial entry
Missing Informed Consent Documents				
	Flx 20mg	2014		
	Placebo	2061		
Missing Parent/Guardian Signature on Informed Consent Documents				
	Placebo	2052		
	Placebo	2057		
Concomitant Medications				
	Flx 20mg	2124	7, 9	Patient smoked marijuana
	Flx 20mg	2178	8	Patient smoked marijuana
	Placebo	2220	3	Patient smoked marijuana
Patient Not Compliant with Study Medication (as judged by the investigator)				
	Flx 20mg	2029	7	
	Flx 20mg	2033	5	
	Flx 20mg	2040	5	
	Flx 20mg	2073	5, 6	
	Placebo	2002	1	
	Placebo	2025	9, Sum	
	Placebo	2038	6	
	Placebo	2050	4	
	Placebo	2057	2	
Missed Visits				
	Flx 20mg	2067	6	
	Flx 20mg	2073	7	
	Flx 20mg	2075	6	
	Flx 20mg	2244	6	
	Placebo	2007	6	
	Placebo	2066	6	

Data for this table were taken from Note-to-File data.

11. Efficacy Evaluation

11.1. Data Sets Analyzed

Lilly Medical uses *intent-to-treat* analyses which are analyses of study participants by the groups to which they were assigned by random allocation, even if the study participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Such an analysis is sometimes stated *analyze as randomized*.

On 23 November 1999 the final analysis database was validated and locked. Subsequent to data lock, a few errors in the database were discovered. These errors remain in the database (see Appendix 16.1.13 for documentation) that was used for all analyses in this clinical study report. In addition, upon Lilly's audit of the site records, it was discovered that laboratory values for several patients were not included in the database for this study. These data are documented in Appendix 16.1.13. These errors are considered minor and did not affect any conclusions in this clinical study report.

Appendix 16.2.4 contains a list of patients and observations excluded from the primary efficacy analysis. All randomized patients with a baseline and at least one postbaseline measurement were included in the efficacy analyses. Of the 96 randomized patients, 95 patients were analyzed. Patient 2207 was not included in the primary analysis because the patient did not have a postbaseline CDRS-R assessment.

11.2. Demographic and Other Baseline Characteristics

11.2.1. Patient Characteristics

Baseline demographic characteristics for all randomized patients are summarized in Table 11.1. The patients randomized in this study were predominantly Caucasian (79%). The mean age of patients in the study was 12.8 years (range = 7.2 to 17.8 years). Two patients were under 8 years of age, which was the lower limit of the inclusion criteria (see Section 10.2 for protocol violations). These patients were included in the categorical age analysis as children. The treatment groups were balanced with respect to the number of adolescents (24 fluoxetine-treated, 24 placebo-treated) and number of children (24 fluoxetine-treated, 24 placebo-treated). Of the 96 patients randomized to treatment, 44 (46%) were female and 52 (54%) were male.

The mean height of patients was 152 cm (range = 66 to 180 cm) and the mean weight of patients was 52 kg (range = 23 to 120 kg). There was an even distribution of patients when considering socioeconomic status of the family. The highest percentage of patients came from homes with both natural parents (45%).

The treatment groups were comparable with respect to all baseline demographic characteristics.

Complete patient listings of demographic characteristics and secondary conditions are presented in Appendix 16.2.5.

Table 11.1. Baseline Patient Characteristics
All Randomized Patients
B1Y-MC-X065

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
Origin				
No. Patients	48	48	96	.195*
African Descent	4 (8.3)	4 (8.3)	8 (8.3)	
Caucasian	35 (72.9)	41 (85.4)	76 (79.2)	
Hispanic	8 (16.7)	2 (4.2)	10 (10.4)	
Other	1 (2.1)	1 (2.1)	2 (2.1)	
Age (yrs)				
No. Patients	48	48	96	.559**
Mean	12.67	13.00	12.84	
Median	13.00	12.98	12.98	
Standard Dev.	2.73	2.78	2.75	
Minimum	7.56	7.16	7.16	
Maximum	17.84	17.80	17.84	
Age Category				
No. Patients	48	48	96	1.00*
Adolesc(13-18yr)	24 (50.0)	24 (50.0)	48 (50.0)	
Child(8-12yr)	24 (50.0)	24 (50.0)	48 (50.0)	
Gender				
No. Patients	48	48	96	1.00*
Female	22 (45.8)	22 (45.8)	44 (45.8)	
Male	26 (54.2)	26 (54.2)	52 (54.2)	

RMP.B1YP.JCLLIB2(DES1EM05)
RMP.B1YO.X065REP(DES1EM05)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.1. Baseline Patient Characteristics
All Randomized Patients
B1Y-MC-X065 (continued)

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
Height (cm)				
No. Patients	37	39	76	.307**
Mean	149.93	153.93	151.99	
Median	149.00	153.00	153.00	
Standard Dev.	20.58	12.59	16.96	
Minimum	66.00	137.00	66.00	
Maximum	180.00	180.00	180.00	
Unspecified	7	7	14	
Weight (kg)				
No. Patients	44	46	90	.418**
Mean	54.07	50.83	52.41	
Median	51.00	49.00	50.00	
Standard Dev.	21.82	15.48	18.81	
Minimum	23.00	26.00	23.00	
Maximum	120.00	99.00	120.00	
Socioeconomic Status				
No. Patients	48	48	96	.665*
Professional	13 (27.1)	16 (33.3)	29 (30.2)	
Skilled	17 (35.4)	18 (37.5)	35 (36.5)	
Semi/Unskilled	18 (37.5)	14 (29.2)	32 (33.3)	

RMP.B1YP.JCLLIB2(DES1EM05)
RMP.B1YO.X065REP(DES1EM05)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.1. Baseline Patient Characteristics
All Randomized Patients
B1Y-MC-X065 (concluded)

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
Family Structure				
No. Patients	48	48	96	.715*
Both Parents	20 (41.7)	23 (47.9)	43 (44.8)	
Nat. Mother	16 (33.3)	12 (25.0)	28 (29.2)	
Other	2 (4.2)	0	2 (2.1)	
Nat.Mthr/Stpfthr	6 (12.5)	9 (18.8)	15 (15.6)	
Nat. Father	1 (2.1)	0	1 (1.0)	
Nat.Fthr/Stpmthr	2 (4.2)	2 (4.2)	4 (4.2)	
Other Relatives	0	1 (2.1)	1 (1.0)	
Adoptive Parents	1 (2.1)	1 (2.1)	2 (2.1)	

RMP.B1YP.JCLLIB2(DES1EM05)
RMP.B1YO.X065REP(DES1EM05)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

11.2.2. Psychiatric History

Table 11.2 summarizes the psychiatric histories of randomized patients at baseline. Following structured and diagnostic interview (described in Section 9.3.4), the research team reached consensus on the primary diagnosis of MDD, and then on the presence or absence of secondary comorbid psychiatric disorders. The most common comorbid disorders diagnosed included anxiety disorders (41%), dysthymia (35%), oppositional and conduct disorders (29%), and attention deficit hyperactivity disorder (ADHD) (24%). The treatment groups were comparable with respect to comorbid psychiatric diagnoses with the exception of anxiety disorders (p=.012). There were 26 fluoxetine-treated patients (54%) with comorbid anxiety disorders at baseline as compared with 13 placebo-treated patients (27%). Approximately half of the patients (54%) had a positive first-degree family history of Axis I disorders.

The average duration of the current episode of depression was 14 weeks (range = 4 to 56 weeks). Patients had suffered an average of 1.7 episodes of depression (range = 1 to 4 episodes) prior to entering this study. The average length of the illness was 18 months (range = 1 to 84 months). The average age for onset of depression was 10.8 years old (range = 5 to 17 years old).

The treatment groups were comparable with respect to these disease characteristics at baseline.

Complete patient listings of psychiatric histories by patient are presented in Appendix 16.2.5.

Table 11.2. Psychiatric History
All Randomized Patients
B1Y-MC-X065

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
Comorbid Ax 1 Diag ADHD: No. (%)				
No. Patients	48	48	96	.339*
No	34 (70.8)	39 (81.3)	73 (76.0)	
Yes	14 (29.2)	9 (18.8)	23 (24.0)	
Comorbid Ax 1 Diag Alcohol Abuse: No. (%)				
No. Patients	48	48	96	1.00*
No	48 (100)	47 (97.9)	95 (99.0)	
Yes	0	1 (2.1)	1 (1.0)	
Comorbid Ax 1 Diag Anxiety: No. (%)				
No. Patients	48	48	96	.012*
No	22 (45.8)	35 (72.9)	57 (59.4)	
Yes	26 (54.2)	13 (27.1)	39 (40.6)	
Comorbid Ax 1 Diag Dysthymia: No. (%)				
No. Patients	48	48	96	.286*
No	28 (58.3)	34 (70.8)	62 (64.6)	
Yes	20 (41.7)	14 (29.2)	34 (35.4)	
Comorbid Ax 1 Diag Func. Enuresis: No. (%)				
No. Patients	48	48	96	1.00*
No	47 (97.9)	48 (100)	95 (99.0)	
Yes	1 (2.1)	0	1 (1.0)	
Comorbid Ax 1 Diag Obsessive Compulsive: No. (%)				
No. Patients	48	48	96	1.00*
No	47 (97.9)	47 (97.9)	94 (97.9)	
Yes	1 (2.1)	1 (2.1)	2 (2.1)	

RMP.B1YP.JCLLIB(DES1EM06)
RMP.B1YO.X065REP(DES1EM06)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.2. Psychiatric History
All Randomized Patients
B1Y-MC-X065 (continued)

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
Comorbid Ax 1 Diag Oppos./Conduct: No. (%)				
No. Patients	48	48	96	.823*
No	35 (72.9)	33 (68.8)	68 (70.8)	
Yes	13 (27.1)	15 (31.3)	28 (29.2)	
Comorbid Ax 1 Diag Simple Phobia: No. (%)				
No. Patients	48	48	96	1.00*
No	47 (97.9)	48 (100)	95 (99.0)	
Yes	1 (2.1)	0	1 (1.0)	
Comorbid Ax 1 Diag Social Phobia: No. (%)				
No. Patients	48	48	96	1.00*
No	47 (97.9)	48 (100)	95 (99.0)	
Yes	1 (2.1)	0	1 (1.0)	
Comorbid Ax 1 Diag Somatization: No. (%)				
No. Patients	48	48	96	1.00*
No	47 (97.9)	48 (100)	95 (99.0)	
Yes	1 (2.1)	0	1 (1.0)	
Pos.1st Deg.Fam.Hstry/Axis I Dsordr(s)				
No. Patients	48	48	96	.876*
No	21 (43.8)	20 (41.7)	41 (42.7)	
Unknown	2 (4.2)	1 (2.1)	3 (3.1)	
Yes	25 (52.1)	27 (56.3)	52 (54.2)	

RMP.B1YP.JCLLIB(DES1EM06)
RMP.B1YO.X065REP(DES1EM06)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.2. Psychiatric History
All Randomized Patients
B1Y-MC-X065 (continued)

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
Duration of Current Episode (weeks)				
No. Patients	48	48	96	.614**
Mean	14.58	13.69	14.14	
Median	12.00	12.00	12.00	
Standard Dev.	9.71	7.47	8.63	
Minimum	4.00	4.00	4.00	
Maximum	56.00	32.00	56.00	
Number of Episodes				
No. Patients	48	48	96	.603**
Mean	1.67	1.75	1.71	
Median	2.00	2.00	2.00	
Standard Dev.	0.72	0.84	0.78	
Minimum	1.00	1.00	1.00	
Maximum	3.00	4.00	4.00	
Length of Illness (months)				
No. Patients	48	48	96	.849**
Mean	18.79	18.00	18.40	
Median	13.00	12.00	12.00	
Standard Dev.	20.93	19.71	20.23	
Minimum	1.00	1.00	1.00	
Maximum	84.00	72.00	84.00	

RMP.B1YP.JCLLIB(DES1EM06)
RMP.B1YO.X065REP(DES1EM06)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

Table 11.2. Psychiatric History
All Randomized Patients
B1Y-MC-X065 (concluded)

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
Age of Illness Onset (years)				
No. Patients	48	48	96	.489**
Mean	10.60	10.98	10.79	
Median	10.00	10.50	10.00	
Standard Dev.	2.73	2.56	2.64	
Minimum	6.00	5.00	5.00	
Maximum	16.00	17.00	17.00	

RMP.B1YP.JCLLIB(DES1EM06)
RMP.B1YO.X065REP(DES1EM06)
* Frequencies are analyzed using a Fishers-Exact test.
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

11.2.3. Previous Treatment of Current Episode

Table 11.3 presents a summary of the treatments previously used by randomized patients for the treatment of their current episode of major depression. The majority of patients (69%) had not received treatment for their current episode. Of the 30 patients who had received previous treatment, 13 (14%) used tricyclic antidepressants, 12 (13%) used psychotherapy, 4 used another unspecified medication, and 1 used a tricyclic antidepressant in combination with another treatment.

A by-patient data listing of previous treatments of the current episode are presented in Appendix 16.2.5.

Table 11.3. Previous Treatment of Current Episode
All Randomized Patients
B1Y-MC-X065

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)
Previous Treatment			
No. Patients	48	48	96
No Rx	35 (72.9)	31 (64.6)	66 (68.8)
Other	2 (4.2)	2 (4.2)	4 (4.2)
Psychotherapy	6 (12.5)	6 (12.5)	12 (12.5)
Tricyclics	5 (10.4)	8 (16.7)	13 (13.5)
TCAs & Other	0	1 (2.1)	1 (1.0)

RMP.B1YP.JCLLIB2(DES1EM07)
RMP.B1YO.X065REP(DES1EM07)
XDES0001

11.2.4. Concomitant Medications

Table 11.4 presents a summary of concomitant medications used by randomized patients during the study. The most common concomitant medications used during this study were the over-the-counter, non-steroidal anti-inflammatory medications ibuprofen (21%) and paracetamol (20%). Diphenhydramine hydrochloride was used by 9% of patients in this study. The proportion of patients taking any of the medications shown in Table 11.4 was comparable between the two treatment groups.

Regarding concomitant medications that have the potential to influence symptoms of major depression, including central nervous system active drugs, 3 patients reported using cannabis. Of these patients, no patients reported continuous use (1 patient reported use at three visits and the other 2 patients reported use at one visit).

A by-patient listing of all concomitant medications used during this study is presented in Appendix 16.4.1.

Table 11.4. Concomitant Medications
All Randomized Patients
B1Y-MC-X065

Drug Name	Flx 20mg (N=48) n (%)	Placebo (N=48) n (%)	Total (N=96) n (%)	p-Value*
PATIENTS WITH >= 1 DRUG	31 (64.6)	28 (58.3)	59 (61.5)	.675
PATIENTS WITH NO DRUGS	17 (35.4)	20 (41.7)	37 (38.5)	.675
IBUPROFEN	7 (14.6)	13 (27.1)	20 (20.8)	.208
PARACETAMOL	11 (22.9)	8 (16.7)	19 (19.8)	.609
DIPHENHYDRAMINE HYDROCHLORIDE	7 (14.6)	2 (4.2)	9 (9.4)	.159
ACETYLSALICYLIC ACID	4 (8.3)	2 (4.2)	6 (6.3)	.677
GUAIFENESIN	3 (6.3)	3 (6.3)	6 (6.3)	1.00
AMOXICILLIN	2 (4.2)	3 (6.3)	5 (5.2)	1.00
SALBUTAMOL	3 (6.3)	2 (4.2)	5 (5.2)	1.00
AMOXICILLIN TRIHYDRATE	2 (4.2)	2 (4.2)	4 (4.2)	1.00
ANTIBIOTIC NOS	2 (4.2)	2 (4.2)	4 (4.2)	1.00
ACETYLSALICYLIC ACID/CAFFEINE/SALICYLAMI	2 (4.2)	1 (2.1)	3 (3.1)	
CANNABIS	2 (4.2)	1 (2.1)	3 (3.1)	
ORAL CONTRACEPTIVE NOS	2 (4.2)	1 (2.1)	3 (3.1)	
PHENYLEPHRINE/PHENYLPROPANOLAMINE/BROMPH	3 (6.3)	0	3 (3.1)	
TERFENADINE	2 (4.2)	1 (2.1)	3 (3.1)	

RMP.B1YP.JCLLIB2(DTS1EM08)
RMP.B1YO.X065REP(DTS1EM08)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.4. Concomitant Medications
All Randomized Patients
B1Y-MC-X065 (continued)

Drug Name	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
TERPIN/OPIUM/ANTIMONY POTASSIUM TARTRATE	1	(2.1)	2	(4.2)	3	(3.1)	
AMPICILLIN	2	(4.2)	0		2	(2.1)	
BECLOMETASONE DIPROPIONATE	0		2	(4.2)	2	(2.1)	
BISMUTH SUBSALICYLATE	1	(2.1)	1	(2.1)	2	(2.1)	
CHLORPHENAMINE MALEATE	1	(2.1)	1	(2.1)	2	(2.1)	
CLAVULANATE/AMOXICILLIN	2	(4.2)	0		2	(2.1)	
DOXYCYCLINE	2	(4.2)	0		2	(2.1)	
ETHANOL/PARACETAMOL/DEXTROMETHORPHAN/EPH	0		2	(4.2)	2	(2.1)	
HERBAL PREPARATION	1	(2.1)	1	(2.1)	2	(2.1)	
HOMEOPATHIC AGENT	1	(2.1)	1	(2.1)	2	(2.1)	
MEPYRAMINE/PHENIRAMINE/PHENYLPROPANOLAMI	2	(4.2)	0		2	(2.1)	
PARACETAMOL/CHLORPHENAMINE/DEXTROMETHORP	1	(2.1)	1	(2.1)	2	(2.1)	
PHENACETIN/PARACETAMOL/PHENYLPROPANOLAMI	2	(4.2)	0		2	(2.1)	
PHENOL	1	(2.1)	1	(2.1)	2	(2.1)	
PHENYLPROPANOLAMINE/CLEMASTINE	2	(4.2)	0		2	(2.1)	
PROMETHAZINE HYDROCHLORIDE	2	(4.2)	0		2	(2.1)	

RMP.B1YP.JCLLIB2(DTS1EM08)
RMP.B1YO.X065REP(DTS1EM08)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.4. Concomitant Medications
All Randomized Patients
B1Y-MC-X065 (continued)

Drug Name	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
ACETYLSALICYLIC ACID/CAFFEINE/PARACETAMO	1	(2.1)	0		1	(1.0)	
ACETYLSALICYLIC ACID/CHLORPHENAMINE/PHEN	1	(2.1)	0		1	(1.0)	
ALPRAZOLAM	0		1	(2.1)	1	(1.0)	
ANTACIDS	1	(2.1)	0		1	(1.0)	
ANTIBIOTICS	0		1	(2.1)	1	(1.0)	
ASTEMIZOLE	0		1	(2.1)	1	(1.0)	
BROMPHENIRAMINE/DEXTROMETHORPHAN/PHENYLP	1	(2.1)	0		1	(1.0)	
CEFACLOR	0		1	(2.1)	1	(1.0)	
CEFALEXIN	1	(2.1)	0		1	(1.0)	
CEFPROZIL	0		1	(2.1)	1	(1.0)	
CEFTRIAXONE SODIUM	1	(2.1)	0		1	(1.0)	
CHLORPHENAMINE/PHENYLPROPANOLAMINE	1	(2.1)	0		1	(1.0)	
CLEMASTINE FUMARATE	1	(2.1)	0		1	(1.0)	
CODEINE/CAFFEINE/PARACETAMOL/PIPERYLONE	0		1	(2.1)	1	(1.0)	
CODEINE/GUAIFENESIN/PSEUDOEPHEDRINE	0		1	(2.1)	1	(1.0)	
CODEINE/PARACETAMOL	0		1	(2.1)	1	(1.0)	

RMP.B1YP.JCLLIB2(DTS1EM08)
RMP.B1YO.X065REP(DTS1EM08)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.4. Concomitant Medications
All Randomized Patients
B1Y-MC-X065 (continued)

Drug Name	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
COUGH DROPS	0		1	(2.1)	1	(1.0)	
CROMOGLICATE SODIUM	0		1	(2.1)	1	(1.0)	
DEM45 VIS70	1	(2.1)	0		1	(1.0)	
DESMOPRESSIN	0		1	(2.1)	1	(1.0)	
DIPHENHYDRAMINE	1	(2.1)	0		1	(1.0)	
DIPHENHYDRAMINE/AMMONIUM	1	(2.1)	0		1	(1.0)	
DIPHENHYDRAMINE/PARACETAMOL	0		1	(2.1)	1	(1.0)	
EARDROPS	0		1	(2.1)	1	(1.0)	
ERGOCALCIFEROL/ASCORBIC ACID/FOLIC ACID/	0		1	(2.1)	1	(1.0)	
ERYTHROMYCIN	1	(2.1)	0		1	(1.0)	
ETHINYLESTRADIOL/LEVONORGESTREL	1	(2.1)	0		1	(1.0)	
HYDROCORTISONE/NEOMYCIN/POLYMYXIN B SULF	1	(2.1)	0		1	(1.0)	
IODINATED GLYCEROL	1	(2.1)	0		1	(1.0)	
KAOLIN/PECTIN	0		1	(2.1)	1	(1.0)	
LORACARBEF	1	(2.1)	0		1	(1.0)	
MENTHOL/EUCALYPTUS	0		1	(2.1)	1	(1.0)	

RMP.B1YP.JCLLIB2(DTS1EM08)
RMP.B1YO.X065REP(DTS1EM08)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.4. Concomitant Medications
All Randomized Patients
B1Y-MC-X065 (continued)

Drug Name	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
MEPYRAMINE/PARACETAMOL/PAMABROM	1	(2.1)	0		1	(1.0)	
METRONIDAZOLE	1	(2.1)	0		1	(1.0)	
NAPROXEN SODIUM	1	(2.1)	0		1	(1.0)	
NASAL SPRAY (NOS)	1	(2.1)	0		1	(1.0)	
NITROFURANTOIN	0		1	(2.1)	1	(1.0)	
NORETHISTERONE/MESTRANOL	0		1	(2.1)	1	(1.0)	
PARACETAMOL/HYDROCODONE	0		1	(2.1)	1	(1.0)	
PARACETAMOL/PHENYLPROPANOLAMINE/PHENYLTO	1	(2.1)	0		1	(1.0)	
PHENOXYMETHYLPENICILLIN POTASSIUM	0		1	(2.1)	1	(1.0)	
PHENYLTOLOXAMINE CITRATE	1	(2.1)	0		1	(1.0)	
PHOSPHORIC ACID/INVERT SUGAR	1	(2.1)	0		1	(1.0)	
PROGESTERONE	0		1	(2.1)	1	(1.0)	
PROPRANOLOL HYDROCHLORIDE	1	(2.1)	0		1	(1.0)	
RIMANTADINE HYDROCHLORIDE	1	(2.1)	0		1	(1.0)	
SORBITOL/AMINOACETIC ACID/PHENYLMERCURIC	0		1	(2.1)	1	(1.0)	
SULFAMETHOXAZOLE/TRIMETHOPRIM	0		1	(2.1)	1	(1.0)	

RMP.B1YP.JCLLIB2(DTS1EM08)
RMP.B1YO.X065REP(DTS1EM08)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

Table 11.4. Concomitant Medications
All Randomized Patients
B1Y-MC-X065 (concluded)

Drug Name	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
TETRACYCLINE	1	(2.1)	0		1	(1.0)	
TETRACYCLINE HYDROCHLORIDE	0		1	(2.1)	1	(1.0)	
THEOPHYLLINE	0		1	(2.1)	1	(1.0)	
TRIAMCINOLONE ACETONIDE	1	(2.1)	0		1	(1.0)	

RMP.B1YP.JCLLIB2(DTS1EM08)
RMP.B1YO.X065REP(DTS1EM08)
* Frequencies are analyzed using a Fisher's Exact test.
XDTS0001

11.3. Measurements of Treatment Compliance

Table 11.5 presents a summary of study drug compliance by visit. Compliance with the study drug regimen was assessed by direct questioning and by counting returned study drug. Because the protocol did not specify parameters of treatment noncompliance, Lilly retrospectively defined noncompliance. A patient was defined as noncompliant if he/she failed to take study drug on more than 2 days within a visit interval. If the patient received alternate day therapy, noncompliance was defined as failing to take study drug on more than 1 day within a visit interval.

The study site recorded information concerning study medication for the purpose of drug accountability rather than compliance with the treatment regimen, as detailed in Section 9.4.8. As a result, compliance information was not available for 31 randomized patients (14 fluoxetine-treated, 17 placebo-treated).

As shown in Table 11.5, the percentage of patients with "unspecified" compliance ranged from 29% at Visit 4 to 90% at Visit 10. Of the patients who had recorded compliance information, the majority of patients were compliant with the study drug regimen. The treatment groups were comparable with respect to their study drug compliance.

A complete listing of patient compliance with the study drug regimen by visit is presented in Appendix 16.2.6.

Table 11.5. Patient Compliance by Visit
All Randomized Patients
B1Y-MC-X065

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)
Compliance (Visit: 3)			
No. Patients	48	48	96
Yes	28 (58.3)	28 (58.3)	56 (58.3)
No	1 (2.1)	0	1 (1.0)
Unspecified	19 (39.6)	20 (41.7)	39 (40.6)
Compliance (Visit: 4)			
No. Patients	48	46	94
Yes	35 (72.9)	29 (63.0)	64 (68.1)
No	1 (2.1)	2 (4.3)	3 (3.2)
Unspecified	12 (25.0)	15 (32.6)	27 (28.7)
Compliance (Visit: 5)			
No. Patients	48	43	91
Yes	28 (58.3)	27 (62.8)	55 (60.4)
No	5 (10.4)	4 (9.3)	9 (9.9)
Unspecified	15 (31.3)	12 (27.9)	27 (29.7)
Compliance (Visit: 6)			
No. Patients	46	41	87
Yes	22 (47.8)	25 (61.0)	47 (54.0)
No	4 (8.7)	2 (4.9)	6 (6.9)
Unspecified	20 (43.5)	14 (34.1)	34 (39.1)
Compliance (Visit: 7)			
No. Patients	42	36	78
Yes	18 (42.9)	20 (55.6)	38 (48.7)
No	4 (9.5)	0	4 (5.1)
Unspecified	20 (47.6)	16 (44.4)	36 (46.2)
Compliance (Visit: 8)			
No. Patients	38	31	69
Yes	17 (44.7)	17 (54.8)	34 (49.3)
No	4 (10.5)	1 (3.2)	5 (7.2)
Unspecified	17 (44.7)	13 (41.9)	30 (43.5)

RMP.B1YP.JCLLIB2(DES1EM04)
RMP.B1YO.X065REP(DES1EM04)
XDES0001

Table 11.5. Patient Compliance by Visit
All Randomized Patients
B1Y-MC-X065 (concluded)

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)
Compliance (Visit: 9)			
No. Patients	35	26	61
Yes	16 (45.7)	14 (53.8)	30 (49.2)
No	2 (5.7)	1 (3.8)	3 (4.9)
Unspecified	17 (48.6)	11 (42.3)	28 (45.9)
Compliance (Visit: 10)			
No. Patients	34	25	59
Yes	2 (5.9)	3 (12.0)	5 (8.5)
No	0	1 (4.0)	1 (1.7)
Unspecified	32 (94.1)	21 (84.0)	53 (89.8)

RMP.B1YP.JCLLIB2(DES1EM04)
RMP.B1YO.X065REP(DES1EM04)
XDES0001

11.4. Efficacy Results and Tabulations of Individual Patient Data

11.4.1. Analysis of Efficacy

A total of 96 patients were randomized to fluoxetine 20 mg/day (n=48) or placebo (n=48). Efficacy evaluations were based on CDRS-R total, subtotal, and individual item scores; CGI-Improvement and CGI-Severity scores; BPRS-C total and individual item scores; BDI total scores; and CDI total scores. Assessments were based on the last available measure (the endpoint). For the CDRS-R total, analyses were also performed by visit using an observed case approach and an LOCF approach.

The primary efficacy measure was the CDRS-R total response, defined as a 30% reduction from baseline. CDRS-R total scores were also evaluated using by-visit analyses of the change from baseline to each postbaseline visit. Secondary categorical analyses were performed for CDRS-R total scores using criteria for response at a level of 50% reduction from baseline, remission (based on CDRS-R total score), response (based on CGI-Improvement scores), and recovery (based on CDRS-R total and CGI-Improvement scores).

Secondary continuous analyses included evaluation of the change from baseline to endpoint for the following variables: CDRS-R total, subtotal, and individual item scores; CGI-Severity scores; BPRS-C total and individual item scores; BDI total scores; and CDI total scores. An endpoint analysis was performed for CGI-Improvement scores.

11.4.1.1. Baseline Variability

Treatment-group comparisons were performed for the primary scale (CDRS-R) and for the secondary scales CGI-Severity and BPRS-C at baseline (Table 11.6). The baseline measures for these analyses were the last available measure of Visits 1 and 2.

A CDRS-R total score >40 is considered diagnostic of MDD in children and adolescents (Poznaski et al. 1984). The mean CDRS-R total score at baseline was 58.9 for fluoxetine-treated patients and 57.5 for placebo-treated patients (p=.529).

For all three scales, the two treatment groups were comparable with respect to their baseline severity of depression.

Table 11.6. Baseline Psychiatric Evaluation
All Randomized Patients
B1Y-MC-X065

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
CDRS-R Total				
No. Patients	48	48	96	.529**
Mean	58.9	57.5	58.2	
Median	58.0	54.5	57.0	
Standard Dev.	10.4	10.3	10.3	
Minimum	42.0	42.0	42.0	
Maximum	88.0	82.0	88.0	
CGI-Severity				
No. Patients	48	48	96	.375**
Mean	5.1	4.9	5.0	
Median	5.0	5.0	5.0	
Standard Dev.	0.8	0.8	0.8	
Minimum	4.0	3.0	3.0	
Maximum	7.0	6.0	7.0	
BPRS-C Total				
No. Patients	47	48	95	.368**
Mean	26.3	24.8	25.6	
Median	25.0	24.5	25.0	
Standard Dev.	7.9	8.5	8.2	
Minimum	13.0	3.0	3.0	
Maximum	44.0	48.0	48.0	

RMP.B1YP.JCLLIB2(DES1EM01)
RMP.B1YO.X065REP(DES1EM01)
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

11.4.1.2. Primary Efficacy Analysis: CDRS-R Response Rates

Table 11.7 presents response rates based on the CDRS-R total score. The primary efficacy analysis was the comparison of the proportion of patients responding between treatment groups. A patient was considered to be a responder if his/her CDRS-R total score decreased by at least 30% from baseline to endpoint.

The fluoxetine treatment group demonstrated a statistically significantly higher response rate compared with the placebo treatment group (fluoxetine 58%, placebo 32%, p=.013, Fisher's exact). The response rate of the fluoxetine treatment group was almost twice that of the placebo treatment group.

In addition, CDRS-R response was analyzed using a criterion of at least a 50% reduction from baseline and is presented in Table 14.1 (see Section 14.2.1). The 50% criteria response rate showed the same trend as the 30% response rate, with the fluoxetine treatment group showing rates 1.4 times that of the placebo treatment group (fluoxetine

27%, placebo 19%, p=.467, Fisher's exact). The treatment groups were not statistically different from each other.

In an effort to determine how soon a pediatric population may respond to antidepressant therapy, analyses were performed for patients who had been treated for at least 4 weeks. The CDRS-R response using a 30% criterion was compared between treatment groups when only those patients treated at least 4 weeks were included, as shown in Table 14.2 (see Section 14.2.1). The results were similar to the primary efficacy analysis with the fluoxetine treatment group demonstrating a statistically significantly higher response rate compared with the placebo treatment group (fluoxetine 59%, placebo 34%, p=.031, Fisher's exact).

Table 11.7. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065
Outcome Variable: RESPONSE - 30% REDUCTION FROM BASELINE

			NO		YES	
	Therapy	N	n	%	n	%
A.	Flx 20mg	48	20	41.7	28	58.3
B.	Placebo	47	32	68.1	15	31.9

COMPARISON OF TREATMENT GROUPS

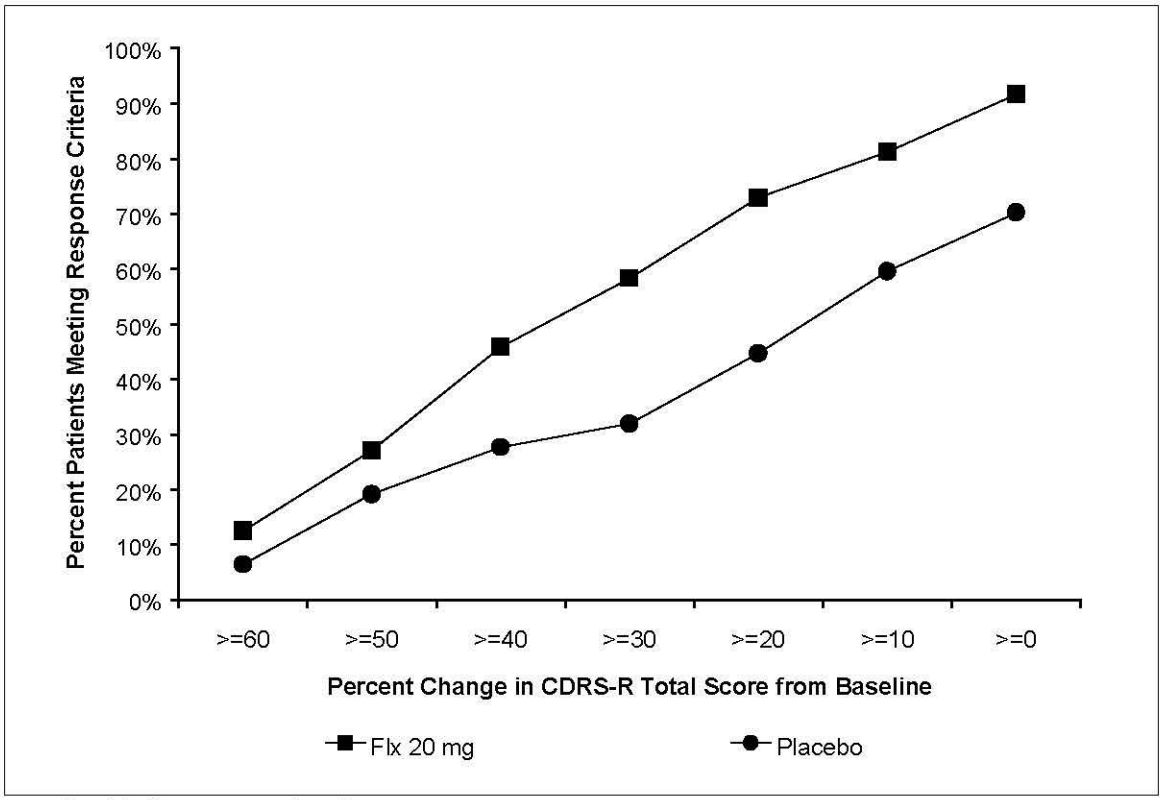
STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.013
Pearson's chi-square test df=1	6.7	<0.01
Cochran-Mantel-Haenszel general association test df=1	6.6	0.010

RMP.B1YP.JCLLIB2(EFS1EM01)
RMP.B1YO.X065REP(EFS1EM01)
XEFS0001

Figure 11.1 presents the percentage of patients by treatment group meeting different percent change from baseline reduction criteria. If the response criteria were something other than 30% or 50%, the same trend is shown for fluoxetine-treated patients as compared with placebo-treated patients. The fluoxetine treatment group had a consistently greater response rate than the placebo treatment group, regardless of the percent change criteria. The percent change from baseline criteria at which the differences between the fluoxetine and placebo treatment groups are the greatest occur at the 20% and 30%.

This graph only displays patients whose change from baseline reduction was ≥0. Four fluoxetine-treated patients and 14 placebo-treated patients were not included because their CDRS-R total scores increased from baseline.

A complete data listing of CDRS-R total scores by patient is presented in Appendix 16.2.7.



Data for this figure were taken from PERCHGD.SAS.

Figure 11.1. CDRS-R Total Score Percent Change Distribution, All Randomized Patients, B1Y-MC-X065.

11.4.1.3. Secondary Efficacy Analyses

11.4.1.3.1. Mean Change in CDRS-R Scores from Baseline to Endpoint

Table 11.8 presents a summary of the change from baseline to endpoint for CDRS-R total and subtotal scores. The treatment effect was statistically significant for the CDRS-R total score, with fluoxetine-treated patients experiencing greater reductions than placebo-treated patients (fluoxetine -20, placebo -11; p=.002).

The CDRS-R subtotal scores presented in Table 11.8 exhibit a similar pattern of statistical significance with the exception of the CDRS-R subjective subtotal score. There were statistically significantly greater reductions in mood, somatic, and behavior subtotal scores in fluoxetine-treated patients as compared with placebo-treated patients.

In addition, the 17 individual items of the CDRS-R were analyzed for change from baseline and are summarized in Table 14.3 (see Section 14.2.1). The majority of the items demonstrated statistically significant changes from baseline, with fluoxetine-treated patients experiencing greater improvement than placebo-treated patients. These items included increased ability to have fun (2), less social withdrawal (3), less excessive fatigue (6), fewer physical complaints (7), higher self-esteem (10), less depressed feelings

(11), fewer morbid thoughts (12), less weeping (14), more normal tempo of speech (16), and reduced hypoactivity (17). The remaining items showed no statistically significant differences between treatment groups. Improvement in all of these items indicates that fluoxetine-treated patients were returning to normal functioning at greater rates than placebo-treated patients.

By-patient data listings of CDRS-R total and subtotal scores and individual items are located in Appendix 16.2.7.

Table 11.8. CDRS-R Scores
Change from Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065

			Baseline		Endpoint		Change		
Variable	Therapy	n	Mean	SD	Mean	SD	Mean	SD	p-Value *1
TOTAL	Flx 20mg	48	58.9	10.4	38.7	14.6	-20.2	13.5	.002
	Placebo	47	57.5	10.4	47.0	16.9	-10.5	15.9	
MOOD SUBTOTAL	Flx 20mg	48	15.1	3.5	9.3	3.6	-5.8	4.1	<.001
	Placebo	47	14.6	3.1	12.0	4.7	-2.6	4.9	
SOMATIC SUBTOTAL	Flx 20mg	48	20.3	3.9	13.7	6.0	-6.6	5.4	.001
	Placebo	47	18.7	3.8	15.7	5.2	-2.9	5.3	
SUBJECTIVE SUBTOTAL	Flx 20mg	48	11.3	2.8	7.8	3.1	-3.5	3.2	.147
	Placebo	47	11.6	3.6	9.2	3.9	-2.4	4.3	
BEHAVIOR SUBTOTAL	Flx 20mg	48	12.2	2.8	7.9	3.7	-4.3	3.7	.028
	Placebo	47	12.6	2.9	10.1	4.4	-2.6	3.9	

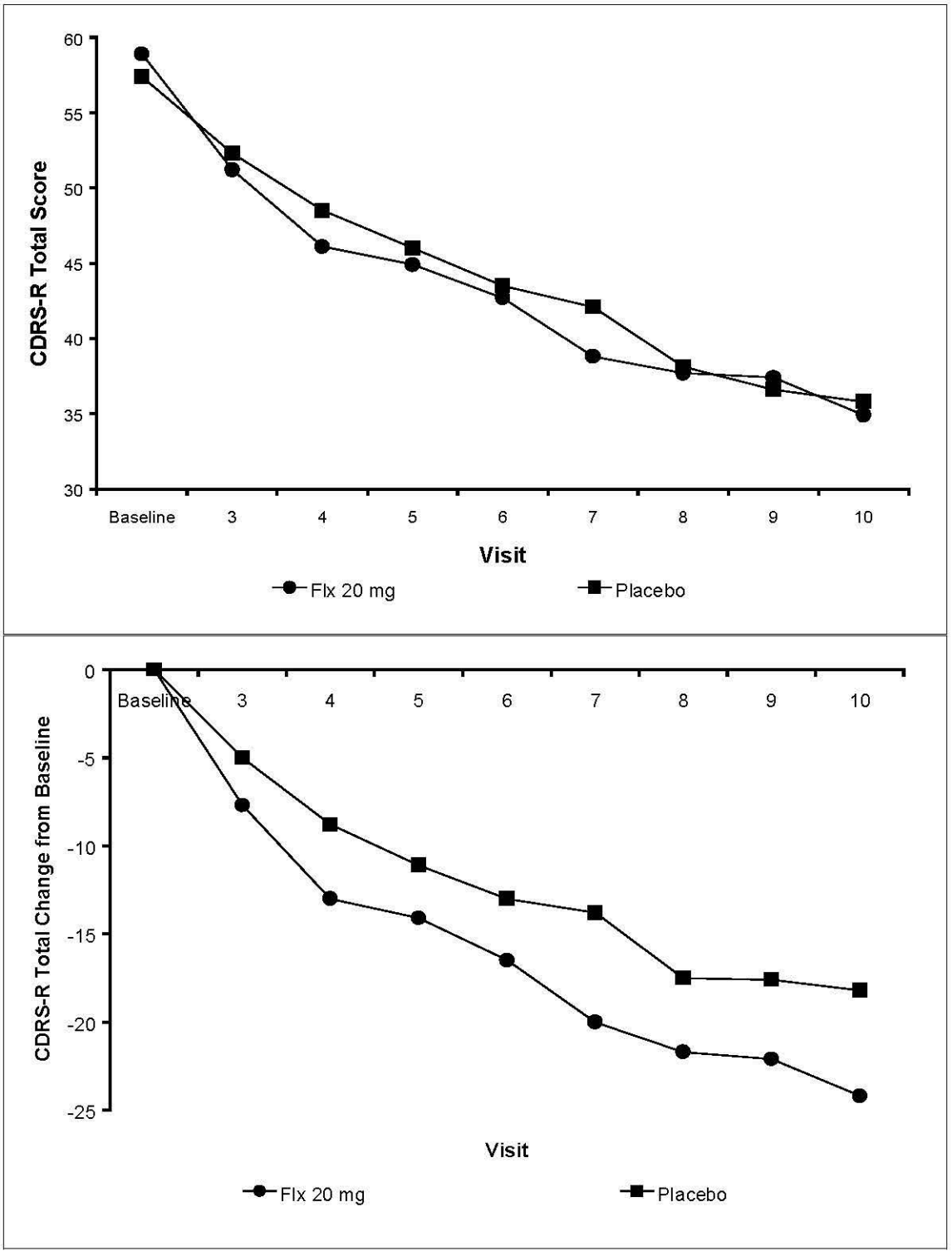
*1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3EM13)
RMP.B1YO.X065REP(PRCNEM13)

11.4.1.3.2. Longitudinal Analyses of CDRS-R Total Scores

11.4.1.3.2.1. By Visit Analysis: Observed Cases and LOCF

Figure 11.2 presents the mean score and change from baseline for the CDRS-R total score for both treatment groups by visit (observed cases). Tables 11.9 and 11.10 display the CDRS-R total change from baseline to each visit for observed cases and LOCF, respectively.

For the observed cases, as shown in Figure 11.2 and Table 11.9, there was an increasingly greater difference between the change from baseline measures for each treatment group over time with fluoxetine-treated patients consistently showing a greater reduction from baseline as compared with placebo-treated patients. The only statistically significant difference between the treatment groups occurred at Visit 7 (Week 5) with fluoxetine-treated patients showing greater improvement than placebo-treated patients (fluoxetine -20, placebo -14; p=.039). As can be seen in this analysis, a greater number of placebo-treated patients discontinued from the study over time as compared with fluoxetine-treated patients, especially after Visit 7. At the last visit of the study, only 34 fluoxetine-treated patients and 25 placebo-treated patients remained.



Data for these figures were taken from RMP.B1YO.X065REP (PRCNEM15).

Figure 11.2. CDRS-R Total Score versus Visit by Treatment Group for all Observed Cases, All Randomized Patients, B1Y-MC-X065.

Table 11.9. CDRS-R Total Score
Change from Baseline to Each Visit (Observed Cases)
All Randomized Patients
B1Y-MC-X065

Visit	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
3	Flx 20mg	48	58.9	10.4	51.2	11.6	-7.7	10.5	.197
	Placebo	46	57.4	10.5	52.3	10.7	-5.0	9.1	
4	Flx 20mg	47	59.1	10.4	46.1	13.2	-13.0	11.9	.078
	Placebo	45	57.2	10.3	48.5	11.1	-8.8	10.9	
5	Flx 20mg	46	59.1	10.5	44.9	12.5	-14.1	11.5	.203
	Placebo	43	57.1	10.4	46.0	12.9	-11.1	10.8	
6	Flx 20mg	42	59.2	10.7	42.7	12.5	-16.5	11.7	.179
	Placebo	39	56.5	10.2	43.5	12.8	-13.0	11.3	
7	Flx 20mg	39	58.8	9.6	38.8	12.8	-20.0	11.0	.039
	Placebo	36	55.9	9.3	42.1	15.1	-13.8	14.3	
8	Flx 20mg	38	59.4	10.3	37.7	14.2	-21.7	14.0	.207
	Placebo	31	55.7	8.6	38.1	12.9	-17.5	13.1	
9	Flx 20mg	34	59.5	10.2	37.4	13.6	-22.1	14.1	.232
	Placebo	25	54.2	7.9	36.6	13.0	-17.6	14.6	
10	Flx 20mg	34	59.1	10.2	34.9	12.0	-24.2	12.4	.106
	Placebo	25	54.0	8.0	35.8	13.5	-18.2	15.6	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3EM15)
RMP.B1YO.X065REP(PRCNEM15)

In contrast to the observed case analysis, the LOCF analysis (Table 11.10), in which all patients' last available measure was carried forward for analysis at each visit, indicates that fluoxetine-treated patients had a statistically significantly greater improvement than placebo-treated patients at the majority of visits. At Visit 5 (Week 3) and throughout the remainder of the study, fluoxetine-treated patients had statistically significantly greater reductions in their CDRS-R total change from baseline than placebo-treated patients. By Visit 10, fluoxetine-treated patients had an LOCF CDRS-R total change from baseline score 10 points lower than placebo-treated patients.

Table 11.10. CDRS-R Total Score
Change from Baseline to Each Visit (LOCF)
All Randomized Patients
B1Y-MC-X065

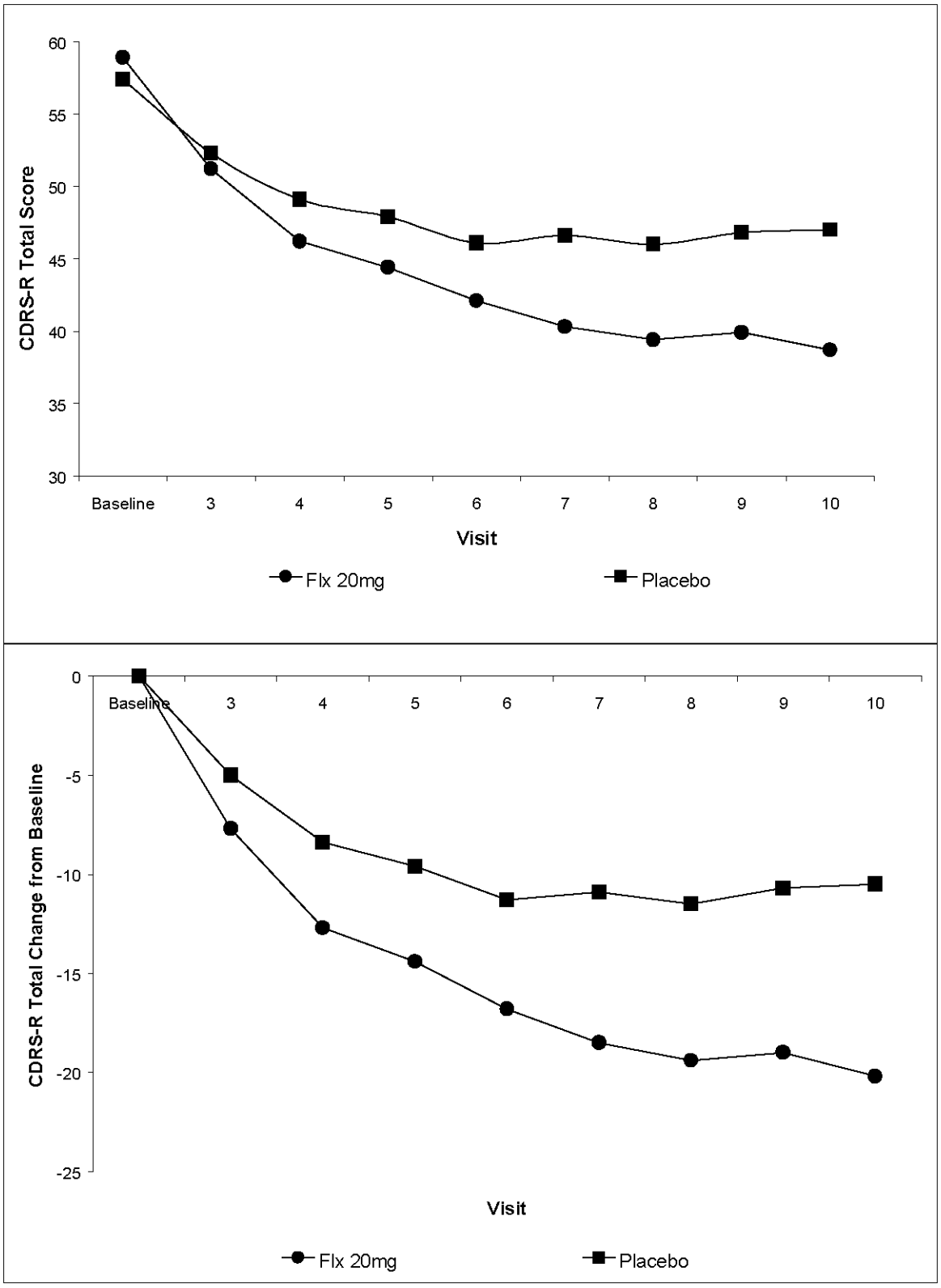
Visit	Therapy	n	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Change Mean	Change SD	Overall p-Value *1
3	Flx 20mg	48	58.9	10.4	51.2	11.6	-7.7	10.5	.197
	Placebo	46	57.4	10.5	52.3	10.7	-5.0	9.1	
4	Flx 20mg	48	58.9	10.4	46.2	13.0	-12.7	12.0	.074
	Placebo	47	57.5	10.4	49.1	11.7	-8.4	10.8	
5	Flx 20mg	48	58.9	10.4	44.4	12.6	-14.4	11.4	.046
	Placebo	47	57.5	10.4	47.9	13.9	-9.6	11.7	
6	Flx 20mg	48	58.9	10.4	42.1	12.4	-16.8	11.5	.028
	Placebo	47	57.5	10.4	46.1	14.9	-11.3	12.2	
7	Flx 20mg	48	58.9	10.4	40.3	13.1	-18.5	11.9	.006
	Placebo	47	57.5	10.4	46.6	16.7	-10.9	14.4	
8	Flx 20mg	48	58.9	10.4	39.4	14.5	-19.4	14.0	.009
	Placebo	47	57.5	10.4	46.0	16.4	-11.5	15.1	
9	Flx 20mg	48	58.9	10.4	39.9	15.4	-19.0	14.4	.008
	Placebo	47	57.5	10.4	46.8	16.6	-10.7	15.2	
10	Flx 20mg	48	58.9	10.4	38.7	14.6	-20.2	13.5	.002
	Placebo	47	57.5	10.4	47.0	16.9	-10.5	15.9	

* 1 Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
RMP.B1YP.JCLLIB2(LAS3EM16)
RMP.B1YO.X065REP(PRCNEM16)

The difference in statistical significance and magnitude of the by-visit observed analysis results as compared with the by-visit LOCF analysis results was examined further. The observed case analysis indicated a trend towards continuing efficacy whereas the LOCF analysis showed statistical significance of efficacy from Visit 5 until the end of the study.

Figure 11.3 presents a line plot of the CDRS-R total by visit by treatment group for the LOCF analysis. As compared to Figure 11.2, the line plot of the observed cases, this plot generally shows a greater difference in the treatment groups for both the means as well as the change from baselines. The main difference in the graphs is with the placebo treatment group. In the observed cases graph (Figure 11.2), the placebo scores declined throughout the study. In the LOCF graph (Figure 11.3), the placebo scores declined at first and then leveled off.

Table 11.11 presents the change from baseline results at Visit 10 for the observed cases and LOCF analyses. The LOCF analysis indicates that fluoxetine treatment is statistically superior to placebo treatment (p=.002). The observed-case p-value indicates a trend towards continuing efficacy (p=.106) for fluoxetine treatment over placebo treatment. This difference is partially explained by the smaller sample size available at Visit 10 (completers only) in addition to the decreased mean observed for the placebo treatment group at Visit 10. Only 25 of the 48 patients in the placebo treatment group remained in the study at Visit 10 (most dropped out due to lack of efficacy), leaving only those patients who believed that study medication (placebo in this case) improved their symptoms, ie, the only remaining patients could be considered placebo responders. In support, when analyzing the endpoint LOCF score, the mean change of the placebo treatment group was -10.5 compared with an observed-case mean change score of -18.2. The mean changes for the fluoxetine treatment group only differed by a score of 4 (-24.2 for observed cases versus -20.2 for LOCF).



Data were taken from RMP.B1YO.X065REP (PRCNEM16).

Figure 11.3. CDRS-R Total Score versus Visit by Treatment Group (LOCF), All Randomized Patients, B1Y-MC-X065.

Table 11.11. CDRS-R Total Score
Mean Change From Baseline to Visit 10
All Randomized Patients
B1Y-MC-X065

Treatment Group	Observed			LOCF		
	n	Mean	p-Value	n	Mean	p-Value
Fluoxetine 20 mg	34	-24.2	0.106	48	-20.2	0.002
Placebo	25	-18.2		47	-10.5	

Data were taken from RMP.B1YO.X065REP (PRCNEM15) and RMP.B1YO.X065REP (PRCNEM16).

11.4.1.3.2.2. Repeated Measures Analysis

Figure 11.2 displays a line plot of the CDRS-R total score by visit (observed cases) and treatment group. Tables 11.12 and 11.13 present the results of the repeated measures analysis.

A repeated measures analysis was conducted to assess the temporal change in the CDRS-R total score. The CDRS-R total scores at baseline and each postbaseline visit were used as the response variable. The model used an unstructured covariance matrix with visit as the within-patient factor, treatment as the between-patient factor, and the treatment-by-visit interaction. The treatment effect assessed overall shifts due to treatment in the CDRS-R total score across visits. The treatment-by-visit interaction assessed parallelism in the CDRS-R total score across visits among the treatment groups.

Table 11.12 presents the statistical significance of the parameters in the model. The repeated measures ANOVA of the CDRS-R total score did not detect a statistically significant interaction between treatment group and time (p=.220). This indicates that the two treatment groups followed the same time course, ie, that the plots of the means across time were approximately parallel (see Figure 11.2). Upon further investigation, it was found that there was a significant time effect (p<.001), but there was not a significant treatment effect (p=.135). Evaluation of the individual time periods (see Table 11.13) indicates that there was a statistically significant within-treatment decrease in CDRS-R total score change from baseline to all subsequent visits for both treatment groups. Although the overall treatment effect was not significant, a contrast of the change from baseline to Visit 10 between treatment groups using repeated measures analysis confirmed the CDRS-R total change from baseline to endpoint analysis (p=.011, see Table 11.12).

Table 11.13 displays the least-squares change from baseline means for each treatment group at each postbaseline visit. The least-squares mean at each postbaseline visit incorporates information from all patients and estimates the average CDRS-R total score using the assumption that all patients had completed the study. The magnitude of these results is more consistent with the LOCF analysis as compared with the observed analysis in the by-visit analyses in the previous section.

Table 11.12. CDRS-R Total Score
Repeated Measures Model Parameters
All Randomized Patients
B1Y-MC-X065

Parameter	ndf	ddf	F-Test Value	p-Value
Treatment	1	83.1	2.28	0.135
Visit	8	73.9	22.5	<0.001
Treatment-by-Visit	8	73.9	1.38	0.220
Contrast between Treatment, Change from Baseline to Visit 10	1	64.6	6.86	0.011

Data were taken from RMP.B1YSEMS1.SASPGM (CDRSREP.SAS).
Abbreviations: ddf = denominator degrees of freedom; ndf = numerator degrees of freedom.

Table 11.13. CDRS-R Total Score
Repeated Measures Least-Squares Means
All Randomized Patients
B1Y-MC-X065

	Fluoxetine 20 mg		Placebo	
Visit	LS Mean	p-Value[1]	LS Mean	p-Value[1]
1 and 2	58.9		57.5	
3	-7.7	<0.001	-5.1	0.001
4	-12.8	<0.001	-8.6	<0.001
5	-14.3	<0.001	-10.4	<0.001
6	-16.5	<0.001	-12.8	<0.001
7	-19.4	<0.001	-12.2	<0.001
8	-20.2	<0.001	-14.2	<0.001
9	-20.1	<0.001	-13.6	<0.001
10	-21.3	<0.001	-12.3	<0.001

Data were taken from RMP.B1YSEMS1.SASPGM (CDRSREP.SAS).
[1]Within treatment change from baseline.
Abbreviation: LS = least-squares.

11.4.1.3.3. CDRS-R Total Remission Rates

As described in Section 9.7.1, a remitter was defined as a patient who had an endpoint CDRS-R total score ≤28. The number of patients meeting criteria for remission are presented in Table 11.14.

The fluoxetine treatment group had a higher frequency of patients demonstrating remission than the placebo treatment group, but the two treatment groups did not differ statistically significantly in their remission rates (fluoxetine 31%, placebo 19%; p=.238, Fisher's exact).

The CDRS-R remission criteria was also compared between treatment groups when only those patients treated at least 4 weeks were included, as shown in Table 14.4 (see Section 14.2.1). The results were similar to the original remission analysis with no statistically significant differences between treatment groups (fluoxetine 30%, placebo 22%; p=.467, Fisher's exact).

Table 11.14. CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065
Outcome Variable: REMISSION - SCORE <=28

			NO		YES	
	Therapy	N	n	%	n	%
A.	Flx 20mg	48	33	68.8	15	31.3
B.	Placebo	47	38	80.9	9	19.1

COMPARISON OF TEATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.238
Pearson's chi-square test df=1	1.8	0.175
Cochran-Mantel-Haenszel general association test df=1	1.8	0.177

RMP.B1YP.JCLLIB2(EFS1EM02)
RMP.B1YO.X065REP(EFS1EM02)
XEFS0001

11.4.1.3.4. CGI-Improvement Endpoint Analysis

For analysis of CGI-Improvement, an ANOVA was performed on the endpoint values. The endpoint measures total improvement in direct comparison to the patient's condition at baseline. These results are shown in Table 11.15.

The analysis showed statistical significance for treatment, with fluoxetine-treated patients experiencing greater improvement than placebo-treated patients (fluoxetine mean = 2.5, placebo mean = 3.2; p=.015, Fisher's exact). A CGI-Improvement score of 2 corresponded to a rating of much improved and a score of 3 corresponded to a rating of minimally improved.

Complete data listings for CGI-Improvement scores by patient are located in Appendix 16.2.7.

Table 11.15. CGI-Improvement Scores
Endpoint Analysis
All Randomized Patients
B1Y-MC-X065

Variable	Flx 20mg (N=48)	Placebo (N=48)	Total (N=96)	p-Value
CGI-Improvement				
No. Patients	48	47	95	.015**
Mean	2.5	3.2	2.9	
Median	2.0	3.0	3.0	
Standard Dev.	1.3	1.5	1.4	
Minimum	1.0	1.0	1.0	
Maximum	5.0	6.0	6.0	

RMP.B1YP.JCLLIB2(DES1EM02)
RMP.B1YO.X065REP(DES1EM02)
** Means are analyzed using a Type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.
XDES0001

11.4.1.3.5. CGI-Improvement Response Rates

A patient was defined as a CGI-Improvement responder if his/her last available treatment CGI-Improvement score was 1 (very much improved) or 2 (much improved), as defined in Section 9.7.1. Table 11.16 presents response rates based on the CGI-Improvement score.

Fluoxetine-treated patients demonstrated a statistically significantly higher response rates as compared with placebo-treated patients (fluoxetine 56%, placebo 34%; p=.040).

The CGI-Improvement response analysis results are similar to the primary efficacy analysis results for CDRS-R total response.

Table 11.16. CGI-Improvement Score
Number of Patients Meeting Criteria for Response
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065
Outcome Variable: RESPONSE - SCORE = 1 OR 2

			NO		YES	
	Therapy	N	n	%	n	%
A.	Flx 20mg	48	21	43.8	27	56.3
B.	Placebo	47	31	66.0	16	34.0

COMPARISON OF TREATMENT GROUPS

STATISTICS	P-VALUE
Fisher's exact test (2-tailed)	0.040
Pearson's chi-square test df=1	0.030
Cochran-Mantel-Haenszel general association test df=1	0.031

RMP.B1YP.JCLLIB2(EFS1EM03)
RMP.B1YO.X065REP(EFS1EM03)
XEFS0001

11.4.1.3.6. CDRS-R Total/CGI-Improvement Recovery Rates

Table 11.17 presents the proportion of patients meeting criteria for recovery for each treatment group. Patients with a CDRS-R total endpoint score ≤28 and a CGI-Improvement endpoint score of 1 or 2 were defined as recovered (see Section 9.7.1).

The recovery rate for fluoxetine-treated patients was approximately 1.5 times higher than the recovery rate for placebo-treated patients. The two treatment groups did not differ significantly from each other in recovery rates.

**Table 11.17. CDRS-R Total and CGI-Improvement Scores
Number of Patients Meeting Criteria for Recovery
All Randomized Patients
B1Y-MC-X065**

Protocol: B1Y-MC-X065
Outcome Variable: RECOVERY - CDRS-R <=28 AND CGI-IMPROVEMENT = 1 OR 2

			NO		YES	
	Therapy	N	n	%	n	%
A.	Flx 20mg	48	34	70.8	14	29.2
B.	Placebo	47	38	80.9	9	19.1

COMPARISON OF TREATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.339
Pearson's chi-square test df=1	1.3	0.254
Cochran-Mantel-Haenszel general association test df=1	1.3	0.257

RMP.B1YP.JCLLIB2(EFS1EM04)
RMP.B1YO.X065REP(EFS1EM04)
XEFS0001

11.4.1.3.7. Mean Change in Secondary Efficacy Variable Scores from Baseline to Endpoint

The mean change from baseline scores for secondary efficacy variables were compared between treatment groups. Results for CGI-Severity, BPRS-C total, BDI total, and CDI total scores are presented in Table 11.18. The sample sizes for the BDI and CDI are small because the BDI was only administered to adolescents (ages 13 to ≤18) and the CDI was only administered to children (ages 8 to <13).

CGI-Severity scores were statistically significantly different between the treatment groups. Fluoxetine-treated patients experienced greater reductions in the severity of their illness than placebo-treated patients (fluoxetine –2.0, placebo –1.0; p=.003).

BPRS-C total, BDI total, and CDI total scores exhibited the same trend as CGI-Severity scores with fluoxetine-treated patients experiencing greater numerical reductions in the change from baseline than placebo-treated patients. There were no statistically significant differences between the treatment groups.

In addition, analysis of the BPRS-C individual items (see Table 14.5, Section 14.2.2) indicated that fluoxetine-treated patients experienced statistically significant improvement for several of the 21 items. Fluoxetine-treated patients experienced greater improvement than placebo-treated patients for the items depressive mood (4), feelings of inferiority (5), hyperactivity (10), underproductive speech (13), and emotional

withdrawal (14). For hyperactivity, the score for fluoxetine-treated patients actually increased while the score for placebo-treated patients decreased. This is interpreted as a decrease of hypoactivity for fluoxetine-treated patients and an increased lack of activity for placebo-treated patients. The remaining items showed no significant treatment effect. Improvement in several items, including hyperactivity, indicate that fluoxetine-treated patients were displaying increased levels of activity, which is associated with the patients returning to normal functioning at greater rates than placebo-treated patients.

By-patient data listings for CGI-Severity, BPRS-C total, CDI total, and BDI total scores and individual items are located in Appendix 16.2.7.

Table 11.18. Secondary Efficacy Variable Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065

			Baseline		Endpoint		Change		
Variable	Therapy	n	Mean	SD	Mean	SD	Mean	SD	p-Value *1
CGI Severity	Flx 20mg	48	5.1	0.8	3.1	1.5	-2.0	1.4	.003
	Placebo	47	4.9	0.8	3.9	1.7	-1.1	1.6	
BPRS-C Total	Flx 20mg	47	26.3	7.9	18.0	9.9	-8.4	8.4	.087
	Placebo	47	24.7	8.5	20.0	10.1	-4.7	12.0	
BDI Total	Flx 20mg	23	17.6	12.0	11.7	13.6	-5.9	9.8	.795
	Placebo	19	14.8	8.6	9.6	10.3	-5.2	8.7	
CDI Total	Flx 20mg	23	16.1	10.5	10.3	10.4	-5.8	8.8	.594
	Placebo	20	17.8	13.2	13.4	8.6	-4.4	7.9	

*1 Type III Sums of Squares from analysis of variance (ANOVA): PROC GLM model=treatment
RMP.B1YP.JCLLIB2(LAS3EM23)
RMP.B1YO.X065REP(PRCNEM23)

11.4.2. Statistical/Analytical Issues

Please refer to Section 9.7.1 and Appendix 16.1.6 for further details regarding statistical methodology.

11.4.2.1. Adjustments for Covariates

There were no covariates included in the ANOVA or categorical analyses performed. Treatment was the only independent variable included in the model. Please refer to Section 9.7.1. and Appendix 16.1.6 for further details regarding statistical methodology.

11.4.2.2. Handling of Dropouts or Missing Data

For most of the analyses, the endpoint (the last available measure from the postbaseline visits) was analyzed. One exception was the by-visit observed analysis of the CDRS-R total score, which only included patients active in the study at the visit of interest. A repeated measures analysis of the CDRS-R total score was also performed. For this analysis, the least-squares mean at each postbaseline visit incorporated information from all patients and estimated the average CDRS-R total score using the assumption that all patients had completed the study.

11.4.2.3. Interim Analyses and Data Monitoring

No interim analyses were conducted on data from this study. The last patient completed the study on 28 February 1995. The site database was unblinded to therapy assignment during the Spring of 1995. The data from this study were first presented at the New Clinical Drug Evaluation Unit (NCDEU) Program in May 1995.

11.4.2.4. Multiple Comparisons/Multiplicity

Two treatment groups were analyzed in this study. No adjustments were made to the p-values for multiple comparisons.

11.4.2.5. Use of an "Efficacy Subset" of Patients

All analyses were performed on an intent-to-treat population. Patient 2207 was not included in the primary efficacy analysis because the patient did not have a postbaseline CDRS-R assessment performed.

11.4.2.6. Examination of Subgroups

Subgroup analyses were performed to examine the consistency of treatment effect over the strata of various demographic populations. The subgroups that were candidates for analysis were age (8 to <13 years, 13 to ≤18 years) and gender (male, female).

Table 11.19 summarizes the CDRS-R total response rates with respect to each subgroup along with the Breslow-Day test results for comparing between-strata differences in the response rates between treatment groups. Statistically significant results from the

Breslow-Day test indicate differences between the strata with respect to treatment differences in the response rates. Neither age category nor gender had a statistically significant Breslow-Day p-value for the homogeneity of odds ratio.

Table 11.19. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
Efficacy Subgroup Analysis
All Randomized Patients
B1Y-MC-X065

		Fluoxetine			Placebo				
Subgroup of Interest	Subgroup	N	n	%	N	n	%	Homogeneity of Odds Ratio p-Value[1]	Between Group Comparison Within Subgroup p-Value[2]
Age	8 to <13	24	15	63	23	9	39	.718	.148
	13 to ≤18	24	13	54	24	6	25		.075
Gender	Female	22	12	55	21	6	29	.993	.124
	Male	26	16	62	26	9	35		.095

Data for this table were taken from RMP.B1YO.X065REP (EFS1EM25).
[1]The homogeneity of odds ratio p-value is taken from the Breslow-Day test.
[2]The between group comparison p-value is taken from the Fisher's exact test.
Abbreviations: N = total number of patients included in the subgroup; n = total number of patients meeting criteria for response.

Table 11.20 summarizes the statistical evaluation of both the change from baseline to endpoint for the CDRS-R total score while accounting for subgroup effect and the change from baseline within subgroup strata. Neither age category nor gender had statistically significant treatment-by-subgroup interactions. There was a statistically significantly greater improvement in the CDRS-R total score for fluoxetine-treated patients compared with placebo-treated patients within both subgroups of age and gender. Overall, the treatment effect of fluoxetine was consistent for the two subgroups examined when analyzing the CDRS-R total change from baseline scores.

**Table 11.20. CDRS-R Total Score
Change from Baseline to Endpoint
Efficacy Subgroup Analysis
All Randomized Patients
B1Y-MC-X065**

Subgroup of Interest	Therapy by Subgroup Interaction[1]	Subgroup Term[1]	Subgroup	N	Therapy	Baseline N	Baseline Mean	Baseline SD	Change Mean	Change SD	Therapy p-Value[2]
Age (years)	0.846	0.873	8 to <13	47	Flx 20mg	24	55.7	7.6	-19.6	12.2	0.032
					Placebo	23	54.1	7.4	-10.5	15.8	
			13 to ≤18	48	Flx 20mg	24	62.0	11.8	-20.7	14.8	0.028
					Placebo	24	60.8	11.9	-10.4	16.4	
Gender	0.823	0.672	Female	43	Flx 20mg	22	61.7	11.1	-20.5	12.1	0.040
					Placebo	21	58.2	10.3	-11.6	15.3	
			Male	52	Flx 20mg	26	56.5	9.2	-19.9	14.8	0.022
					Placebo	26	56.9	10.7	-9.6	16.6	

Data for this table were taken from RMP.B1YO.X065REP (CUSEM026).
Type III Sum of Squares used.
[1]PROC GLM model = therapy, subgroup, and therapy by subgroup for interaction and subgroup p-values.
[2]PROC GLM model = therapy for the therapy p-value within subgroups.
Abbreviations: SD = standard deviation.

11.4.3. Additional Analyses

As discussed in Section 9.4.2, study medication for this trial was provided from two sources. Fifty-four patients (25 fluoxetine-treated, 29 placebo-treated) received blinded study medication prepared by the pharmacy at [redacted] at [redacted] (site-prepared). Forty-two patients (23 fluoxetine-treated, 19 placebo-treated) received blinded study medication prepared by Eli Lilly and Company (Lilly-provided). One patient (2207) received blinded Lilly-prepared study medication and did not have a postbaseline CDRS-R score; therefore, this patient was not included in these analyses. Additional subgroup analyses for these two groups were performed for CDRS-R response rates (Table 11.21) and the change from baseline to endpoint for CDRS-R total score (Table 11.22).

As shown in Table 11.21, the Breslow-Day test, which compares between-subgroup differences in the response rates between treatment groups, was not statistically significant (p=.448) for study medication type. When patients received site-prepared study medication, 15 (60%) fluoxetine-treated patients and 8 (28%) placebo-treated patients responded to treatment, as measured by response on the CDRS-R total score (30% reduction from baseline to endpoint). Similarly, when patients received Lilly-provided study medication, 13 (57%) fluoxetine-treated patients and 7 (39%) placebo-treated patients responded to treatment.

Overall, the treatment effect was consistent regardless of study medication preparation methods when analyzing CDRS-R total response.

Table 11.21. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
Efficacy Subgroup Analysis of Study Medication
All Randomized Patients
B1Y-MC-X065

		Fluoxetine			Placebo			Homogeneity of Odds
Subgroup of Interest	Subgroup	N	n	%	N	n	%	Ratio p-Value[1]
Study Medication	Site	25	15	60	29	8	28	0.448
	Lilly	23	13	57	18	7	39	

Data for this table were taken from RMP.B1YO.X065REP (EFS1EM70).
[1]The homogeneity of odds ratio p-value is taken from the Breslow-Day test.
Abbreviations: N = total number of patients included in the subgroup; n = total number of patients meeting criteria for response.

Table 11.22 summarizes the statistical evaluation of both the change from baseline to endpoint for the CDRS-R total score while accounting for subgroup effect and the change from baseline within subgroups. There was not a statistically significant treatment-by-subgroup interaction for the two subgroups of patients by study medication received.

Overall, the treatment effect was consistent regardless of study medication preparation methods when analyzing CDRS-R total change from baseline scores.

Table 11.22. CDRS-R Total Score
Change from Baseline to Endpoint
Efficacy Subgroup Analysis of Study Medication
All Randomized Patients
B1Y-MC-X065

	Therapy by Subgroup					Baseline			Change	
Subgroup	Interaction[1]	Subgroup[1]	Subgroup	N	Therapy	N	Mean	SD	Mean	SD
Study Medication	0.673	0.504	Site	54	Flx 20mg	25	56.7	10.8	-19.8	13.7
					Placebo	29	55.9	10.9	-9.2	13.8
			Lilly	41	Flx 20mg	23	61.2	9.6	-20.6	13.5
					Placebo	18	60.0	9.4	-12.6	19.2

Data for this table were taken from RMP.B1YO.X065REP (CUSEM071).
Type III Sum of Squares used.
[1]PROC GLM model = therapy, subgroup, and therapy by subgroup for interaction and subgroup p-values.
Abbreviations: SD = standard deviation.

11.4.4. Tabulation of Individual Response Data

By-patient data listings for all efficacy measures are located in Appendices 16.2.7 and 16.4.1 through 16.4.4.

11.4.5. By-Patient Displays

No additional by-patient displays were evaluated.

11.4.6. Efficacy Conclusions

Ninety-six patients were randomized to treatment, with 48 patients receiving fluoxetine 20 mg/day and 48 receiving placebo. Patients were predominantly Caucasian (79%) and the treatment groups were balanced with respect to gender and age category (children versus adolescents). Patients came from a variety of socioeconomic backgrounds. Patients were rigorously evaluated for a primary diagnosis of MDD. This diagnostic evaluation also included evaluation of secondary comorbid diagnoses, which are commonly associated with MDD. Numerous patients had secondary comorbid diagnoses including anxiety disorders, dysthymia, oppositional and conduct disorders, and ADHD. The average age for onset of depression was 10.8 years old. At baseline, patients randomized to treatment had moderate to severe depression, as evidenced by mean baseline CDRS-R total scores of 58.9 for fluoxetine-treated patients and 57.5 for placebo-treated patients. The demographic profile of the pediatric population studied is considered representative of the pediatric population that currently requires appropriate diagnosis and treatment of depressive disorders.

Fluoxetine 20 mg/day was effective in the treatment of MDD in this pediatric population as demonstrated by response on the CDRS-R total score, defined as at least a 30% reduction from baseline, when patients were treated for up to 8 weeks ($p=.013$) and for at least 4 weeks ($p=.031$). The observed response rates on the CDRS-R total score (58% fluoxetine, 32% placebo) and the CGI-Improvement scores (56% fluoxetine, 34% placebo) are similar to the rates seen in depressed adults treated with fluoxetine.

The superiority of fluoxetine treatment over placebo treatment was demonstrated by the statistically significant changes in mean CDRS-R total scores from baseline to endpoint ($p=.002$), including statistically significant changes in the mood ($p<.001$), somatic ($p=.001$), and behavior ($p=.028$) subtotal scores after up to 8 weeks of treatment.

Analysis of the individual items that comprise the CDRS-R and BPRS-C scales demonstrate that fluoxetine-treated patients returned to normal functioning, showing increased levels of interest and overall activity, at a greater rate than placebo-treated patients.

The clinician's global impressions of improvement and severity also support the effectiveness of fluoxetine 20 mg/day in the treatment of MDD after 8 weeks of therapy. Endpoint analysis ($p=.015$) and response analysis ($p=.040$) for CGI-Improvement scores

demonstrated the superiority of fluoxetine over placebo. In addition, the mean change in CGI-Severity scores from baseline to endpoint was statistically significant for fluoxetine-treated patients as compared with placebo-treated patients (p=.003).

Greater attrition from the placebo treatment group was seen as compared with fluoxetine-treated patients. Despite this differential rate of attrition, LOCF analysis of mean CDRS-R total scores over time indicates that fluoxetine treatment was statistically significantly superior to placebo treatment after 3 weeks (Visit 5) of treatment. This treatment effect persisted for the duration of the study.

Analyses of the efficacy variables that demonstrated statistical superiority of fluoxetine treatment over placebo treatment are summarized in the following table.

Efficacy Variable Analyzed	p-Value
Response, at least a 30% reduction in CDRS-R Total score from baseline (at endpoint)	.013
Response, at least a 30% reduction in CDRS-R Total score from baseline (after at least 4 weeks of treatment)	.031
Mean change from baseline to endpoint in CDRS-R Total score	.002
Mean change from baseline to endpoint in CDRS-R Mood Subtotal score	<.001
Mean change from baseline to endpoint in CDRS-R Somatic Subtotal score	.001
Mean change from baseline to endpoint in CDRS-R Behavior Subtotal score	.028
Endpoint analysis of CGI-Improvement score	.015
Response, CGI-Improvement score of 1 or 2 at endpoint	.040
Mean change from baseline to endpoint in CGI-Severity score	.003

Data for this table were taken from RMP.B1YO.X065REP (EFS1EM01), RMP.B1YO.X065REP (EFS1EM06), RMP.B1YO.X065REP (PRCNEM13), RMP.B1YO.X065REP (DES1EM02), RMP.B1YO.X065REP (EFS1EM03), and RMP.B1YO.X065REP (PRCNEM23).

Although not statistically significant, several other categorical analyses of the CDRS-R total score (response defined as at least a 50% reduction from baseline, remission, and recovery) and continuous analyses of the BPRS-C, BDI, and CDI Total scores demonstrated numerical superiority of fluoxetine treatment over placebo treatment.

The BPRS-C was designed to capture other symptoms in addition to specific depressive symptoms. Given that the patients in this study had comorbid diagnoses in addition to MDD, interpretation of data from this scale is somewhat difficult. Although the total score did not demonstrate statistically significant changes over the course of the study, the numerical scores indicate that fluoxetine-treated patients showed slightly greater improvement than placebo-treated patients. Also, analysis of individual items demonstrated statistically significant improvement for fluoxetine-treated patients over placebo-treated patients for several items, indicating a return to normal functioning for fluoxetine-treated patients.

The self-report measures, BDI and CDI, were administered only to adolescents and children, respectively. Although statistical significance was not observed for these

measures, this could in part be a result of the smaller sample sizes. In addition, it has been noted in the literature that these self-report measures are somewhat unreliable as children tend to rate themselves as having minimal or no symptoms when diagnosis has been confirmed through clinical interview [redacted] CDRS-R total response, defined as at least a 30% reduction in CDRS-R total score from baseline, and mean change in CDRS-R total score from baseline to endpoint were evaluated with respect to subgroups of age (8 to <13, 13 to ≤18), gender (male, female), and study medication type (site-prepared, Lilly-provided). There were no differences in the effectiveness of fluoxetine treatment for any of the subgroups analyzed.

The data from this study are similar to adult data in regards to observed response rates, onset of response, and the fact that the majority of patients showed improvement in their depressive symptoms by the end of the acute treatment study. Taken as a whole, the measures used in this study, CDRS-R, CGI-Severity, CGI-Improvement, and BPRS-C, support the effectiveness of fluoxetine 20 mg/day in the acute treatment of major depressive disorder in children and adolescents.

12. Safety Evaluation

The safety of fluoxetine versus placebo in pediatric patients diagnosed with MDD was evaluated in all 96 randomized patients in this study. At baseline, a medical history, including psychiatric history and evaluation of secondary conditions, a physical examination, and an ECG were performed. Adverse events and vital signs, including blood pressure, heart rate, weight, and height, were monitored at each visit during the study. Adverse events were recorded, regardless of potential causality, using a standardized interviewer-elicited format (the Side-Effects Checklist and to a lesser extent, the Fluoxetine Side-Effects Checklist). Non-solicited adverse events were collected from source records. Clinical laboratory tests, including complete blood count, blood chemistry, electrolytes, thyroid panel, and urinalysis, were performed at baseline (Visit 1), Visit 6, and endpoint (Visit 10 or discontinuation).

12.1. Extent of Exposure

Exposure to study drug was estimated based on the number of days the patient participated in the study and represents the potential exposure of patients to study drug. Table 12.1 presents the exposure data, which was calculated by subtracting the first dose date from the last dose date plus 1. Missing doses were not taken into consideration in this calculation. Two patients received alternate day dosing. Patient 2162 received alternate day dosing at Visits 6 and 8. Patient 2212 received alternate day dosing from Visits 7 through 10. These patients' exposure calculations were not adjusted.

The mean number of days on treatment for all randomized patients reflects the differences in the number and timing of patient discontinuations between treatment groups. Fluoxetine-treated patients were exposed for an average of 50 ± 12 days (ranged from 14 to 63 days), whereas placebo-treated patients were exposed for an average of 43 ± 17 days (ranged from 0 to 69 days). Patient 2207 (placebo) was randomized to treatment, but was discontinued 2 days later due to patient decision. Although the patient did not discontinue until 2 days after randomization, the patient never took a dose of medication (see Appendix 16.4.4).

The patient disposition listing indicates the number of days of therapy received by each patient (see Appendix 16.2.2).

Table 12.1. Duration of Study Drug Exposure
All Randomized Patients
B1Y-MC-X065

Variable	Flx 20mg (N=48)	Placebo (N=48)
Exposure (days)		
No. Patients	48	48
Mean	50.0	43.3
Median	56.0	50.5
Standard Dev.	11.8	16.7
Minimum	14.0	0.0
Maximum	63.0	69.0

RMP.B1YP.JCLLIB2(DES1EM03)
RMP.B1YO.X065REP(DES1EM03)
XDES0001

12.2. Adverse Events

An adverse event is defined as any undesirable experience (or unanticipated benefit) that occurs after informed consent for the study has been obtained.

Adverse events were collected at each visit using a Side-Effects Checklist. Patients were questioned about specific adverse events as listed on the Checklist at the end of each visit. Non-solicited adverse events were recorded in source documents during each visit and were collected for analysis. The Fluoxetine Side-Effects Checklist was developed by [redacted] and was implemented in this study starting in January 1993. As a result, this checklist was only administered to a subset of patients. Because data from the Fluoxetine Side-Effects Checklist were not collected for all patients, this data is presented separately in Section 14.3.1.3 as a supplement to the safety data presented in this section.

The following sections detail the analysis of treatment-emergent solicited and non-solicited adverse events. Patient listings of adverse events are presented in Appendix 16.2.1.

12.2.1. Brief Summary of Adverse Events

Of the 96 randomized patients in this study, 92 (96%) reported at least one treatment-emergent solicited adverse event, and 85 (89%) reported at least one non-solicited adverse event. There were no statistically significant differences in frequencies of adverse events reported in fluoxetine-treated patients as compared with placebo-treated patients.

Two serious adverse events of suicide attempt occurred in patients receiving fluoxetine treatment during the study. Both events were considered to have unknown causality as determined by the principal investigator and occurred early in the study (after 12 and

15 days of therapy, respectively). One patient discontinued from the study as a result. Four additional fluoxetine-treated patients were discontinued from the study due to adverse events. Two patients were discontinued for hypomania, 1 for increased impulsivity, and 1 for rash. Three of the events (increased impulsivity, rash, and one event of hypomania) were reported as possibly related to fluoxetine treatment.

12.2.2. Display of Adverse Events

The Side-Effects Checklist is a 30-item symptom checklist, which includes general symptoms such as trouble sleeping, diarrhea, headaches, and trouble eating (see Appendix 16.1.2). The patient was asked by the clinician if he/she was having trouble with the specific symptoms contained on the Checklist. The clinician also recorded the intensity of frequency of these symptoms based on conversation with the patient.

The Side-Effects Checklist scored intensity as displayed in Table 12.2.

Table 12.2. Intensity Scores from the Side-Effects Checklist B1Y-MC-X065

Term on Side-Effects Checklist	Value on the Checklist
Not at all	0
Just a little	1
Pretty much	2
Very much	3
Don't know	4

Data for this table were taken from the Side-Effects Checklist shown in Appendix 16.1.2.
For the analysis presented in Table 12.3, a score of "don't know = 4" was set to "not at all = 0." For the analysis presented in Table 14.7, a score of "don't know = 4" was set to "missing."

Treatment-emergent solicited adverse events are those events which first occurred or worsened (as defined by increase in intensity score on the Side-Effects Checklist) after initiation of treatment. Adverse events were coded using the terms specified on the Side-Effects Checklist.

Treatment-emergent solicited adverse events are summarized by decreasing frequency (ordered by fluoxetine treatment) in Table 12.3.

Table 12.3. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
B1Y-MC-X065

Event Classification	Flx 20mg (N=48) n (%)	Placebo (N=48) n (%)	Total (N=96) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	47 (97.9)	45 (93.8)	92 (95.8)	.617
PATIENTS WITH NO TESS	1 (2.1)	3 (6.3)	4 (4.2)	.617
14. COLD OR SNIFFLES	22 (45.8)	22 (45.8)	44 (45.8)	1.00
24. SLEEPING	17 (35.4)	15 (31.3)	32 (33.3)	.829
06. DIARRHEA	16 (33.3)	9 (18.8)	25 (26.0)	.162
08. MUSCLE CRAMPS	15 (31.3)	10 (20.8)	25 (26.0)	.352
09. BEING SICK TO YOUR STOMACH	15 (31.3)	18 (37.5)	33 (34.4)	.668
07. STOMACHACHES	14 (29.2)	16 (33.3)	30 (31.3)	.826
21. SITTING STILL	14 (29.2)	13 (27.1)	27 (28.1)	1.00
23. FEELING SLEEPY	14 (29.2)	11 (22.9)	25 (26.0)	.642
32. PAYING ATTENTION	14 (29.2)	9 (18.8)	23 (24.0)	.339
16. DIZZINESS	13 (27.1)	13 (27.1)	26 (27.1)	1.00
26. GETTING ALONG WITH PARENTS	13 (27.1)	12 (25.0)	25 (26.0)	1.00
03. DRY MOUTH AND LIPS	12 (25.0)	10 (20.8)	22 (22.9)	.809
22. TIREDNESS	12 (25.0)	14 (29.2)	26 (27.1)	.819
30. NOT BEING HAPPY	12 (25.0)	12 (25.0)	24 (25.0)	1.00
15. HEADACHE	11 (22.9)	12 (25.0)	23 (24.0)	1.00
18. SHAKINESS	11 (22.9)	6 (12.5)	17 (17.7)	.285
27. GETTING ALONG WITH KIDS	11 (22.9)	11 (22.9)	22 (22.9)	1.00
28. CRYING	11 (22.9)	14 (29.2)	25 (26.0)	.642
13. RASHES	10 (20.8)	5 (10.4)	15 (15.6)	.261
25. BAD DREAMS	10 (20.8)	9 (18.8)	19 (19.8)	1.00
12. ITCHY OR SCRATCHY SKIN	9 (18.8)	9 (18.8)	18 (18.8)	1.00
20. DOING THINGS WITH YOUR HANDS	9 (18.8)	9 (18.8)	18 (18.8)	1.00
31. BEING SAD	9 (18.8)	11 (22.9)	20 (20.8)	.802
04. WETNESS IN MOUTH	8 (16.7)	5 (10.4)	13 (13.5)	.552
19. PRONOUNCING WORDS	8 (16.7)	7 (14.6)	15 (15.6)	1.00
29. GETTING MAD	8 (16.7)	12 (25.0)	20 (20.8)	.452
01. EATING	7 (14.6)	8 (16.7)	15 (15.6)	1.00
02. DRINKING	7 (14.6)	8 (16.7)	15 (15.6)	1.00
05. CONSTIPATION	7 (14.6)	7 (14.6)	14 (14.6)	1.00
17. PLAYING SPORTS	7 (14.6)	7 (14.6)	14 (14.6)	1.00
10. WETTING THE BED	4 (8.3)	3 (6.3)	7 (7.3)	1.00
11. URINATING	3 (6.3)	3 (6.3)	6 (6.3)	1.00

1 Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effect checklist or a new occurrence after baseline. Baseline is the highest score of item at visit 1 and 2.
RMP.B1YT.JCLLIB2(AES2E28A)
RMP.B1YO.X065REP(AES2E28A)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Non-solicited adverse events were collected from source documents and progress notes. Adverse events were captured regardless of relationship to study medication. Although these events were captured during the study, the severity of these events was not recorded. Because severities of non-solicited adverse events could not be determined from source documentation, an analysis of treatment-emergence could not be performed. Table 12.4 presents the frequency of all events that occurred during treatment, including those collected at baseline.

Table 12.4. Non-Solicited Adverse Events Occurring During Treatment Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients B1Y-MC-X065

Event Classification	Flx 20mg (N=48) n (%)	Placebo (N=48) n (%)	p-Value*
PATIENTS WITH >= 1 EVENT	46 (95.8)	39 (81.3)	.051
PATIENTS WITH NO EVENTS	2 (4.2)	9 (18.8)	.051
ANXIETY	18 (37.5)	17 (35.4)	1.00
HYPERKINESIA	18 (37.5)	16 (33.3)	.831
PHARYNGITIS	12 (25.0)	7 (14.6)	.306
DEPRESSION	9 (18.8)	8 (16.7)	1.00
VOMITING	7 (14.6)	2 (4.2)	.159
NAUSEA	6 (12.5)	2 (4.2)	.268
DIARRHEA	5 (10.4)	0	.056
FLU SYNDROME	5 (10.4)	4 (8.3)	1.00
HEADACHE	5 (10.4)	4 (8.3)	1.00
NEUROSIS	5 (10.4)	2 (4.2)	.435
PAIN	5 (10.4)	4 (8.3)	1.00
RASH	5 (10.4)	3 (6.3)	.714
ABDOMINAL PAIN	4 (8.3)	3 (6.3)	1.00
FEVER	4 (8.3)	2 (4.2)	.677
MALAISE	4 (8.3)	2 (4.2)	.677
MANIC REACTION	4 (8.3)	2 (4.2)	.677
COUGH INCREASED	3 (6.3)	2 (4.2)	1.00
INFECTION	3 (6.3)	2 (4.2)	1.00
INSOMNIA	3 (6.3)	1 (2.1)	.617
NERVOUSNESS	3 (6.3)	5 (10.4)	.714
RHINITIS	3 (6.3)	4 (8.3)	1.00
SINUSITIS	3 (6.3)	0	
SOMNOLENCE	3 (6.3)	1 (2.1)	.617
URINARY INCONTINENCE	3 (6.3)	3 (6.3)	1.00
ABNORMAL DREAMS	2 (4.2)	2 (4.2)	1.00
ACCIDENTAL INJURY	2 (4.2)	1 (2.1)	
CHEST PAIN	2 (4.2)	0	
DIZZINESS	2 (4.2)	5 (10.4)	.435
MENSTRUAL DISORDER	2 (4.2)	0	
MYALGIA	2 (4.2)	2 (4.2)	1.00
SUICIDE ATTEMPT	2 (4.2)	0	
UNEXPECTED BENEFIT	2 (4.2)	1 (2.1)	
ACNE	1 (2.1)	1 (2.1)	
AKATHISIA	1 (2.1)	1 (2.1)	
ANOREXIA	1 (2.1)	1 (2.1)	
ASTHENIA	1 (2.1)	1 (2.1)	
ASTHMA	1 (2.1)	1 (2.1)	

RMP.B1YP.JCLLIB2(AES1EM01)
RMP.B1YO.X065REP(AES1EM01)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0001

Table 12.4. Non-Solicited Adverse Events Occurring During Treatment Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients B1Y-MC-X065 (continued)

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	p-Value*
BACK PAIN	1	(2.1)	0		
BONE PAIN	1	(2.1)	0		
BRONCHITIS	1	(2.1)	0		
CONSTIPATION	1	(2.1)	0		
CYSTITIS	1	(2.1)	1	(2.1)	
DEPERSONALIZATION	1	(2.1)	0		
DRY MOUTH	1	(2.1)	1	(2.1)	
DYSMENORRHEA	1	(2.1)	0		
DYSPNEA	1	(2.1)	0		
EAR PAIN	1	(2.1)	1	(2.1)	
EPISTAXIS	1	(2.1)	0		
EYE DISORDER	1	(2.1)	1	(2.1)	
GASTROENTERITIS	1	(2.1)	0		
GASTROINTESTINAL DISORDER	1	(2.1)	0		
LARYNGITIS	1	(2.1)	0		
LEG CRAMPS	1	(2.1)	1	(2.1)	
MIGRAINE	1	(2.1)	0		
OVARIAN DISORDER	1	(2.1)	0		
PALLOR	1	(2.1)	0		
PERSONALITY DISORDER	1	(2.1)	0		
PNEUMONIA	1	(2.1)	0		
PRURITUS	1	(2.1)	0		
SLEEP DISORDER	1	(2.1)	0		
SWEATING	1	(2.1)	0		
THINKING ABNORMAL	1	(2.1)	2	(4.2)	
TOOTH DISORDER	1	(2.1)	0		
TREMOR	1	(2.1)	1	(2.1)	
URINARY TRACT INFECTION	1	(2.1)	1	(2.1)	
URTICARIA	1	(2.1)	0		
VASODILATATION	1	(2.1)	1	(2.1)	
ADDICTION	0		1	(2.1)	
AGITATION	0		2	(4.2)	
ALLERGIC REACTION	0		4	(8.3)	.117
AMNESIA	0		1	(2.1)	
ARTHRALGIA	0		1	(2.1)	
CHILLS	0		1	(2.1)	
CONJUNCTIVITIS	0		1	(2.1)	
EMOTIONAL LABILITY	0		1	(2.1)	
FUNGAL DERMATITIS	0		1	(2.1)	

RMP.B1YP.JCLLIB2(AES1EM01)
RMP.B1YO.X065REP(AES1EM01)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0001

Table 12.4. Non-Solicited Adverse Events Occurring During Treatment Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients B1Y-MC-X065 (concluded)

Event Classification	Flx 20mg (N=48) n (%)	Placebo (N=48) n (%)	p-Value*
HOSTILITY	0	1 (2.1)	
INCREASED APPETITE	0	2 (4.2)	
PHOTOPHOBIA	0	1 (2.1)	
PHOTOSENSITIVITY REACTION	0	2 (4.2)	
QT INTERVAL PROLONGED	0	1 (2.1)	
YAWN	0	1 (2.1)	

RMP.B1YP.JCLLIB2(AES1EM01)
RMP.B1YO.X065REP(AES1EM01)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0001

Data from the Fluoxetine Side-Effects Checklist are presented separately in Section 14.3.1.3 as a supplement to the safety data presented in this section.

12.2.3. Analysis of Adverse Events

As shown in Table 12.3, of the 96 patients randomized in the study, a total of 92 patients, 47 (98%) fluoxetine-treated and 45 (94%) placebo-treated, reported at least one treatment-emergent solicited adverse event.

Overall, the percentages of patients reporting treatment-emergent solicited adverse events were high relative to other adult studies. However, these adverse events were collected using an interviewer-elicited format, which typically results in higher reporting percentages. This format is commonly used in pediatric studies because asking a more general question about the patient's well being is not as informative as using a Checklist. Although the overall percentages are high, they are consistent for the two treatment groups. No treatment-emergent solicited adverse events occurred in statistically significantly different percentages of fluoxetine-treated and placebo-treated patients.

The most frequently reported treatment-emergent solicited adverse event was cold or sniffles (46% fluoxetine, 46% placebo). Other frequently reported treatment-emergent solicited adverse events by fluoxetine-treated patients included trouble sleeping (35%), diarrhea (33%), muscle cramps (31%), and being sick to your stomach (31%). Other frequently reported treatment-emergent solicited adverse events by placebo-treated included being sick to your stomach (38%), stomachaches (33%), tiredness (29%), and crying (29%).

For the primary analysis of the Side-Effects Checklist (see Table 12.3), the intensity score of "don't know = 4" was set to "not at all = 0." Treatment-emergent solicited

adverse events were also evaluated using a more conservative method of determining treatment-emergence (see Table 14.7, Section 14.3.1.1). In this analysis, the intensity score of "don't know = 4" was set to "missing." For both analyses "missing" values for a known event were then assumed to have an intensity score based on whether the event occurred at baseline or postbaseline. Baseline events were assigned an intensity score of 1 and postbaseline events were assigned an intensity score of 3. Treatment-emergence for these events was determined using these values. There were no statistically significant differences between treatment groups in both of the analyses.

Treatment-emergent solicited adverse events were also analyzed by maximum intensity (see Table 14.8, Section 14.3.1.1). The Side-Effects Checklist measured intensity, rather than severity, as is typically done in Lilly-sponsored trials. An intensity score of "1," which meant the event occurred "just a little" (according to the Side-Effects Checklist), was mapped to the term "mild" for severity analysis in Lilly's system. Similarly, a score of "2" (pretty much) mapped to moderate, and a score of "3" (very much) mapped to severe. There were no statistically significant differences between treatment groups in the incidence of treatment-emergent solicited adverse events that were classified as "severe," ie, those that occurred the most frequently (very much).

Non-solicited adverse events were collected from source documents. These included any adverse events that were noted during the time the patient was in the office apart from Checklist items. In an effort to thoroughly account for all adverse events that were reported during the study, Lilly collected non-solicited adverse events from each and every visit (during the acute treatment period) at which they were found. Because of the manner in which these events were recorded in the source documentation, there is no record of severity of these events. As a result, a determination of treatment-emergence could not be performed. Overall reporting percentages are higher than those typically observed in adult studies, but this can be attributed to the fact that this analysis includes all adverse events reported throughout the acute treatment period and is a conservative method of collecting adverse event data.

As shown in Table 12.4, 46 (96%) fluoxetine-treated and 39 (81%) placebo-treated patients reported at least one non-solicited adverse event during the course of treatment. None of the non-solicited adverse events occurred in statistically significantly different percentages of fluoxetine-treated and placebo-treated patients. The two most frequently reported non-solicited adverse events were anxiety (38% fluoxetine, 35% placebo) and hyperkinesia (38% fluoxetine, 33% placebo). As these events occurred with comparable frequency in the two treatment groups, the events may be reflective of the pediatric population under study. In addition, fluoxetine-treated patients reported more gastrointestinal events than placebo-treated patients, although none of these events occurred in statistically significant different percentages of patients.

The incidence of non-solicited adverse events by body system is presented in Table 14.9 (see Section 14.3.1.2).

12.2.4. Listing of Adverse Events by Patient

Complete listings of all adverse events by patient are located in Appendix 16.2.1.

12.3. Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events

12.3.1. Deaths

There were no deaths during this study.

12.3.2. Serious Adverse Events

Two serious adverse events of suicide attempt occurred in patients receiving fluoxetine treatment during the study (Table 12.5).

Patient 2051 was discontinued from the study after receiving 15 days of fluoxetine treatment due to a suicide attempt. The patient was hospitalized after intentional overdose including Pamprin®, Momentum®, and Dibromm® following a fight with her boyfriend. She was treated in the emergency room and admitted to the psychiatric unit. The event was considered to have unknown causality as determined by the principal investigator.

Patient 2163 was hospitalized for a suicide attempt after receiving 12 days of fluoxetine treatment. The patient intentionally overdosed on unknown pills, possibly including ibuprofen and phenergan. The patient was treated in the emergency room and released. The event was considered to have unknown causality as determined by the principal investigator. The patient remained in the study and completed the entire protocol.

Table 12.5. Serious Adverse Events
All Randomized Patients
B1Y-MC-X065

Patient	Therapy	Actual Term	Days in Therapy at Onset	Remarks
2051	Flx 20mg	Suicide Attempt	15	Hospitalized
2163	Flx 20mg	Suicide Attempt	12	Other

Data for this table were taken from RMP.B1YO.X065REP (AEL1EM01).

12.3.3. Nonserious Clinically Significant Adverse Events

Four additional fluoxetine-treated patients were discontinued from the study due to adverse events (Table 12.6). Two were discontinued for hypomania, 1 for increased impulsivity, and 1 for rash on the abdomen and extremities. Three of the events were considered possibly related to fluoxetine treatment, as determined by the principal investigator.

Table 12.6. Discontinuations Due to Adverse Events
All Randomized Patients
B1Y-MC-X065

Patient	Therapy	Actual Term	Days in Therapy at Discontinuation	Relationship to Study Drug	Visit Discontinued
2019	Flx 20mg	Increased Impulsivity	27	Possible	6
2030	Flx 20mg	Rash	25	Possible	6
2119	Flx 20mg	Hypomania	27	Unknown	6
2231	Flx 20mg	Hypomania	41	Possible	8

Data for this table were taken from RMP.B1YO.X065REP (AEL1EM01) and RMP.B1YO.X065REP (RDL1EM01).
See Appendix 16.1.13 for documentation of discontinuation visit and days in therapy for Patient 2119.

12.3.4. Narratives of Deaths, Serious Adverse Events, and Nonserious Clinically Significant Adverse Events

Patient summaries for patients who experienced serious adverse events or adverse events leading to discontinuation from the study are presented in Section 14.3.3.

12.4. Clinical Laboratory Evaluation

Clinical laboratory data (including complete blood count, blood chemistry, electrolytes, thyroid panel, and urinalysis) were collected at baseline (Visit 1), Visit 6, and endpoint (Visit 10 or discontinuation).

12.4.1. Change from Baseline to Endpoint

Table 12.7 presents a summary of the changes in laboratory values from baseline to endpoint.

Of the 96 randomized patients in this study, data from up to 31 patients (16 fluoxetine-treated, 15 placebo-treated) were available for analysis of change from baseline to endpoint for laboratory analytes included in the complete blood count (CBC) panel. There was a statistically significant difference between treatment groups for the change in white blood cells (WBC). Fluoxetine-treated patients experienced a mean decrease of 0.66 GI/L (SD 1.12) in WBC as compared with a mean decrease of 1.57 GI/L (SD 2.79) for placebo-treated patients (p=.012). The decreases observed were not considered to be clinically relevant.

Data from up to 68 patients (33 fluoxetine-treated, 35 placebo-treated) were available for analysis of change from baseline to endpoint for laboratory analytes included in the blood chemistry panel. There were statistically significant differences between treatment groups for the change in aspartate transaminase (AST) and alkaline phosphatase levels. Fluoxetine-treated patients experienced a mean decrease of 1.79 U/L (SD 11.65) in AST levels over the course of the study as compared with a mean increase of 2.94 U/L

(SD 9.08) for placebo-treated patients (p=.022). Fluoxetine-treated patients experienced a mean decrease of 25.5 (SD 26.6) in alkaline phosphatase levels over the course of the study as compared with a mean decrease of 11.6 (SD 41.0) for placebo-treated patients (p=.006). The differences observed were not considered to be clinically relevant.

There were very few patients with data available for analysis of change from baseline to endpoint for laboratory analytes included in the electrolyte panel, thyroid panel, and urinalysis.

Table 12.7. Laboratory Analysis
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065

Research Project Code: B1Y
Laboratory Test Group: Complete Blood Count

				Baseline		Change to Endpoint		p-Values	
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy	Model
HCT	1	Flx 20mg	16	40.3813	3.6931	-0.6500	2.0788	.615	FULL1
		Placebo	15	40.6133	3.0227	-0.7133	3.2798		
HGB	mml/L-Fe	Flx 20mg	16	8.475	0.821	-0.151	0.393	.601	FULL1
		Placebo	15	8.568	0.687	-0.232	0.568		
RBC	TI/L	Flx 20mg	16	4.761	0.420	-0.088	0.239	.685	FULL1
		Placebo	15	4.742	0.358	-0.109	0.330		
MCHC	mml/L-Fe	Flx 20mg	16	33.8	0.8	-0.1	0.9	.969	FULL1
		Placebo	15	34.0	0.7	-0.3	0.8		
MCH	fmol(Fe)	Flx 20mg	16	1.781	0.085	0.003	0.034	.393	FULL1
		Placebo	15	1.808	0.073	-0.009	0.031		
WBC	GI/L	Flx 20mg	16	8.14	2.20	-0.66	1.12	.012	FULL1
		Placebo	15	8.91	1.71	-1.57	2.79		
BANDS	1	Flx 20mg	4	0.028	0.029	-0.005	0.031	.543	FULL1
		Placebo	2	0.015	0.007	0.025	0.035		
POLYS	1	Flx 20mg	16	0.483	0.097	0.038	0.104	.322	FULL1
		Placebo	13	0.589	0.096	-0.022	0.128		
LYMPHS	1	Flx 20mg	16	0.416	0.085	-0.041	0.092	.171	FULL1
		Placebo	13	0.328	0.107	0.018	0.127		
MONOS	1	Flx 20mg	16	0.065	0.034	-0.006	0.035	1.00	FULL1
		Placebo	13	0.058	0.023	-0.005	0.034		
EOSN	1	Flx 20mg	10	0.028	0.030	0.012	0.023	.971	FULL1
		Placebo	10	0.021	0.011	0.012	0.022		
BASO	1	Flx 20mg	3	0.009	0.002	0.005	0.008	.514	FULL1
		Placebo	4	0.008	0.004	0.009	0.008		

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Table 12.7. Laboratory Analysis
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (continued)

Research Project Code: B1Y
Laboratory Test Group: Complete Blood Count

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy	p-Values Model
MCV	fL	Flx 20mg	16	84.9	3.9	0.3	1.4	.685	FULL1
		Placebo	15	85.7	3.2	0.5	2.3		
PLTCT	GI/L	Flx 20mg	16	286.9	86.8	-22.4	59.9	1.00	FULL1
		Placebo	15	279.7	60.2	-18.3	27.3		
RDW	1	Flx 20mg	14	0.123	0.005	-0.001	0.004	.592	FULL1
		Placebo	15	0.121	0.005	-0.002	0.004		
MPV	fL	Flx 20mg	14	9.23	1.25	0.06	0.46	.898	FULL1
		Placebo	15	9.00	0.85	0.05	0.63		
ATLYMP	GI/L	Flx 20mg	14	0.000	0.000	0.000	0.000	*	FULL1
		Placebo	12	0.000	0.000	0.000	0.000		
ATLYMP	1	Flx 20mg	1	0.030		-0.020			

XLAS0006

Table 12.7. Laboratory Analysis
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (continued)

Research Project Code: B1Y
Laboratory Test Group: Blood Chemistry

				Baseline		Change to Endpoint		p-Values	
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy	Model
AST	U/L	Flx 20mg	33	34.15	16.85	-1.79	11.65	.022	FULL1
		Placebo	35	27.80	11.67	2.94	9.08		
ALT	U/L	Flx 20mg	33	25.73	7.31	0.70	8.62	.827	FULL1
		Placebo	35	23.14	22.30	-0.46	20.44		
LDH	U/L	Flx 20mg	34	566.0	105.9	26.7	121.5	.502	FULL1
		Placebo	35	540.3	163.7	1.5	157.1		
ALKPH	U/L	Flx 20mg	33	194.8	72.0	-25.5	26.6	.006	FULL1
		Placebo	33	168.5	72.6	-11.6	41.0		
ALBUM	g/L	Flx 20mg	34	44.1	2.9	-1.7	2.5	.313	FULL1
		Placebo	35	44.1	2.9	56.0	337.2		

XLAS0006

Table 12.7. Laboratory Analysis
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (continued)

Research Project Code: B1Y
Laboratory Test Group: Electrolytes

				Baseline		Change to Endpoint		p-Values	
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy	Model
SODIUM	mmol/L	Placebo	1	140.0		-2.0			

XLAS0006

Table 12.7. Laboratory Analysis
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (continued)

Research Project Code: B1Y
Laboratory Test Group: THYROID PANEL

				Baseline		Change to Endpoint		p-Values	
Lab Test	Lab Unit	Therapy	n	Mean	SD	Mean	SD	Therapy	Model
T4-RIA	nmol/L	Flx 20mg	3	90.1	7.8	-1.7	16.8		
TSH	mU/L	Flx 20mg	3	0.833	0.153	0.333	0.757		

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Table 12.7. Laboratory Analysis
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (continued)

Research Project Code: B1Y
Laboratory Test Group: Urinalysis

Lab Test	Lab Unit	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy	p-Values Model
U-SPGR	NO UNITS	Flx 20mg	3	1.0293	0.0015	-0.0097	0.0072	.225	FULL1
		Placebo	1	1.0230		0.0010			
U-PH	U	Flx 20mg	3	5.67	0.58	1.67	0.76	.225	FULL1
		Placebo	1	7.00		0.00			

RMP.B1YP.JCLLIB2(LAS6EM01)
RMP.B1YO.X065REP(LAS6EM01)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA) on the ranks:
PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA on the ranks using the mean square for error.

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**Table 12.7. Laboratory Analysis
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (concluded)**

Legend of Lab Test Code Abbreviations:

Abbrev.	Description
HCT	HEMATOCRIT
HGB	HEMOGLOBIN
RBC	ERYTHROCYTE COUNT
MCHC	MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)
MCH	MEAN CELL HEMOGLOBIN (MCH)
WBC	LEUKOCYTE COUNT
BANDS	BANDS
POLYS	NEUTROPHILS, SEGMENTED
LYMPHS	LYMPHOCYTES
MONOS	MONOCYTES
EOSN	EOSINOPHILS
BASO	BASOPHILS
MCV	MEAN CELL VOLUME (MCV)
PLTCT	PLATELET COUNT
RDW	RBC DISTRIBUTION WIDTH
MPV	MEAN PLATELET VOLUME
ATLYMP	LYMPHOCYTES, ATYPICAL
U-SPGR	UA-SPECIFIC GRAVITY
U-PH	UA-PH
AST	AST/SGOT
ALT	ALT/SGPT
LDH	LACTIC DEHYDROGENASE
ALKPH	ALKALINE PHOSPHATASE
T4-RIA	THYROXINE, TOTAL-T4
TSH	THYROID STIM. HORMONE
SODIUM	SODIUM
ALBUM	ALBUMIN

12.4.2. Treatment-Emergent Abnormal Values

The laboratory reference ranges used in this study were established by [redacted] The reference ranges used for each patient are included in the by-patient listing of laboratory values contained in Appendix 16.2.8.

Laboratory values that became abnormal or went out of range during the study were evaluated. The proportion of patients with abnormal laboratory values was summarized and compared across treatment groups. The results are displayed in Table 14.11 (see Section 14.3.4). There were no statistically significant or clinically relevant differences in treatment-emergent abnormal laboratory values between treatment groups.

12.4.3. Listing of Individual Laboratory Measurements by Patient and Each Abnormal Laboratory Value

A listing of individual laboratory measurements by patient and their associated lab ranges is located in Appendix 16.2.8.

A listing of all patients who had an abnormal laboratory value during the study is provided in Table 14.12 (see Section 14.3.4).

Overall, few abnormalities in laboratory values were observed. Table 12.8 displays patients who had notable abnormal laboratory values during the study. Four patients (2 fluoxetine-treated, 2 placebo-treated) had elevated lactic dehydrogenase levels. Three patients (1 fluoxetine-treated, 2 placebo-treated) had elevated alanine transaminase/serum glutamic pyruvic transaminase (ALT/SGPT) levels during the study. Three patients (2 fluoxetine-treated, 1 placebo-treated) had elevated levels of aspartate transaminase/serum oxaloacetic transaminase (AST/SGOT) during the study. At baseline (Visit 1), 1 placebo-treated patient had an elevated cortisol level. Since notable abnormal laboratory values occurred in both treatment groups, there did not appear to be any trends indicating that these abnormalities were due to fluoxetine treatment.

Table 12.8. Laboratory Analysis
Notable Abnormal Values
All Randomized Patients
B1Y-MC-X065

Lab Test	Patient Number	Treatment Group	Units	Reference Range	Laboratory Value	Visit
Lactic dehydrogenase	2030	Flx 20mg	U/L	340-770	1025	6
Lactic dehydrogenase	2173	Flx 20mg	U/L	420-750	922	6
Lactic dehydrogenase	2233	Placebo	U/L	420-750	953	1
Lactic dehydrogenase	2252	Placebo	U/L	420-750	1248	1
ALT/SGPT	2178	Flx 20mg	U/L	5-30	59	10
ALT/SGPT	2038	Placebo	U/L	8-36	65	6
ALT/SGPT	2167	Placebo	U/L	10-45	143	1
AST/SGOT	2178	Flx 20mg	U/L	16-38	72	10
AST/SGOT	2237	Flx 20mg	U/L	16-46	113	1
AST/SGOT	2237	Flx 20mg	U/L	16-46	82	10
AST/SGOT	2233	Placebo	U/L	16-46	82	1
Cortisol	2179	Placebo	nmol/L	0-28	69	1

Data for this table were taken from RMP.B1YO.X065REP (LAL3EM67).
Abbreviations: ALT/SGPT = alanine transaminase/serum glutamic pyruvic transaminase; AST/SGOT = aspartate transaminase/serum oxaloacetic transaminase.

12.5. Vital Signs and Electrocardiograms

Vital signs, including blood pressure, heart rate, weight, and height, were recorded at each visit. ECGs were collected at baseline only (Visit 1) and were not analyzed statistically. A complete listing of individual ECGs is presented in Appendix 16.4.3.

Table 12.9 presents a summary of the change from baseline to endpoint for the vital signs collected during the study. There were no statistically significant or clinically relevant changes in any of the vital signs examined.

Appendix 16.4.2 contains a patient listing of vital signs by visit.

Table 12.9. Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065

Research Project Code: B1Y

			-----Baseline------		Change to -----Endpoint-----		p-Values
Variables Analyzed	Therapy	n	Mean	SD	Mean	SD	Therapy
HEIGHT	Flx 20mg	37	149.9	20.6	1.3	3.2	.432
	Placebo	40	154.5	12.6	0.7	3.5	
WEIGHT	Flx 20mg	43	54.0	22.1	-0.1	1.9	.119
	Placebo	43	50.6	15.6	0.5	1.3	
SI_HR	Flx 20mg	42	83.0	11.9	-3.6	14.4	.179
	Placebo	43	83.5	13.0	0.4	12.4	
SI_SYSBP	Flx 20mg	43	114.5	14.5	1.4	10.9	.971
	Placebo	43	114.9	15.1	1.3	13.0	
SI_DIABP	Flx 20mg	43	60.7	8.0	1.2	7.5	.624
	Placebo	43	61.9	7.5	2.0	7.8	

RMP.B1YP.JCLLIB2(LAS6EM03)
RMP.B1YO.X065REP(LAS6EM03)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

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Table 12.9. Vital Signs
Change from Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (concluded)

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Legend of Variable Abbreviations:
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Abbrev.     Description
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HEIGHT      Height cm
SI_DIABP    Sitting Diastolic Blood Pressure mmHG
SI_HR       Sitting Heart Rate bpm
SI_SYSBP    Sitting Systolic Blood Pressure mmHG
WEIGHT      Weight kg
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12.6. Examination of Subgroups

Table 12.10 presents a summary of subgroup analyses of treatment-emergent solicited adverse events. The subgroups analyzed included age category (8 to <13, 13 to ≤18) and gender (male, female).

A statistically significant difference across age groups was observed for two treatment-emergent solicited adverse events when comparing between-strata differences based on the Breslow-Day test. The odds ratio p-value for muscle cramps was statistically significant (p=.036). This indicates that fluoxetine-treated children experienced more muscle cramps than placebo-treated children (p=.049) as compared with adolescents in both treatment groups (p=.740). The odd ratios p-value for trouble with playing sports was also statistically significant (p=.039). However, within each age strata, the comparison between treatment groups was not statistically significant.

The treatment effect of fluoxetine was consistent across gender for all of the treatment-emergent solicited adverse events.

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065

SECL Event - Have you had trouble with:	AGE	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	8 - <13	24	4	(16.7)	24	2	(8.3)	.166	.666
	13 - <=18	24	3	(12.5)	24	6	(25.0)		.461
02. DRINKING	8 - <13	24	4	(16.7)	24	5	(20.8)	.811	1.00
	13 - <=18	24	3	(12.5)	24	3	(12.5)		1.00
03. DRY MOUTH AND LIPS	8 - <13	24	7	(29.2)	24	4	(16.7)	.330	.494
	13 - <=18	24	5	(20.8)	24	6	(25.0)		1.00
04. WETNESS IN MOUTH	8 - <13	24	4	(16.7)	24	2	(8.3)	.714	.666
	13 - <=18	24	4	(16.7)	24	3	(12.5)		1.00
05. CONSTIPATION	8 - <13	24	4	(16.7)	24	4	(16.7)	1.00	1.00
	13 - <=18	24	3	(12.5)	24	3	(12.5)		1.00
06. DIARRHEA	8 - <13	24	11	(45.8)	24	5	(20.8)	.363	.125
	13 - <=18	24	5	(20.8)	24	4	(16.7)		1.00
07. STOMACHACHES	8 - <13	24	4	(16.7)	24	9	(37.5)	.070	.193
	13 - <=18	24	10	(41.7)	24	7	(29.2)		.547

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	AGE	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	8 - <13	24	10	(41.7)	24	3	(12.5)	.036	.049
	13 - <=18	24	5	(20.8)	24	7	(29.2)		.740
09. BEING SICK TO YOUR STOMACH	8 - <13	24	6	(25.0)	24	9	(37.5)	.498	.534
	13 - <=18	24	9	(37.5)	24	9	(37.5)		1.00
10. WETTING THE BED	8 - <13	24	3	(12.5)	24	3	(12.5)	.348	1.00
	13 - <=18	24	1	(4.2)	24	0			1.00
11. URINATING	8 - <13	24	3	(12.5)	24	2	(8.3)	.265	1.00
	13 - <=18	24	0		24	1	(4.2)		1.00
12. ITCHY OR SCRATCHY SKIN	8 - <13	24	8	(33.3)	24	6	(25.0)	.222	.752
	13 - <=18	24	1	(4.2)	24	3	(12.5)		.609
13. RASHES	8 - <13	24	6	(25.0)	24	3	(12.5)	.961	.461
	13 - <=18	24	4	(16.7)	24	2	(8.3)		.666
14. COLD OR SNIFFLES	8 - <13	24	12	(50.0)	24	12	(50.0)	1.00	1.00
	13 - <=18	24	10	(41.7)	24	10	(41.7)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	AGE	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	8 - <13	24	6	(25.0)	24	8	(33.3)	.487	.752
	13 - <=18	24	5	(20.8)	24	4	(16.7)		1.00
16. DIZZINESS	8 - <13	24	7	(29.2)	24	6	(25.0)	.646	1.00
	13 - <=18	24	6	(25.0)	24	7	(29.2)		1.00
17. PLAYING SPORTS	8 - <13	24	7	(29.2)	24	4	(16.7)	.039	.494
	13 - <=18	24	0		24	3	(12.5)		.234
18. SHAKINESS	8 - <13	24	5	(20.8)	24	3	(12.5)	.832	.701
	13 - <=18	24	6	(25.0)	24	3	(12.5)		.461
19. PRONOUNCING WORDS	8 - <13	24	5	(20.8)	24	5	(20.8)	.705	1.00
	13 - <=18	24	3	(12.5)	24	2	(8.3)		1.00
20. DOING THINGS WITH YOUR HANDS	8 - <13	24	4	(16.7)	24	5	(20.8)	.601	1.00
	13 - <=18	24	5	(20.8)	24	4	(16.7)		1.00
21. SITTING STILL	8 - <13	24	7	(29.2)	24	9	(37.5)	.239	.760
	13 - <=18	24	7	(29.2)	24	4	(16.7)		.494

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	AGE	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	8 - <13	24	6	(25.0)	24	7	(29.2)	1.00	1.00
	13 - <=18	24	6	(25.0)	24	7	(29.2)		1.00
23. FEELING SLEEPY	8 - <13	24	7	(29.2)	24	6	(25.0)	.801	1.00
	13 - <=18	24	7	(29.2)	24	5	(20.8)		.740
24. SLEEPING	8 - <13	24	8	(33.3)	24	6	(25.0)	.643	.752
	13 - <=18	24	9	(37.5)	24	9	(37.5)		1.00
25. BAD DREAMS	8 - <13	24	5	(20.8)	24	3	(12.5)	.419	.701
	13 - <=18	24	5	(20.8)	24	6	(25.0)		1.00
26. GETTING ALONG WITH PARENTS	8 - <13	24	7	(29.2)	24	6	(25.0)	.821	1.00
	13 - <=18	24	6	(25.0)	24	6	(25.0)		1.00
27. GETTING ALONG WITH KIDS	8 - <13	24	5	(20.8)	24	6	(25.0)	.627	1.00
	13 - <=18	24	6	(25.0)	24	5	(20.8)		1.00
28. CRYING	8 - <13	24	5	(20.8)	24	6	(25.0)	.857	1.00
	13 - <=18	24	6	(25.0)	24	8	(33.3)		.752

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	AGE	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	8 - <13	24	4	(16.7)	24	8	(33.3)	.377	.318
	13 - <=18	24	4	(16.7)	24	4	(16.7)		1.00
30. NOT BEING HAPPY	8 - <13	24	3	(12.5)	24	5	(20.8)	.323	.701
	13 - <=18	24	9	(37.5)	24	7	(29.2)		.760
31. BEING SAD	8 - <13	24	2	(8.3)	24	4	(16.7)	.478	.666
	13 - <=18	24	7	(29.2)	24	7	(29.2)		1.00
32. PAYING ATTENTION	8 - <13	24	7	(29.2)	24	5	(20.8)	.779	.740
	13 - <=18	24	7	(29.2)	24	4	(16.7)		.494

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	GENDER	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	Female	22	4	(18.2)	22	5	(22.7)	.807	1.00
	Male	26	3	(11.5)	26	3	(11.5)		1.00
02. DRINKING	Female	22	4	(18.2)	22	2	(9.1)	.167	.664
	Male	26	3	(11.5)	26	6	(23.1)		.465
03. DRY MOUTH AND LIPS	Female	22	6	(27.3)	22	4	(18.2)	.594	.721
	Male	26	6	(23.1)	26	6	(23.1)		1.00
04. WETNESS IN MOUTH	Female	22	4	(18.2)	22	1	(4.5)	.256	.345
	Male	26	4	(15.4)	26	4	(15.4)		1.00
05. CONSTIPATION	Female	22	3	(13.6)	22	3	(13.6)	1.00	1.00
	Male	26	4	(15.4)	26	4	(15.4)		1.00
06. DIARRHEA	Female	22	6	(27.3)	22	3	(13.6)	.895	.457
	Male	26	10	(38.5)	26	6	(23.1)		.368
07. STOMACHACHES	Female	22	6	(27.3)	22	7	(31.8)	.961	1.00
	Male	26	8	(30.8)	26	9	(34.6)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	GENDER	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	Female	22	9	(40.9)	22	4	(18.2)	.235	.185
	Male	26	6	(23.1)	26	6	(23.1)		1.00
09. BEING SICK TO YOUR STOMACH	Female	22	8	(36.4)	22	7	(31.8)	.305	1.00
	Male	26	7	(26.9)	26	11	(42.3)		.382
10. WETTING THE BED	Female	22	2	(9.1)	22	1	(4.5)	.649	1.00
	Male	26	2	(7.7)	26	2	(7.7)		1.00
11. URINATING	Female	22	2	(9.1)	22	2	(9.1)	1.00	1.00
	Male	26	1	(3.8)	26	1	(3.8)		1.00
12. ITCHY OR SCRATCHY SKIN	Female	22	3	(13.6)	22	6	(27.3)	.116	.457
	Male	26	6	(23.1)	26	3	(11.5)		.465
13. RASHES	Female	22	4	(18.2)	22	2	(9.1)	.977	.664
	Male	26	6	(23.1)	26	3	(11.5)		.465
14. COLD OR SNIFFLES	Female	22	11	(50.0)	22	10	(45.5)	.681	1.00
	Male	26	11	(42.3)	26	12	(46.2)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	GENDER	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	Female	22	5	(22.7)	22	6	(27.3)	.800	1.00
	Male	26	6	(23.1)	26	6	(23.1)		1.00
16. DIZZINESS	Female	22	9	(40.9)	22	6	(27.3)	.163	.526
	Male	26	4	(15.4)	26	7	(26.9)		.499
17. PLAYING SPORTS	Female	22	4	(18.2)	22	2	(9.1)	.243	.664
	Male	26	3	(11.5)	26	5	(19.2)		.703
18. SHAKINESS	Female	22	8	(36.4)	22	4	(18.2)	.676	.310
	Male	26	3	(11.5)	26	2	(7.7)		1.00
19. PRONOUNCING WORDS	Female	22	4	(18.2)	22	3	(13.6)	.763	1.00
	Male	26	4	(15.4)	26	4	(15.4)		1.00
20. DOING THINGS WITH YOUR HANDS	Female	22	3	(13.6)	22	2	(9.1)	.567	1.00
	Male	26	6	(23.1)	26	7	(26.9)		1.00
21. SITTING STILL	Female	22	6	(27.3)	22	6	(27.3)	.837	1.00
	Male	26	8	(30.8)	26	7	(26.9)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	GENDER	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	Female	22	6	(27.3)	22	5	(22.7)	.384	1.00
	Male	26	6	(23.1)	26	9	(34.6)		.541
23. FEELING SLEEPY	Female	22	6	(27.3)	22	5	(22.7)	.873	1.00
	Male	26	8	(30.8)	26	6	(23.1)		.755
24. SLEEPING	Female	22	10	(45.5)	22	6	(27.3)	.186	.347
	Male	26	7	(26.9)	26	9	(34.6)		.764
25. BAD DREAMS	Female	22	5	(22.7)	22	7	(31.8)	.170	.736
	Male	26	5	(19.2)	26	2	(7.7)		.419
26. GETTING ALONG WITH PARENTS	Female	22	5	(22.7)	22	6	(27.3)	.498	1.00
	Male	26	8	(30.8)	26	6	(23.1)		.755
27. GETTING ALONG WITH KIDS	Female	22	6	(27.3)	22	5	(22.7)	.627	1.00
	Male	26	5	(19.2)	26	6	(23.1)		1.00
28. CRYING	Female	22	7	(31.8)	22	7	(31.8)	.458	1.00
	Male	26	4	(15.4)	26	7	(26.9)		.499

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

Table 12.10. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (concluded)

SECL Event - Have you had trouble with:	GENDER	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	Female	22	5	(22.7)	22	7	(31.8)	.893	.736
	Male	26	3	(11.5)	26	5	(19.2)		.703
30. NOT BEING HAPPY	Female	22	7	(31.8)	22	7	(31.8)	1.00	1.00
	Male	26	5	(19.2)	26	5	(19.2)		1.00
31. BEING SAD	Female	22	4	(18.2)	22	5	(22.7)	.961	1.00
	Male	26	5	(19.2)	26	6	(23.1)		1.00
32. PAYING ATTENTION	Female	22	6	(27.3)	22	4	(18.2)	.918	.721
	Male	26	8	(30.8)	26	5	(19.2)		.523

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM033)
RMP.B1YO.X065REP(CUSEM033)

12.7. Additional Analyses

As discussed in Section 9.4.2, study medication for this trial was provided from two sources. Fifty-four patients (25 fluoxetine-treated, 29 placebo-treated) received blinded study medication prepared by the pharmacy at [redacted] (site-prepared). Forty-two patients (23 fluoxetine-treated, 19 placebo-treated) received blinded study medication prepared by Eli Lilly and Company (Lilly-provided). An additional subgroup analysis was performed for treatment-emergent solicited adverse events (Table 12.11).

A statistically significant difference across study medication subgroups was observed for four treatment-emergent solicited adverse events when comparing between-strata differences based on the Breslow-Day test. The odds ratio p-values were statistically significant for dry mouth and lips (p=.047), constipation (p=.045), diarrhea (p=.006), and muscle cramps (p=.037).

The within strata p-values for dry mouth and lips and constipation were not statistically significant for either of the comparisons. Overall, the within strata p-values were not statistically significant for the subgroup of patients who received Lilly-provided study medication, except for diarrhea and muscle cramps.

The treatment effect of fluoxetine was consistent for patients who received either method of preparing study medication for all of the treatment-emergent solicited adverse events.

Table 12.11. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis by Study Medication
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065

SECL Event - Have you had trouble with:	STUDY MEDICATION	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
01. EATING	Lilly	23	4	(17.4)	19	2	(10.5)	.301	.673
	Site	25	3	(12.0)	29	6	(20.7)		.480
02. DRINKING	Lilly	23	4	(17.4)	19	2	(10.5)	.301	.673
	Site	25	3	(12.0)	29	6	(20.7)		.480
03. DRY MOUTH AND LIPS	Lilly	23	9	(39.1)	19	3	(15.8)	.047	.169
	Site	25	3	(12.0)	29	7	(24.1)		.309
04. WETNESS IN MOUTH	Lilly	23	4	(17.4)	19	1	(5.3)	.398	.356
	Site	25	4	(16.0)	29	4	(13.8)		1.00
05. CONSTIPATION	Lilly	23	5	(21.7)	19	1	(5.3)	.045	.197
	Site	25	2	(8.0)	29	6	(20.7)		.262
06. DIARRHEA	Lilly	23	11	(47.8)	19	1	(5.3)	.006	.005
	Site	25	5	(20.0)	29	8	(27.6)		.545
07. STOMACHACHES	Lilly	23	8	(34.8)	19	6	(31.6)	.465	1.00
	Site	25	6	(24.0)	29	10	(34.5)		.552

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM072)
RMP.B1YO.X065REP(CUSEM072)

Table 12.11. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis by Study Medication
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	STUDY MEDICATION	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
08. MUSCLE CRAMPS	Lilly	23	11	(47.8)	19	3	(15.8)	.037	.048
	Site	25	4	(16.0)	29	7	(24.1)		.517
09. BEING SICK TO YOUR STOMACH	Lilly	23	10	(43.5)	19	7	(36.8)	.188	.757
	Site	25	5	(20.0)	29	11	(37.9)		.232
10. WETTING THE BED	Lilly	23	3	(13.0)	19	1	(5.3)	.356	.613
	Site	25	1	(4.0)	29	2	(6.9)		1.00
11. URINATING	Lilly	23	3	(13.0)	19	1	(5.3)	.112	.613
	Site	25	0		29	2	(6.9)		.493
12. ITCHY OR SCRATCHY SKIN	Lilly	23	5	(21.7)	19	2	(10.5)	.222	.428
	Site	25	4	(16.0)	29	7	(24.1)		.517
13. RASHES	Lilly	23	5	(21.7)	19	2	(10.5)	.943	.428
	Site	25	5	(20.0)	29	3	(10.3)		.449
14. COLD OR SNIFFLES	Lilly	23	11	(47.8)	19	9	(47.4)	.950	1.00
	Site	25	11	(44.0)	29	13	(44.8)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM072)
RMP.B1YO.X065REP(CUSEM072)

Table 12.11. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis by Study Medication
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	STUDY MEDICATION	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
15. HEADACHE	Lilly	23	8	(34.8)	19	6	(31.6)	.431	1.00
	Site	25	3	(12.0)	29	6	(20.7)		.480
16. DIZZINESS	Lilly	23	6	(26.1)	19	6	(31.6)	.612	.742
	Site	25	7	(28.0)	29	7	(24.1)		.766
17. PLAYING SPORTS	Lilly	23	4	(17.4)	19	3	(15.8)	.814	1.00
	Site	25	3	(12.0)	29	4	(13.8)		1.00
18. SHAKINESS	Lilly	23	5	(21.7)	19	0		.076	.053
	Site	25	6	(24.0)	29	6	(20.7)		1.00
19. PRONOUNCING WORDS	Lilly	23	4	(17.4)	19	2	(10.5)	.569	.673
	Site	25	4	(16.0)	29	5	(17.2)		1.00
20. DOING THINGS WITH YOUR HANDS	Lilly	23	5	(21.7)	19	1	(5.3)	.067	.197
	Site	25	4	(16.0)	29	8	(27.6)		.347
21. SITTING STILL	Lilly	23	5	(21.7)	19	5	(26.3)	.492	1.00
	Site	25	9	(36.0)	29	8	(27.6)		.566

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM072)
RMP.B1YO.X065REP(CUSEM072)

Table 12.11. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis by Study Medication
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (continued)

SECL Event - Have you had trouble with:	STUDY MEDICATION	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
22. TIREDNESS	Lilly	23	5	(21.7)	19	2	(10.5)	.168	.428
	Site	25	7	(28.0)	29	12	(41.4)		.395
23. FEELING SLEEPY	Lilly	23	6	(26.1)	19	1	(5.3)	.104	.105
	Site	25	8	(32.0)	29	10	(34.5)		1.00
24. SLEEPING	Lilly	23	9	(39.1)	19	4	(21.1)	.208	.317
	Site	25	8	(32.0)	29	11	(37.9)		.777
25. BAD DREAMS	Lilly	23	5	(21.7)	19	3	(15.8)	.679	.709
	Site	25	5	(20.0)	29	6	(20.7)		1.00
26. GETTING ALONG WITH PARENTS	Lilly	23	6	(26.1)	19	4	(21.1)	.786	1.00
	Site	25	7	(28.0)	29	8	(27.6)		1.00
27. GETTING ALONG WITH KIDS	Lilly	23	5	(21.7)	19	4	(21.1)	.961	1.00
	Site	25	6	(24.0)	29	7	(24.1)		1.00
28. CRYING	Lilly	23	5	(21.7)	19	3	(15.8)	.293	.709
	Site	25	6	(24.0)	29	11	(37.9)		.380

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM072)
RMP.B1YO.X065REP(CUSEM072)

Table 12.11. Treatment-Emergent Solicited Adverse Events
Side-Effect Checklist Subgroup Analysis by Study Medication
Significant (p<.05) Difference in Odds Ratio
All Randomized Patients
B1Y-MC-X065 (concluded)

SECL Event - Have you had trouble with:	STUDY MEDICATION	Flx 20mg N	Flx 20mg n	Flx 20mg (%)	Placebo N	Placebo n	Placebo (%)	p-Values: Homogeneity of Odds Ratio p-Value*	p-Values: Between Group Comparison p-Value**
29. GETTING MAD	Lilly	23	4	(17.4)	19	2	(10.5)	.154	.673
	Site	25	4	(16.0)	29	10	(34.5)		.212
30. NOT BEING HAPPY	Lilly	23	7	(30.4)	19	5	(26.3)	.642	1.00
	Site	25	5	(20.0)	29	7	(24.1)		.755
31. BEING SAD	Lilly	23	5	(21.7)	19	3	(15.8)	.302	.709
	Site	25	4	(16.0)	29	8	(27.6)		.347
32. PAYING ATTENTION	Lilly	23	9	(39.1)	19	4	(21.1)	.482	.317
	Site	25	5	(20.0)	29	5	(17.2)		1.00

* The homogeneity of odds ratio p-Value is derived from the Breslow-Day test.
**The between group comparison within strata p-Value is from the Fisher's Exact Test.
Treatment-Emergent Solicited = was present at baseline and worsened as defined
by increase in score on the side-effect checklist or new occurrence after baseline.
RMP.B1YP.SASPGM(CUSEM072)
RMP.B1YO.X065REP(CUSEM072)

12.8. Safety Conclusions

Fluoxetine-treated patients were exposed to fluoxetine 20 mg daily for an average of 50 days during this study. Placebo-treated patients were exposed to study medication for an average of 43 days.

The most complete source of adverse event information for this study was the Side-Effects Checklist. Of the 96 randomized patients in this study, 92 (96%) reported at least one treatment-emergent solicited adverse event. Although the use of this interviewer-elicited format for collection of adverse events resulted in higher reporting percentages than those seen in adult patients, there were no statistically significant differences in the reporting of treatment-emergent solicited adverse events for any of the 30 items of the Checklist between the two treatment groups. The most frequently reported treatment-emergent solicited adverse event was cold or sniffles (46% fluoxetine, 46% placebo), which is a common complaint in this age group.

Non-solicited adverse events were also captured from source documentation; however, since severities for these events were not known, treatment-emergence could not be determined. Of the 96 randomized patients in this study, 85 (89%) reported at least one non-solicited adverse event. High reporting percentages were observed for this analysis, but these can be attributed to the fact that the analysis included all adverse events reported during the treatment period. There were no statistically significant differences in the reporting of any non-solicited adverse event between the two treatment groups. The two most frequently reported non-solicited adverse events were anxiety (38% fluoxetine, 35% placebo) and hyperkinesia (38% fluoxetine, 33% placebo). Due to the manner in which non-solicited adverse events were captured, it is uncertain as to whether these were pretreatment (randomization) events. The similar percentages of occurrence in placebo-treated and fluoxetine-treated patients strongly suggest that these adverse events are likely related to comorbid conditions and are not treatment related.

Two serious adverse events of suicide attempt occurred in patients receiving fluoxetine therapy during the study. Both events were considered to have unknown causality as determined by the principal investigator and occurred early in the study (after 12 and 15 days of therapy, respectively). One of these events resulted in study discontinuation for the patient. Four additional fluoxetine-treated patients were discontinued due to adverse events (2 for hypomania, 1 for increased impulsivity, and 1 for rash). Three of the events (hypomania, increased impulsivity, and rash) were considered possibly related to fluoxetine treatment.

There were no clinically relevant findings in the analyses of laboratory analytes or vital signs.

Subgroup analyses demonstrated that there were no clinically relevant differences in frequency of treatment-emergent solicited adverse events on the basis of age (8 to <13,

13 to ≤18), gender (male, female), or study medication type (site-prepared, Lilly-provided).

The overall safety and tolerability profile of fluoxetine in this depressed pediatric population was consistent with the profile observed in adult studies of depression.

13. Discussion and Overall Conclusions

This 8-week acute treatment study evaluated the efficacy, safety, and tolerability of fluoxetine 20 mg/day versus placebo in 96 children and adolescents rigorously diagnosed with MDD, as defined by the DSM-III-R.

This study was the first well-controlled trial published in the literature that unequivocally demonstrated the effectiveness of an antidepressant in the treatment of depressed children and adolescents. The thoroughness of the study design contributed significantly to these results. A large sample size was used and patients were rigorously evaluated over a 3-week diagnostic evaluation period, including primary and secondary comorbid diagnoses. The population studied included patients from a range of socioeconomic backgrounds. All patients in this study were self-identified as having depression, which was confirmed upon thorough clinical interview. The 1-week placebo lead-in period allowed for disqualification of placebo responders. Although a differential attrition rate was observed for placebo-treated patients, the placebo response rate in this study was similar to adult findings and was not excessively low. The demographic profile of the pediatric population studied is considered representative of the pediatric population that is currently in need of appropriate diagnosis and treatment.

Overall, the results from this study are similar to adult data in regards to observed response rates, onset of response, and the fact that the majority of patients showed improvement in their depressive symptoms after 8 weeks of treatment. Fifty-eight percent of patients randomized to fluoxetine responded as compared with only 32% of patients randomized to placebo after up to 8 weeks of treatment. There was a greater attrition rate from the placebo treatment group as compared with the fluoxetine treatment group. Despite this differential rate of attrition, LOCF analysis of mean CDRS-R total scores over time indicates that fluoxetine treatment was statistically superior to placebo treatment after 3 weeks of treatment, and that this treatment effect persisted for the duration of the study. Fluoxetine-treated patients demonstrated a statistically significant improvement in their depressive symptoms over placebo-treated patients on a variety of scales, including the CDRS-R, CGI-Severity, and CGI-Improvement, as well as individual items that comprise the CDRS-R and BPRS-C. Additionally, fluoxetine-treated patients demonstrated directional, although not statistically significant, improvement on additional categorical analyses of the CDRS-R scale and the BPRS-C, CDI, and BDI total scores as compared with placebo-treated patients. There were no statistically significant differences in the effectiveness of fluoxetine treatment for any of the subgroups analyzed, which included analyses based on age (children versus adolescents), gender (boys versus girls), and study medication type (site-prepared versus Lilly-provided).

The overall safety and tolerability profile of fluoxetine in this depressed pediatric population was consistent with the profile observed in adult studies of depression. There were no statistically significant differences in frequencies of treatment-emergent solicited

and non-solicited adverse events reported in fluoxetine-treated patients as compared with placebo-treated patients. Both methods for collection of adverse event data (solicited and non-solicited) were conservative and resulted in high reporting percentages; however, despite the conservative nature of these data collection methods, there were no statistically significant differences in the reporting of any adverse event between treatment groups. The most frequently reported treatment-emergent solicited adverse event was cold or sniffles, which is a common complaint in this population. The 2 most frequently reported non-solicited adverse events were anxiety and hyperkinesia. Because non-solicited adverse events included those present at the onset of treatment, which had the potential to include events associated with comorbid diagnoses of ADHD, oppositional and conduct disorders in these patients, it is not surprising that these events were reported in high frequency. Also, when one considers that MDD can manifest in children and adolescents as agitation, increased activity, irritability, and hyperkinesia, these reporting percentages are considered reflective of the patient population under study. There were no differences in the reporting of treatment-emergent solicited adverse events of fluoxetine treatment for any of the subgroups analyzed, which included analyses based on age, gender, and study medication type.

The findings of this study have significant public health value as they provide clear guidelines for rigorous diagnosis of pediatric patients for both primary and comorbid conditions and give guidelines for effective acute treatment of depression in this population.

14. Tables, Figures, and Graphics Not Included in Other Sections

14.1. Demographic Data Summary

No additional demographic analyses were performed.

14.2. Efficacy Data Summary

This section contains additional analyses of the CDRS-R and BPRS-C scales.

14.2.1. Additional Analyses of CDRS-R Total and Individual Item Scores

Table 14.1 presents CDRS-R response rates, where response is defined as a 50% or greater reduction in CDRS-R total score from baseline. Thirteen (27%) fluoxetine-treated patients and 9 (19%) placebo-treated patients met this criterion for response. Although the difference between the two treatment groups was not statistically significant, a greater number of fluoxetine-treated patients demonstrated improvement as compared with placebo-treated patients.

Table 14.1. CDRS-R Total Score
Number of Patients Meeting Criteria for 50% Response
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065
Outcome Variable: RESPONSE - 50% REDUCTION FROM BASELINE

		NO		YES	
Therapy	N	n	%	n	%
A. Flx 20mg	48	35	72.9	13	27.1
B. Placebo	47	38	80.9	9	19.1

COMPARISON OF TREATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.467
Pearson's chi-square test df=1	0.8	0.359
Cochran-Mantel-Haenszel general association test df=1	0.8	0.362

RMP.B1YP.JCLLIB2(EFS1EM05)
RMP.B1YO.X065REP(EFS1EM05)
XEFS0001

Table 14.2 presents CDRS-R response rates for all patients who completed at least 4 weeks of treatment, where response was defined as a 30% or greater reduction in CDRS-R total score from baseline. Twenty (59%) fluoxetine-treated patients and 14 (34%) placebo-treated patients met this criterion for response following a minimum of 4 weeks of treatment. The difference between treatment groups was statistically significant (p=.031, Fisher's exact).

Table 14.2. CDRS-R Total Score
Number of Patients Meeting Criteria for Response
Randomized Patients Treated at Least 4 Weeks
B1Y-MC-X065

Protocol: B1Y-MC-X065
Outcome Variable: RESPONSE - 30% REDUCTION FROM BASELINE

		NO		YES	
Therapy	N	n	%	n	%
A. Flx 20mg	46	19	41.3	27	58.7
B. Placebo	41	27	65.9	14	34.1

COMPARISON OF TREATMENT GROUPS

STATISTICS	P-VALUE
Fisher's exact test (2-tailed)	0.031
Pearson's chi-square test df=1	0.022
Cochran-Mantel-Haenszel general association test df=1	0.023

RMP.B1YP.JCLLIB2(EFS1EM06)
RMP.B1YO.X065REP(EFS1EM06)
XEFS0001

Table 14.3 presents the change from baseline to endpoint for the 17 individual items that comprise the CDRS-R total scores. There were statistically significant differences in favor of fluoxetine treatment for 10 of the 17 items.

Table 14.3. CDRS-R Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
CDRS01	Flx 20mg	48	4.4	1.6	-1.0	2.1	.910
	Placebo	47	4.8	1.4	-1.0	1.5	
CDRS02	Flx 20mg	48	4.3	1.1	-1.9	1.6	.003
	Placebo	47	4.1	1.1	-0.9	1.7	
CDRS03	Flx 20mg	48	3.6	1.1	-1.4	1.3	.007
	Placebo	47	3.7	1.2	-0.6	1.4	
CDRS04	Flx 20mg	48	3.8	1.2	-1.1	1.4	.266
	Placebo	47	3.6	1.2	-0.7	1.6	
CDRS05	Flx 20mg	48	3.2	1.1	-0.8	1.3	.888
	Placebo	47	3.1	1.1	-0.9	1.4	
CDRS06	Flx 20mg	48	4.4	1.5	-1.6	2.2	.011
	Placebo	47	4.1	1.4	-0.5	1.8	
CDRS07	Flx 20mg	48	4.0	1.1	-1.3	1.6	.016
	Placebo	47	3.7	1.4	-0.5	1.7	
CDRS08	Flx 20mg	48	4.4	1.3	-1.3	1.4	.067
	Placebo	47	4.6	1.1	-0.7	1.7	
CDRS09	Flx 20mg	48	2.1	1.2	-0.6	1.2	.682
	Placebo	47	2.3	1.0	-0.7	1.1	

RMP.B1YP.JCLLIB2(LAS6EM04)
RMP.B1YO.X065REP(LAS6EM04)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

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Table 14.3. CDRS-R Individual Item Scores
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (continued)

Research Project Code: B1Y

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.

XLAS0006

Table 14.3. CDRS-R Individual Item Scores
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (continued)

Legend of Variable Abbreviations:

Abbrev.	Description
CDRS01	Schoolwork
CDRS02	Fun
CDRS03	Social Withdrawal
CDRS04	Sleep
CDRS05	Appetite
CDRS06	Fatigue
CDRS07	Phyiscal Complaints
CDRS08	Irritability
CDRS09	Guilt

Table 14.3. CDRS-R Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065 (continued)

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
CDRS10	Flx 20mg	48	4.0	1.0	-1.3	1.4	.029
	Placebo	47	4.0	1.2	-0.7	1.5	
CDRS11	Flx 20mg	48	4.2	1.2	-1.8	1.6	.003
	Placebo	47	4.0	1.2	-0.7	1.6	
CDRS12	Flx 20mg	48	2.7	1.3	-1.2	1.2	.039
	Placebo	47	2.7	1.4	-0.6	1.5	
CDRS13	Flx 20mg	48	2.4	1.0	-0.4	1.0	.976
	Placebo	47	2.6	1.3	-0.4	1.4	
CDRS14	Flx 20mg	48	3.3	1.6	-1.6	1.5	.001
	Placebo	47	3.0	1.3	-0.5	1.8	
CDRS15	Flx 20mg	48	3.2	1.2	-1.1	1.4	.068
	Placebo	47	3.0	1.2	-0.6	1.3	
CDRS16	Flx 20mg	48	1.9	0.7	-0.5	0.8	.024
	Placebo	47	1.7	0.6	-0.1	0.7	
CDRS17	Flx 20mg	48	3.0	1.3	-1.2	1.3	<.001
	Placebo	47	2.4	1.0	-0.1	1.1	

RMP.B1YP.JCLLIB2(LAS6EM04)
RMP.B1YO.X065REP(LAS6EM04)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
XLAS0006

**Table 14.3. CDRS-R Individual Item Scores
Change From Baseline to Endpoint
All Randomized Patients
B1Y-MC-X065 (concluded)**

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Legend of Variable Abbreviations:
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Abbrev.     Description
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CDRS10      Self-Esteem
CDRS11      Depressed
CDRS12      Morbid Ideation
CDRS13      Sucidal
CDRS14      Weeping
CDRS15      Depressed Affect
CDRS16      Speech
CDRS17      Hypoactivity
```

Table 14.4 presents CDRS-R remission rates for all patients who completed at least 4 weeks of treatment, where remission was defined as a patient having a CDRS-R total score of ≤28 at endpoint. Fourteen (30%) fluoxetine-treated patients and 9 (22%) placebo-treated patients met this criterion for remission. Although the difference between the two treatment groups was not statistically significant, a greater number of fluoxetine-treated patients demonstrated improvement as compared with placebo-treated patients.

Table 14.4. CDRS-R Total Score
Number of Patients Meeting Criteria for Remission
Randomized Patients Treated at Least 4 Weeks
B1Y-MC-X065

Protocol: B1Y-MC-X065
Outcome Variable: REMISSION - SCORE <=28

			NO		YES	
	Therapy	N	n	%	n	%
A.	Flx 20mg	46	32	69.6	14	30.4
B.	Placebo	41	32	78.0	9	22.0

COMPARISON OF TREATMENT GROUPS

STATISTICS	VALUE	P-VALUE
Fisher's exact test (2-tailed)		0.467
Pearson's chi-square test df=1	0.8	0.370
Cochran-Mantel-Haenszel general association test df=1	0.8	0.373

RMP.B1YP.JCLLIB2(EFS1EM07)
RMP.B1YO.X065REP(EFS1EM07)
XEFS0001

14.2.2. Analysis of BPRS-C Individual Items

Table 14.5 presents the change from baseline to endpoint for the 21 items that comprise the BPRS-C Total scores. There were statistically significant differences for 5 of the 21 items in favor of fluoxetine treatment.

Table 14.5. BPRS-C Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
BPRS01	Flx 20mg	48	2.1	1.4	-0.2	1.2	.515
	Placebo	47	2.1	1.2	-0.1	1.2	
BPRS02	Flx 20mg	48	1.4	1.2	-0.4	1.1	.964
	Placebo	47	1.5	1.3	-0.4	1.7	
BPRS03	Flx 20mg	48	1.0	1.3	0.2	1.2	.266
	Placebo	47	0.7	1.1	0.5	1.4	
BPRS04	Flx 20mg	48	3.7	0.9	-1.9	1.5	<.001
	Placebo	47	3.4	1.0	-0.7	1.7	
BPRS05	Flx 20mg	48	3.0	1.0	-1.5	1.4	.002
	Placebo	47	2.9	1.0	-0.6	1.5	
BPRS06	Flx 20mg	48	0.9	1.1	-0.4	1.1	.608
	Placebo	47	0.9	1.3	-0.2	1.5	
BPRS07	Flx 20mg	48	0.1	0.4	-0.0	0.6	.566
	Placebo	47	0.2	0.7	-0.1	0.8	

RMP.B1YP.JCLLIB2(LAS6EM06)
RMP.B1YO.X065REP(LAS6EM06)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
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Table 14.5. BPRS-C Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065 (continued)

Legend of Variable Abbreviations:

Abbrev.	Description
BPRS01	Uncooperativeness
BPRS02	Hospitilty
BPRS03	Manipulativeness
BPRS04	Depressive Mood
BPRS05	Feelings of Inferiority
BPRS06	Suicidal Ideation
BPRS07	Peculiar Fantasis

Table 14.5. BPRS-C Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065 (continued)

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
BPRS08	Flx 20mg	48	0.1	0.5	-0.1	0.5	.682
	Placebo	47	0.1	0.4	-0.1	0.4	
BPRS09	Flx 20mg	48	0.2	0.7	-0.1	0.8	.697
	Placebo	47	0.1	0.6	-0.1	0.8	
BPRS10	Flx 20mg	48	0.9	1.2	0.4	1.4	<.001
	Placebo	47	1.1	1.3	-0.5	1.0	
BPRS11	Flx 20mg	48	2.6	1.2	-0.4	1.4	.679
	Placebo	47	2.7	1.2	-0.6	1.3	
BPRS12	Flx 20mg	48	0.0	0.1	0.2	0.7	.310
	Placebo	47	0.0	0.1	0.0	0.5	
BPRS13	Flx 20mg	48	1.8	1.1	-0.8	1.3	.032
	Placebo	47	1.5	1.1	-0.2	1.5	
BPRS14	Flx 20mg	48	2.2	1.2	-1.2	1.3	.004
	Placebo	47	1.9	1.1	-0.5	1.2	

RMP.B1YP.JCLLIB2(LAS6EM06)
RMP.B1YO.X065REP(LAS6EM06)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
XLAS0006

Table 14.5. BPRS-C Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065 (continued)

Legend of Variable Abbreviations:

Abbrev.	Description
BPRS08	Delusions
BPRS09	Hallucinations
BPRS10	Hyperactivity
BPRS11	Distractibility
BPRS12	Speech or voice pressure
BPRS13	Underproductive speech
BPRS14	Emotional withdrawal

Table 14.5. BPRS-C Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065 (continued)

Research Project Code: B1Y

Variables Analyzed	Therapy	n	Baseline Mean	Baseline SD	Change to Endpoint Mean	Change to Endpoint SD	p-Values Therapy
BPRS15	Flx 20mg	48	1.5	1.3	-0.7	1.3	.131
	Placebo	47	1.2	1.2	-0.3	1.3	
BPRS16	Flx 20mg	48	1.1	1.1	0.0	1.6	.452
	Placebo	47	1.2	1.2	-0.2	1.1	
BPRS17	Flx 20mg	48	0.9	1.3	0.1	1.7	.729
	Placebo	47	0.8	1.2	-0.0	1.1	
BPRS18	Flx 20mg	48	2.8	1.6	-1.1	1.5	.682
	Placebo	47	2.7	1.4	-1.0	1.9	
BPRS19	Flx 20mg	47	0.0	0.0	0.0	0.0	.320
	Placebo	47	0.0	0.1	-0.0	0.1	
BPRS20	Flx 20mg	48	0.1	0.9	-0.1	0.9	.420
	Placebo	47	0.0	0.1	-0.0	0.1	
BPRS21	Flx 20mg	48	0.0	0.0	0.0	0.0	.315
	Placebo	47	0.1	0.4	-0.1	0.4	

RMP.B1YP.JCLLIB2(LAS6EM06)
RMP.B1YO.X065REP(LAS6EM06)
Note: n = Total number of patients in each treatment group having the variable in both baseline and postbaseline visits.

Note: Models:

FULL1 - Type III Sums of Squares from an analysis of variance (ANOVA): PROC GLM model=treatment.
Least-squares mean option in PROC GLM from the ANOVA using the mean square for error.
XLAS0006

Table 14.5. BPRS-C Individual Item Scores Change From Baseline to Endpoint All Randomized Patients B1Y-MC-X065 (concluded)

Legend of Variable Abbreviations:

Abbrev.	Description
BPRS15	Blunted Affect
BPRS16	Tension
BPRS17	Anxiety
BPRS18	Sleep Difficulties
BPRS19	Disorientation
BPRS20	Speech Deviance
BPRS21	Stereotypy

14.3. Safety Data Summary

This section contains additional analyses of adverse events and laboratory analytes.

14.3.1. Displays of Adverse Events

14.3.1.1. Additional Analyses of Treatment-Emergent Solicited Adverse Events

The Side-Effects Checklist scored intensity as displayed in Table 14.6.

Table 14.6. Intensity Scores from the Side-Effects Checklist B1Y-MC-X065

Term on Side-Effects Checklist	Value on the Checklist
Not at all	0
Just a little	1
Pretty much	2
Very much	3
Don't know	4

Data for this table were taken from the Side-Effects Checklist shown in Appendix 16.1.2.
For the analysis presented in Table 12.3, a score of "don't know = 4" was set to "not at all = 0." For the analysis presented in Table 14.7, a score of "don't know = 4" was set to "missing."

Treatment-emergent solicited adverse events are those events which first occurred or worsened (as defined by increase in intensity score on the Side-Effects Checklist) after initiation of treatment. Adverse events were coded using the terms specified on the Side-Effects Checklist.

For the primary analysis of the Side-Effects Checklist (see Table 12.3), the intensity score of "don't know = 4" was set to "not at all = 0." Treatment-emergent solicited adverse events were also evaluated using a more conservative method of determining treatment-emergence (see Table 14.7). In this analysis, the intensity score of "don't know = 4" was set to "missing." "Missing" values for a known event were then assumed to have an intensity score based on whether the event occurred at baseline or postbaseline. Baseline events were assigned an intensity score of 1 and postbaseline events were assigned an intensity score of 3. Treatment-emergence for these events was determined using these values. There were no statistically significant differences between treatment groups in this analysis, nor were there any differences in the conclusions from these two analyses.

Table 14.7. Treatment-Emergent Solicited Adverse Events - Method 2 Side-Effects Checklist Incidence by Decreasing Frequency (Ordered by Fluoxetine) All Randomized Patients B1Y-MC-X065

Event Classification	Flx 20mg (N=48) n (%)	Placebo (N=48) n (%)	Total (N=96) n (%)	p-Value*
PATIENTS WITH >= 1 TESS	47 (97.9)	45 (93.8)	92 (95.8)	.617
PATIENTS WITH NO TESS	1 (2.1)	3 (6.3)	4 (4.2)	.617
14. COLD OR SNIFFLES	22 (45.8)	22 (45.8)	44 (45.8)	1.00
24. SLEEPING	17 (35.4)	15 (31.3)	32 (33.3)	.829
06. DIARRHEA	16 (33.3)	9 (18.8)	25 (26.0)	.162
08. MUSCLE CRAMPS	15 (31.3)	11 (22.9)	26 (27.1)	.491
09. BEING SICK TO YOUR STOMACH	15 (31.3)	18 (37.5)	33 (34.4)	.668
07. STOMACHACHES	14 (29.2)	16 (33.3)	30 (31.3)	.826
21. SITTING STILL	14 (29.2)	13 (27.1)	27 (28.1)	1.00
23. FEELING SLEEPY	14 (29.2)	11 (22.9)	25 (26.0)	.642
26. GETTING ALONG WITH PARENTS	14 (29.2)	12 (25.0)	26 (27.1)	.819
32. PAYING ATTENTION	14 (29.2)	10 (20.8)	24 (25.0)	.480
03. DRY MOUTH AND LIPS	13 (27.1)	10 (20.8)	23 (24.0)	.633
16. DIZZINESS	13 (27.1)	14 (29.2)	27 (28.1)	1.00
18. SHAKINESS	12 (25.0)	7 (14.6)	19 (19.8)	.306
22. TIREDNESS	12 (25.0)	15 (31.3)	27 (28.1)	.650
25. BAD DREAMS	12 (25.0)	10 (20.8)	22 (22.9)	.809
28. CRYING	12 (25.0)	15 (31.3)	27 (28.1)	.650
30. NOT BEING HAPPY	12 (25.0)	13 (27.1)	25 (26.0)	1.00
15. HEADACHE	11 (22.9)	12 (25.0)	23 (24.0)	1.00
27. GETTING ALONG WITH KIDS	11 (22.9)	11 (22.9)	22 (22.9)	1.00
13. RASHES	10 (20.8)	5 (10.4)	15 (15.6)	.261
12. ITCHY OR SCRATCHY SKIN	9 (18.8)	9 (18.8)	18 (18.8)	1.00
19. PRONOUNCING WORDS	9 (18.8)	8 (16.7)	17 (17.7)	1.00
20. DOING THINGS WITH YOUR HANDS	9 (18.8)	9 (18.8)	18 (18.8)	1.00
31. BEING SAD	9 (18.8)	12 (25.0)	21 (21.9)	.622
04. WETNESS IN MOUTH	8 (16.7)	8 (16.7)	16 (16.7)	1.00
29. GETTING MAD	8 (16.7)	12 (25.0)	20 (20.8)	.452
01. EATING	7 (14.6)	8 (16.7)	15 (15.6)	1.00
02. DRINKING	7 (14.6)	8 (16.7)	15 (15.6)	1.00
05. CONSTIPATION	7 (14.6)	9 (18.8)	16 (16.7)	.785
17. PLAYING SPORTS	6 (12.5)	7 (14.6)	13 (13.5)	1.00
10. WETTING THE BED	4 (8.3)	3 (6.3)	7 (7.3)	1.00
11. URINATING	3 (6.3)	3 (6.3)	6 (6.3)	1.00

1 Treatment-Emergent Solicited = was present at baseline and worsened as defined by increase in score on the side-effect checklist or new occurrence after baseline. Baseline is the highest score of item at visits 1 and 2.
RMP.B1YP.JCLLIB2(AES2EM28)
RMP.B1YO.X065REP(AES2EM28)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0002

Treatment-emergent solicited adverse events were also analyzed by maximum intensity (see Table 14.8). The Side-Effects Checklist measured intensity, rather than severity, as is typically done in Lilly-sponsored trials. An intensity score of "1," which meant the event occurred "just a little" (according to the Side-Effects Checklist), was mapped to the term "mild" for severity analysis in Lilly's system. Similarly, a score of "2" (pretty much) mapped to moderate, and a score of "3" (very much) mapped to severe. There were no statistically significant differences between treatment groups in the incidence of

treatment-emergent solicited adverse events that were classified as "severe," ie, those that occurred the most frequently (very much).

Table 14.8. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist By Maximum Intensity All Randomized Patients B1Y-MC-X065

Maximum Severity	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
PATIENTS WITH >= 1 TESS							
Mild	6	(12.5)	7	(14.6)	13	(13.5)	
Moderate	12	(25.0)	7	(14.6)	19	(19.8)	
Severe	29	(60.4)	31	(64.6)	60	(62.5)	.833
Total	47	(97.9)	45	(93.8)	92	(95.8)	.617
14. COLD OR SNIFFLES							
Mild	6	(12.5)	6	(12.5)	12	(12.5)	
Moderate	7	(14.6)	7	(14.6)	14	(14.6)	
Severe	9	(18.8)	9	(18.8)	18	(18.8)	1.00
Total	22	(45.8)	22	(45.8)	44	(45.8)	1.00
24. SLEEPING							
Mild	4	(8.3)	5	(10.4)	9	(9.4)	
Moderate	4	(8.3)	1	(2.1)	5	(5.2)	
Severe	9	(18.8)	9	(18.8)	18	(18.8)	1.00
Total	17	(35.4)	15	(31.3)	32	(33.3)	.829
06. DIARRHEA							
Mild	10	(20.8)	4	(8.3)	14	(14.6)	
Moderate	2	(4.2)	2	(4.2)	4	(4.2)	
Severe	4	(8.3)	3	(6.3)	7	(7.3)	1.00
Total	16	(33.3)	9	(18.8)	25	(26.0)	.162
08. MUSCLE CRAMPS							
Mild	7	(14.6)	3	(6.3)	10	(10.4)	
Moderate	3	(6.3)	4	(8.3)	7	(7.3)	
Severe	5	(10.4)	3	(6.3)	8	(8.3)	.714
Total	15	(31.3)	10	(20.8)	25	(26.0)	.352

RMP.B1YP.JCLLIB2(AES8EM40)
RMP.B1YO.X065REP(AES8EM40)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.8. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist By Maximum Intensity All Randomized Patients B1Y-MC-X065 (continued)

Maximum Severity	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
09. BEING SICK TO YOUR STOMACH							
Mild	5	(10.4)	7	(14.6)	12	(12.5)	
Moderate	4	(8.3)	4	(8.3)	8	(8.3)	
Severe	6	(12.5)	7	(14.6)	13	(13.5)	1.00
Total	15	(31.3)	18	(37.5)	33	(34.4)	.668
07. STOMACHACHES							
Mild	5	(10.4)	4	(8.3)	9	(9.4)	
Moderate	4	(8.3)	7	(14.6)	11	(11.5)	
Severe	5	(10.4)	5	(10.4)	10	(10.4)	1.00
Total	14	(29.2)	16	(33.3)	30	(31.3)	.826
21. SITTING STILL							
Mild	6	(12.5)	3	(6.3)	9	(9.4)	
Moderate	3	(6.3)	4	(8.3)	7	(7.3)	
Severe	5	(10.4)	6	(12.5)	11	(11.5)	1.00
Total	14	(29.2)	13	(27.1)	27	(28.1)	1.00
23. FEELING SLEEPY							
Mild	2	(4.2)	2	(4.2)	4	(4.2)	
Moderate	7	(14.6)	3	(6.3)	10	(10.4)	
Severe	5	(10.4)	6	(12.5)	11	(11.5)	1.00
Total	14	(29.2)	11	(22.9)	25	(26.0)	.642
32. PAYING ATTENTION							
Mild	3	(6.3)	1	(2.1)	4	(4.2)	
Moderate	2	(4.2)	6	(12.5)	8	(8.3)	
Severe	9	(18.8)	2	(4.2)	11	(11.5)	.051
Total	14	(29.2)	9	(18.8)	23	(24.0)	.339

RMP.B1YP.JCLLIB2(AES8EM40)
RMP.B1YO.X065REP(AES8EM40)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.8. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist By Maximum Intensity All Randomized Patients B1Y-MC-X065 (continued)

Maximum Severity	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
16. DIZZINESS							
Mild	4	(8.3)	5	(10.4)	9	(9.4)	
Moderate	2	(4.2)	2	(4.2)	4	(4.2)	
Severe	7	(14.6)	6	(12.5)	13	(13.5)	1.00
Total	13	(27.1)	13	(27.1)	26	(27.1)	1.00
26. GETTING ALONG WITH PARENTS							
Mild	2	(4.2)	3	(6.3)	5	(5.2)	
Moderate	3	(6.3)	6	(12.5)	9	(9.4)	
Severe	8	(16.7)	3	(6.3)	11	(11.5)	.199
Total	13	(27.1)	12	(25.0)	25	(26.0)	1.00
03. DRY MOUTH AND LIPS							
Mild	6	(12.5)	3	(6.3)	9	(9.4)	
Moderate	3	(6.3)	3	(6.3)	6	(6.3)	
Severe	3	(6.3)	4	(8.3)	7	(7.3)	1.00
Total	12	(25.0)	10	(20.8)	22	(22.9)	.809
22. TIREDNESS							
Mild	2	(4.2)	3	(6.3)	5	(5.2)	
Moderate	7	(14.6)	4	(8.3)	11	(11.5)	
Severe	3	(6.3)	7	(14.6)	10	(10.4)	.317
Total	12	(25.0)	14	(29.2)	26	(27.1)	.819
30. NOT BEING HAPPY							
Mild	1	(2.1)	2	(4.2)	3	(3.1)	
Moderate	4	(8.3)	4	(8.3)	8	(8.3)	
Severe	7	(14.6)	6	(12.5)	13	(13.5)	1.00
Total	12	(25.0)	12	(25.0)	24	(25.0)	1.00

RMP.B1YP.JCLLIB2(AES8EM40)
RMP.B1YO.X065REP(AES8EM40)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.8. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist By Maximum Intensity All Randomized Patients B1Y-MC-X065 (continued)

Maximum Severity	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
15. HEADACHE							
Mild	6	(12.5)	3	(6.3)	9	(9.4)	
Moderate	2	(4.2)	2	(4.2)	4	(4.2)	
Severe	3	(6.3)	7	(14.6)	10	(10.4)	.317
Total	11	(22.9)	12	(25.0)	23	(24.0)	1.00
18. SHAKINESS							
Mild	3	(6.3)	2	(4.2)	5	(5.2)	
Moderate	3	(6.3)	2	(4.2)	5	(5.2)	
Severe	5	(10.4)	2	(4.2)	7	(7.3)	.435
Total	11	(22.9)	6	(12.5)	17	(17.7)	.285
27. GETTING ALONG WITH KIDS							
Mild	4	(8.3)	5	(10.4)	9	(9.4)	
Moderate	3	(6.3)	3	(6.3)	6	(6.3)	
Severe	4	(8.3)	3	(6.3)	7	(7.3)	1.00
Total	11	(22.9)	11	(22.9)	22	(22.9)	1.00
28. CRYING							
Mild	3	(6.3)	4	(8.3)	7	(7.3)	
Moderate	5	(10.4)	5	(10.4)	10	(10.4)	
Severe	3	(6.3)	5	(10.4)	8	(8.3)	.714
Total	11	(22.9)	14	(29.2)	25	(26.0)	.642
13. RASHES							
Mild	4	(8.3)	2	(4.2)	6	(6.3)	
Moderate	1	(2.1)	1	(2.1)	2	(2.1)	
Severe	5	(10.4)	2	(4.2)	7	(7.3)	.435
Total	10	(20.8)	5	(10.4)	15	(15.6)	.261

RMP.B1YP.JCLLIB2(AES8EM40)
RMP.B1YO.X065REP(AES8EM40)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.8. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist By Maximum Intensity All Randomized Patients B1Y-MC-X065 (continued)

Maximum Severity	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
25. BAD DREAMS							
Mild	4	(8.3)	2	(4.2)	6	(6.3)	
Moderate	1	(2.1)	3	(6.3)	4	(4.2)	
Severe	5	(10.4)	4	(8.3)	9	(9.4)	1.00
Total	10	(20.8)	9	(18.8)	19	(19.8)	1.00
12. ITCHY OR SCRATCHY SKIN							
Mild	2	(4.2)	6	(12.5)	8	(8.3)	
Moderate	2	(4.2)	1	(2.1)	3	(3.1)	
Severe	5	(10.4)	2	(4.2)	7	(7.3)	.435
Total	9	(18.8)	9	(18.8)	18	(18.8)	1.00
20. DOING THINGS WITH YOUR HANDS							
Mild	4	(8.3)	3	(6.3)	7	(7.3)	
Moderate	2	(4.2)	3	(6.3)	5	(5.2)	
Severe	3	(6.3)	3	(6.3)	6	(6.3)	1.00
Total	9	(18.8)	9	(18.8)	18	(18.8)	1.00
31. BEING SAD							
Mild	3	(6.3)	4	(8.3)	7	(7.3)	
Moderate	3	(6.3)	1	(2.1)	4	(4.2)	
Severe	3	(6.3)	6	(12.5)	9	(9.4)	.486
Total	9	(18.8)	11	(22.9)	20	(20.8)	.802
04. WETNESS IN MOUTH							
Mild	7	(14.6)	1	(2.1)	8	(8.3)	
Moderate	0		2	(4.2)	2	(2.1)	
Severe	1	(2.1)	2	(4.2)	3	(3.1)	1.00
Total	8	(16.7)	5	(10.4)	13	(13.5)	.552

RMP.B1YP.JCLLIB2(AES8EM40)
RMP.B1YO.X065REP(AES8EM40)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.8. Treatment-Emergent Solicited Adverse Events Side-Effects Checklist By Maximum Intensity All Randomized Patients B1Y-MC-X065 (continued)

Maximum Severity	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
19. PRONOUNCING WORDS							
Mild	2	(4.2)	4	(8.3)	6	(6.3)	
Moderate	3	(6.3)	2	(4.2)	5	(5.2)	
Severe	3	(6.3)	1	(2.1)	4	(4.2)	.617
Total	8	(16.7)	7	(14.6)	15	(15.6)	1.00
29. GETTING MAD							
Mild	2	(4.2)	4	(8.3)	6	(6.3)	
Moderate	3	(6.3)	3	(6.3)	6	(6.3)	
Severe	3	(6.3)	5	(10.4)	8	(8.3)	.714
Total	8	(16.7)	12	(25.0)	20	(20.8)	.452
01. EATING							
Mild	1	(2.1)	2	(4.2)	3	(3.1)	
Moderate	2	(4.2)	3	(6.3)	5	(5.2)	
Severe	4	(8.3)	3	(6.3)	7	(7.3)	1.00
Total	7	(14.6)	8	(16.7)	15	(15.6)	1.00
02. DRINKING							
Mild	0		1	(2.1)	1	(1.0)	
Moderate	4	(8.3)	4	(8.3)	8	(8.3)	
Severe	3	(6.3)	3	(6.3)	6	(6.3)	1.00
Total	7	(14.6)	8	(16.7)	15	(15.6)	1.00
05. CONSTIPATION							
Mild	4	(8.3)	5	(10.4)	9	(9.4)	
Moderate	0		1	(2.1)	1	(1.0)	
Severe	3	(6.3)	1	(2.1)	4	(4.2)	.617
Total	7	(14.6)	7	(14.6)	14	(14.6)	1.00

RMP.B1YP.JCLLIB2(AES8EM40)
RMP.B1YO.X065REP(AES8EM40)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

Table 14.8. Treatment-Emergent Solicited Adverse Events
Side-Effects Checklist
By Maximum Intensity
All Randomized Patients
B1Y-MC-X065 (concluded)

Maximum Severity	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)	Total (N=96) n	(%)	p-Value*
17. PLAYING SPORTS							
Mild	2	(4.2)	4	(8.3)	6	(6.3)	
Moderate	1	(2.1)	3	(6.3)	4	(4.2)	
Severe	4	(8.3)	0		4	(4.2)	.117
Total	7	(14.6)	7	(14.6)	14	(14.6)	1.00
10. WETTING THE BED							
Mild	2	(4.2)	1	(2.1)	3	(3.1)	
Moderate	0		1	(2.1)	1	(1.0)	
Severe	2	(4.2)	1	(2.1)	3	(3.1)	1.00
Total	4	(8.3)	3	(6.3)	7	(7.3)	1.00
11. URINATING							
Mild	1	(2.1)	3	(6.3)	4	(4.2)	
Moderate	1	(2.1)	0		1	(1.0)	
Severe	1	(2.1)	0		1	(1.0)	1.00
Total	3	(6.3)	3	(6.3)	6	(6.3)	1.00

RMP.B1YP.JCLLIB2(AES8EM40)
RMP.B1YO.X065REP(AES8EM40)
* Frequencies are analyzed using a Fisher's Exact test.
XAES0008

14.3.1.2. Additional Analysis of Non-Solicited Adverse Events

The incidence of non-solicited adverse events by body system is presented in Table 14.9. The majority of non-solicited adverse events captured affected the nervous system (fluoxetine 69%, placebo 65%), with anxiety (fluoxetine 38%, placebo 35%) and hyperkinesia (fluoxetine 38%, placebo 33%) being the most common complaints. Adverse events affecting the body as a whole occurred in 46% of fluoxetine-treated and 40% of placebo-treated patients. The most common events were flu syndrome (fluoxetine 10%, placebo 8%) and headache (fluoxetine 10%, placebo 8%). Respiratory adverse events occurred in 42% of fluoxetine-treated and 27% of placebo-treated patients, with the most common event being pharyngitis (fluoxetine 25%, placebo 15%). Complaints involving the digestive system were reported by 33% of fluoxetine-treated and 17% of placebo-treated patients. The most common events were vomiting (fluoxetine 15%, placebo 4%) and nausea (fluoxetine 13%, placebo 4%). The event of rash (fluoxetine 10%, placebo 6%) was the only notable event of the skin and appendages body system and urinary incontinence (fluoxetine 6%, placebo 6%) was the only notable event of the urogenital system. The incidence of adverse events in the remaining body systems was <10% for both treatment groups.

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065

Body System: Overall

Event Classification	Flx 20mg (N=48) n (%)	Placebo (N=48) n (%)
PATIENTS WITH >= 1 EVENT	46 (95.8)	39 (81.3)
PATIENTS WITH NO EVENTS	2 (4.2)	9 (18.8)

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: BODY AS A WHOLE

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	22	(45.8)	19	(39.6)
PATIENTS WITH NO EVENTS	26	(54.2)	29	(60.4)
FLU SYNDROME	5	(10.4)	4	(8.3)
HEADACHE	5	(10.4)	4	(8.3)
PAIN	5	(10.4)	4	(8.3)
ABDOMINAL PAIN	4	(8.3)	3	(6.3)
FEVER	4	(8.3)	2	(4.2)
MALAISE	4	(8.3)	2	(4.2)
INFECTION	3	(6.3)	2	(4.2)
ALLERGIC REACTION	0		4	(8.3)
ACCIDENTAL INJURY	2	(4.2)	1	(2.1)
UNEXPECTED BENEFIT	2	(4.2)	1	(2.1)
ASTHENIA	1	(2.1)	1	(2.1)
CHEST PAIN	2	(4.2)	0	
PHOTOSENSITIVITY REACTION	0		2	(4.2)

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: BODY AS A WHOLE

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
SUICIDE ATTEMPT	2	(4.2)	0	
BACK PAIN	1	(2.1)	0	
CHILLS	0		1	(2.1)

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: CARDIOVASCULAR SYSTEM

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	3	(6.3)	2	(4.2)
PATIENTS WITH NO EVENTS	45	(93.8)	46	(95.8)
VASODILATATION	1	(2.1)	1	(2.1)
MIGRAINE	1	(2.1)	0	
PALLOR	1	(2.1)	0	
QT INTERVAL PROLONGED	0		1	(2.1)

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: DIGESTIVE SYSTEM

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	16	(33.3)	8	(16.7)
PATIENTS WITH NO EVENTS	32	(66.7)	40	(83.3)
VOMITING	7	(14.6)	2	(4.2)
NAUSEA	6	(12.5)	2	(4.2)
DIARRHEA	5	(10.4)	0	
ANOREXIA	1	(2.1)	1	(2.1)
DRY MOUTH	1	(2.1)	1	(2.1)
INCREASED APPETITE	0		2	(4.2)
CONSTIPATION	1	(2.1)	0	
GASTROENTERITIS	1	(2.1)	0	
GASTROINTESTINAL DISORDER	1	(2.1)	0	
TOOTH DISORDER	1	(2.1)	0	

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: MUSCULOSKELETAL SYSTEM

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	4	(8.3)	4	(8.3)
PATIENTS WITH NO EVENTS	44	(91.7)	44	(91.7)
MYALGIA	2	(4.2)	2	(4.2)
LEG CRAMPS	1	(2.1)	1	(2.1)
ARTHRALGIA	0		1	(2.1)
BONE PAIN	1	(2.1)	0	

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: NERVOUS SYSTEM

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	33	(68.8)	31	(64.6)
PATIENTS WITH NO EVENTS	15	(31.3)	17	(35.4)
ANXIETY	18	(37.5)	17	(35.4)
HYPERKINESIA	18	(37.5)	16	(33.3)
DEPRESSION	9	(18.8)	8	(16.7)
NERVOUSNESS	3	(6.3)	5	(10.4)
DIZZINESS	2	(4.2)	5	(10.4)
NEUROSIS	5	(10.4)	2	(4.2)
MANIC REACTION	4	(8.3)	2	(4.2)
ABNORMAL DREAMS	2	(4.2)	2	(4.2)
INSOMNIA	3	(6.3)	1	(2.1)
SOMNOLENCE	3	(6.3)	1	(2.1)
THINKING ABNORMAL	1	(2.1)	2	(4.2)
AGITATION	0		2	(4.2)
AKATHISIA	1	(2.1)	1	(2.1)

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: NERVOUS SYSTEM

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
TREMOR	1	(2.1)	1	(2.1)
ADDICTION	0		1	(2.1)
AMNESIA	0		1	(2.1)
DEPERSONALIZATION	1	(2.1)	0	
EMOTIONAL LABILITY	0		1	(2.1)
HOSTILITY	0		1	(2.1)
PERSONALITY DISORDER	1	(2.1)	0	
SLEEP DISORDER	1	(2.1)	0	

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: RESPIRATORY SYSTEM

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	20	(41.7)	13	(27.1)
PATIENTS WITH NO EVENTS	28	(58.3)	35	(72.9)
PHARYNGITIS	12	(25.0)	7	(14.6)
RHINITIS	3	(6.3)	4	(8.3)
COUGH INCREASED	3	(6.3)	2	(4.2)
SINUSITIS	3	(6.3)	0	
ASTHMA	1	(2.1)	1	(2.1)
BRONCHITIS	1	(2.1)	0	
DYSPNEA	1	(2.1)	0	
EPISTAXIS	1	(2.1)	0	
LARYNGITIS	1	(2.1)	0	
PNEUMONIA	1	(2.1)	0	
YAWN	0		1	(2.1)

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: SKIN AND APPENDAGES

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	8	(16.7)	5	(10.4)
PATIENTS WITH NO EVENTS	40	(83.3)	43	(89.6)
RASH	5	(10.4)	3	(6.3)
ACNE	1	(2.1)	1	(2.1)
FUNGAL DERMATITIS	0		1	(2.1)
PRURITUS	1	(2.1)	0	
SWEATING	1	(2.1)	0	
URTICARIA	1	(2.1)	0	

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (continued)

Body System: SPECIAL SENSES

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	2	(4.2)	4	(8.3)
PATIENTS WITH NO EVENTS	46	(95.8)	44	(91.7)
EAR PAIN	1	(2.1)	1	(2.1)
EYE DISORDER	1	(2.1)	1	(2.1)
CONJUNCTIVITIS	0		1	(2.1)
PHOTOPHOBIA	0		1	(2.1)

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

Table 14.9. Incidence of Non-Solicited Adverse Events Occurring During Treatment Incidence by Body System and Decreasing Frequency All Randomized Patients B1Y-MC-X065 (concluded)

Body System: UROGENITAL SYSTEM

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	7	(14.6)	5	(10.4)
PATIENTS WITH NO EVENTS	41	(85.4)	43	(89.6)
URINARY INCONTINENCE	3	(6.3)	3	(6.3)
CYSTITIS	1	(2.1)	1	(2.1)
MENSTRUAL DISORDER	2	(4.2)	0	
URINARY TRACT INFECTION	1	(2.1)	1	(2.1)
DYSMENORRHEA	1	(2.1)	0	
OVARIAN DISORDER	1	(2.1)	0	

RMP.B1YP.JCLLIB2(AES1EM02)
RMP.B1YO.X065REP(AES1EM02)
XAES0001

14.3.1.3. Analysis of the Fluoxetine Side-Effects Checklist

A subset of patients in this study recorded adverse events using a Fluoxetine Side-Effectss Checklist starting at Visit 3. This checklist was not used consistently throughout the study nor was it administered to all randomized patients. As a result, Table 14.10 presents a summary of the incidence of all adverse events captured on this checklist during the study. No additional statistical analyses were performed on these data. It should be noted that the Fluoxetine Side-Effects Checklist was designed to collect adverse events possibly related to fluoxetine treatment.

Of the 96 patients randomized in this study, 32 (67%) fluoxetine-treated and 18 (38%) placebo-treated patients reported at least one adverse event on this checklist. The five most frequently reported adverse events by fluoxetine-treated patients were trouble sleeping (40%), restlessness (40%), nausea (40%), headache (33%), and stomach pains (31%). The five most frequently reported adverse events by placebo-treated patients were headache (25%), trouble sleeping (21%), nausea (21%), stomach pains (17%), and feeling dizzy (17%).

Table 14.10. Adverse Events
Fluoxetine Side-Effects Checklist
Observed for All Visits
Incidence by Decreasing Frequency (Ordered by Fluoxetine)
All Randomized Patients
B1Y-MC-X065

Event Classification	Flx 20mg (N=48) n	(%)	Placebo (N=48) n	(%)
PATIENTS WITH >= 1 EVENT	32	(66.7)	18	(37.5)
PATIENTS WITH NO EVENTS	16	(33.3)	30	(62.5)
01. SLEEPING	19	(39.6)	10	(20.8)
07. RESTLESSNESS	19	(39.6)	6	(12.5)
19. NAUSEA	19	(39.6)	10	(20.8)
28. HEADACHE	16	(33.3)	12	(25.0)
22. STOMACH PAINS	15	(31.3)	8	(16.7)
04. FEELING DIZZY	10	(20.8)	8	(16.7)
21. NO APPETITE	10	(20.8)	8	(16.7)
23. DROWSINESS	9	(18.8)	5	(10.4)
29. NIGHTMARES	9	(18.8)	1	(2.1)
06. FEELING TENSE INSIDE	7	(14.6)	4	(8.3)
17. ITCHINESS	5	(10.4)	2	(4.2)
20. VOMITING	5	(10.4)	0	
25. SWEATING	5	(10.4)	1	(2.1)
30. WEIGHT CHANGE	5	(10.4)	4	(8.3)
02. HEART RACING	4	(8.3)	0	
03. HEART POUNDING	4	(8.3)	1	(2.1)
05. FEELING THE ROOM SPIN	4	(8.3)	6	(12.5)
11. DRY MOUTH	4	(8.3)	8	(16.7)
18 LIGHT SENSITIVE EYES	4	(8.3)	2	(4.2)
26. TREMOR	4	(8.3)	2	(4.2)
10. BALANCE	3	(6.3)	2	(4.2)
12. BLURRY VISION	3	(6.3)	1	(2.1)
24. LEG SPASMS AT NIGHT	3	(6.3)	0	
15. DIARRHEA	2	(4.2)	1	(2.1)
27. TINNITUS	2	(4.2)	2	(4.2)
08. NUMBNESS OF HANDS OR FEET	1	(2.1)	2	(4.2)
14. CONSTIPATION	1	(2.1)	1	(2.1)
09. TINGLING IN HANDS OR FEET	0		5	(10.4)

RMP.B1YP.JCLLIB2(AES1EM38)
RMP.B1YO.X065REP(AES1EM38)
XAES0001

14.3.2. Listings of Deaths, Other Serious, and Nonserious Clinically Significant Adverse Events

There were no deaths during this study. Two serious adverse events of suicide attempt occurred in patients receiving fluoxetine treatment, with 1 patient discontinuing the study as a result. Four additional fluoxetine-treated patients were discontinued from the study due to adverse events (2 for hypomania, 1 for increased impulsivity, and 1 for rash on abdomen and extremities). Further details are provided in Sections 12.3 and 14.3.3. Table 14.11 presents a by-patient listing of these events.

Table 14.11. Listing of Serious Adverse Events, Deaths, and Adverse Events Causing Discontinuation
All Randomized Patients
B1Y-MC-X065

Body System: BODY AS A WHOLE
Event Classification: SUICIDE ATTEMPT
Protocol: B1Y-MC-X065

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
1	2051	5	Flx 20mg	15	15	YES	HO,OTH	SUICIDE ATTEMPT
1	2163	4	Flx 20mg	12	12	NO	OTH	SUICIDE ATTEMPT

RMP.B1YP.JCLLIB2(AEL1EM01)
RMP.B1YO.X065REP(AEL1EM01)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.11. Listing of Serious Adverse Events, Deaths, and Adverse Events Causing Discontinuation
All Randomized Patients
B1Y-MC-X065 (continued)

Body System: NERVOUS SYSTEM
Event Classification: MANIC REACTION
Protocol: B1Y-MC-X065

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
1	2119	5	Flx 20mg	20	20	YES	NONE	HYPOMANIC
1	2231	8	Flx 20mg	29	41	YES	NONE	HYPOMANIA

RMP.B1YP.JCLLIB2(AEL1EM01)
RMP.B1YO.X065REP(AEL1EM01)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.11. Listing of Serious Adverse Events, Deaths, and Adverse Events Causing Discontinuation
All Randomized Patients
B1Y-MC-X065 (continued)

Body System: NERVOUS SYSTEM
Event Classification: PERSONALITY DISORDER
Protocol: B1Y-MC-X065

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
1	2019	6	Flx 20mg	27	27	YES	NONE	INCREASED IMPULSIVITY

RMP.B1YP.JCLLIB2(AEL1EM01)
RMP.B1Y0.X065REP(AEL1EM01)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

Table 14.11. Listing of Serious Adverse Events, Deaths, and Adverse Events Causing Discontinuation
All Randomized Patients
B1Y-MC-X065 (concluded)

Body System: SKIN AND APPENDAGES
Event Classification: RASH
Protocol: B1Y-MC-X065

Inv	Pat	Onset Visit	Therapy Group	Onset(First Occur.)Rel. Day of Ther.	Stop(Last Occur.)Rel. Day of Ther.	Event Cause Disc.	Serious Criteria	Actual Term
1	2030	6	Flx 20mg	25	25	YES	NONE	RASH ON ABDOMEN & EXTREMITIES

RMP.B1YP.JCLLIB2(AEL1EM01)
RMP.B1YO.X065REP(AEL1EM01)
Code: CA-Congenital Anomaly CN-Cancer DI-Died HO-Hospitalized LT-Life-threatening OD-Overdose PD-Permanently Disabled
OTH-Other Serious Criteria
XAEL0001

14.3.3. Narratives of Deaths, Other Serious, and Nonserious Clinically Significant Adverse Events

Fluoxetine Study B1Y-MC-X065
Patient Summary

Patient Number 001-2019

Discontinuation
Adverse Event

Study Medication: Fluoxetine **Dose:** 20 mg/day

Age: 9 **Sex:** Male
Origin: Caucasian **Weight:** 39 kg

EVENT: **Actual Term:** Increased Impulsivity
COSTART Term: Personality Disorder

Severity: Unknown
Onset: 11/27/91
Serious?: No

Expectancy?: Unexpected
Causality?: Unknown

1639 Filed?: Not applicable **If "Yes," List Mfr. Control No.:**

Days/Weeks of Therapy: 27 days

Actions: Discontinued from study and medication stopped

Historical Illnesses: None

Secondary Conditions: Dysthymia, Attention Deficit Hyperactivity Disorder, Oppositional Defiant Disorder, Overanxious disoder, Enuretic

Other Adverse Events: Anxiety, depression, hyperkinesia

Laboratory Abnormalities: None

Concomitant Medications: Antacids, Benadryl

Summary:
Patient had increased impulsivity while taking study medication. This was noted at Visit 6. The physician and parent decided to discontinue study medication and discharge patient from study. Patient followed up in an outpatient clinic.

Fluoxetine Study B1Y-MC-X065
Patient Summary

Patient Number 001-2030

Discontinuation Because of Adverse Event

Study Medication: Fluoxetine **Dose:** 20 mg/day

Age: 10 **Sex:** Male
Origin: Caucasian **Weight:** N/A

EVENT: **Actual Term:** Rash on abdomen & extremities
COSTART Term: Rash

Severity: Unknown
Onset: 12/30/91
Serious?: No

Expectancy?: Unexpected
Causality?: Possible

1639 Filed?: Not applicable **If "Yes," List Mfr. Control No.:**

Days/Weeks of Therapy: 25 days

Actions: Patient discontinued from study and study medication stopped

Historical Illnesses: None

Secondary Conditions: None

Other Adverse Events: Abdominal pain, flu syndrome, headache, vomiting, fever, pain, rash, urticaria

Laboratory Abnormalities:
HCT 37.5 (38-44)
MCH 1.92 (1.61-1.86)
LDH 1025 (340-770)
RBC 4.24 (4.4-5.3)
POLY .71 (.4-.7)
LYMPH .21 (.25-.45)

Concomitant Medications: Benadryl, Aspirin

Summary:
Patient appeared with rash on abdomen and extremities, itching and blisters with raised erythema. Patient was given Benadryl on 12/30/91. Medication was stopped and patient was discontinued from study. This occurred at visit 6.

Fluoxetine Study B1Y-MC-X065
Patient Summary

Patient Number 001-2051

Discontinuation Because of Serious Adverse Event

Study Medication: Fluoxetine **Dose:** 20 mg/day

Age: 16 **Sex:** Female
Origin: Caucasian **Weight:** 57 kg

EVENT: **Actual Term:** Suicide Attempt
COSTART Term: Suicide Attempt

Severity: Severe
Onset: 2/14/92
Serious?: Yes

Expectancy?: Unexpected
Causality?: Unknown

1639 Filed?: Not applicable **If "Yes," List Mfr. Control No.:**

Days/Weeks of Therapy: 15 days

Actions: Hospitalization for suicide attempt.

Historical Illnesses: none

Secondary Conditions: none

Other Adverse Events: Manic reaction, insomnia, nausea, nervousness, pallor, somnolence, suicide attempt

Laboratory Abnormalities:
Diphenhydramine 0.19mg/l
Orphenedrine <0.05ug/l
Brompheniramine 0.11ug/l
Acetaminephen <10ug/l (10-20)
PO2 mmHg 20 (80-100)
HCOB3 mMol/l 25 mMol/l (20-24)

Concomitant Medications: Pamprin, Tavist, Momentum, Benadryl Cough Syrup, Dibromm DM Acetaminophen

Summary:
On Feb 13, 1992 patient had fight with boyfriend went home and took 8 tablets of Pamprin, 6 tablets of Momentum, and 15 tablets of Dibromm. Patient was taken to emergency room at 1:00am by mother. In the Emergency Room, patient was given Charcoal 50mg. Seven pre-fragments were expelled and patient was admitted to the psychiatric unit.

Fluoxetine Study B1Y-MC-X065
Patient Summary

Patient Number 001-2119

Discontinuation Because of Adverse Event

Study Medication: Fluoxetine **Dose:** 20 mg/day

Age: 9 **Sex:** Female
Origin: Caucasian **Weight:** 53 kg

EVENT: **Actual Term:** Hypomanic
COSTART Term: Manic Reaction

Severity: Unknown
Onset: 02/16/93
Serious?: No

Expectancy?: Unexpected
Causality?: Possible

1639 Filed?: Not applicable **If "Yes," List Mfr. Control No.:**

Days/Weeks of Therapy: 27 days

Actions: Discontinued from study

Historical Illnesses: None

Secondary Conditions: None

Other Adverse Events: Anxiety Attack

Laboratory Abnormalities: None

Concomitant Medications: None

Summary: Patient presented with hypomanic symptoms at Visit 5. Patient was discontinued from the study and medication stopped.

Fluoxetine Study B1Y-MC-X065
Patient Summary

Patient Number 001-2163 | Significant Adverse Event

Study Medication: Fluoxetine **Dose:** 20 mg/day

Age: 17 **Sex:** Female
Origin: Caucasian **Weight:** 50 kg

EVENT: **Actual Term:** Suicide Attempt
COSTART Term: Suicide Attempt

Severity: Unknown
Onset: 10/18/93
Serious?: Other

Expectancy?: Unexpected
Causality?: Unknown

1639 Filed?: Not applicable **If "Yes," List Mfr. Control No.:**

Days/Weeks of Therapy: 12 days

Actions: Patient went to Emergency Room and was released.

Historical Illnesses: None

Secondary Conditions: overanxious disorder, social phobia, dysthymia, learning disability-math, migraines, oppositional-only when depressed

Other Adverse Events: Anxiety, depression, hyperkinesia, migraine, neurosis, thinking abnormal, abdominal pain, asthenia, menstrual disorder, suicide attempt, nausea, dysmenorrhea

Laboratory Abnormalities: None

Concomitant Medications: Motrin, Ibuprofen, Phenergan, contraceptive pill, Pepto-Bismol, Sinutab, Chlor-Trimeton, cough syrup, Inderal, Tylenol

Summary: On 10/18/93, patient made a suicide attempt and went to the Emergency Room. The suicide attempt was done with unknown pills, possibly Ibuprofen and 4 Phenegran tablets. At the Emergency Room, patient was given activated charcoal with sorbital of 50 gms. Patient was then discharged and sent home.

Fluoxetine Study B1Y-MC-X065
Patient Summary

Patient Number 001-2231

Discontinuation Because of Adverse Event

Study Medication: Fluoxetine **Dose:** 20 mg/day

Age: 11 **Sex:** Male
Origin: Caucasian **Weight:** 54 kg

EVENT: **Actual Term:** hypomania
COSTART Term: Manic reaction

Severity: Unknown
Onset: 12/1/94
Serious?: No

Expectancy?: Unexpected
Causality?: Possible

1639 Filed?: Not applicable **If "Yes," List Mfr. Control No.:**

Days/Weeks of Therapy: 41 days

Actions: Patient discontinued from study.

Historical Illnesses: None

Secondary Conditions: Attention Deficit Hyperactivity Disorder
Oppositional Defiant Disorder

Other Adverse Events: Diarrhea , Hyperkinesia

Laboratory Abnormalities: CHEM-AST 48 (16-46)
MCV 80
CHEM-LDH 873 (432-700)
HEME-POLYCH 1+

Concomitant Medications: None

Summary:
Patient presented at Visit 7 with hypomanic symptoms. Patient continued on study medication until Visit 8. Patient continued to present hypomanic symptoms at Visit 8, therefore, patient was discontinued from study and medication was stopped.

14.3.4. Abnormal Laboratory Values

The laboratory reference ranges used in this study were established by [redacted] These reference ranges were used to determine if a laboratory value was abnormal or became abnormal during the study. Table 14.12 presents the proportion of patients with treatment-emergent abnormal laboratory values for both treatment groups. There were no statistically significant or clinically relevant differences in treatment-emergent abnormal values between the two treatment groups.

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: HEMATOCRIT							
LOW	13	6	(46.2)	11	3	(27.3)	.423
HIGH	16	0		14	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: HEMOGLOBIN							
LOW	12	4	(33.3)	12	3	(25.0)	1.00
HIGH	16	2	(12.5)	14	0		.485

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: ERYTHROCYTE COUNT							
LOW	12	3	(25.0)	14	3	(21.4)	1.00
HIGH	16	2	(12.5)	15	0		.484

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC)							
LOW	16	0		15	1	(6.7)	.484
HIGH	16	0		15	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: MEAN CELL HEMOGLOBIN (MCH)							

LOW	15	2	(13.3)	15	0		.483
HIGH	16	1	(6.3)	13	0		1.00

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: LEUKOCYTE COUNT							
LOW	15	1	(6.7)	14	0		1.00
HIGH	15	0		15	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: BANDS							
LOW	4	0		2	0		
HIGH	3	0		2	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: NEUTROPHILS, SEGMENTED							

LOW	15	3	(20.0)	12	0		.231
HIGH	16	1	(6.3)	13	0		1.00

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: LYMPHOCYTES							
LOW	16	2	(12.5)	10	1	(10.0)	1.00
HIGH	12	3	(25.0)	12	1	(8.3)	.590

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: MONOCYTES							
LOW	16	0		13	0		
HIGH	16	0		13	1	(7.7)	.448

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: EOSINOPHILS							
LOW	10	0		10	0		
HIGH	9	2	(22.2)	10	1	(10.0)	.582

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: BASOPHILS							
LOW	3	0		4	0		
HIGH	3	0		4	1	(25.0)	1.00

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: MEAN CELL VOLUME (MCV)							
LOW	15	1	(6.7)	14	0		1.00
HIGH	14	1	(7.1)	12	1	(8.3)	1.00

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: PLATELET COUNT							
LOW				1	0		
HIGH				1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: RBC DISTRIBUTION WIDTH							
LOW	13	1	(7.7)	15	2	(13.3)	1.00
HIGH	14	0		15	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: RBC MORPHOLOGY							
ABNORMAL	14	0		12	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: UA-SPECIFIC GRAVITY							
LOW	3	0		1	0		
HIGH	3	0		1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-PH							
LOW	3	0		1	0		
HIGH	3	1	(33.3)	1	0		1.00

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: URINE COLOR							

ABNORMAL	3	0		1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
ABNORMAL	3	0		1	0		

Lab Test: UA-APPEARANCE

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-GLUCOSE							
ABNORMAL	3	0		1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: UA-RBC							
ABNORMAL	2	0					

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-CASTS							
ABNORMAL	2	0					

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-PROTEIN							
ABNORMAL	3	0		1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: UA-BILIRUBIN							
ABNORMAL	3	0		1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: UA-NITRITES							
ABNORMAL	3	0		1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: UA-LEUCOCYTE ESTERASE							

ABNORMAL	3	0		1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
ABNORMAL	3	0		1	0		

Lab Test: UA-KETONES

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: DRUG SCREEN, URINE							
ABNORMAL							
	48	1	2.1	48	0	0.0	1.000

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: SQUAMOUS EPITHELIAL CELLS							
ABNORMAL	2	0					

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: AST/SGOT							
LOW	31	1	(3.2)	34	0		.477
HIGH	27	3	(11.1)	31	4	(12.9)	1.00

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: ALT/SGPT							
LOW	32	1	(3.1)	33	1	(3.0)	1.00
HIGH	31	5	(16.1)	34	3	(8.8)	.463

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: LACTIC DEHYDROGENASE							

LOW	30	2	(6.7)	32	0		.230
HIGH	30	6	(20.0)	33	4	(12.1)	.498

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: ALKALINE PHOSPHATASE							
LOW	28	1	(3.6)	29	1	(3.4)	1.00
HIGH	30	0		32	1	(3.1)	1.00

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: THYROXINE, TOTAL-T4							
LOW	3	0					
HIGH	3	0					

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: THYROID STIM. HORMONE							
LOW	3	0					
HIGH	3	0					

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (continued)

Incidence Group	Flx 20mg(1) (Total=48) N	n	(%)	Placebo (2) (Total=48) N	n	(%)	- p-Value *1 - Overall
Lab Test: SODIUM							
LOW				1	0		
HIGH				1	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.12. Laboratory Analysis
Treatment-Emergent Abnormal Values
All Randomized Patients
B1Y-MC-X065 (concluded)

						- p-Value *1 -	
	Flx 20mg(1)			Placebo (2)			
Incidence	(Total=48)			(Total=48)			
Group	N	n	(%)	N	n	(%)	Overall
Lab Test: ALBUMIN							
LOW	32	0		35	0		
HIGH	32	0		34	0		

RMP.B1YP.JCLLIB2(LAS4E31A)
RMP.B1Y0.X065REP(LAS4E31A)
* Frequencies are analyzed using a Fisher's Exact test.
Note:Total = Total number of patients in the treatment group having both baseline and endpoint visits.
N = Total number of at risk patients with the lab test.
n = Total number of at risk patients with the specific lab result (e.g. HIGH).
XLAS0004

Table 14.13 provides a by-patient listing of all abnormal laboratory values that occurred during the study with their associated reference ranges. Clinically relevant laboratory abnormalities are discussed in Section 12.4.3.

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2001
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 6
Complete Blood Count			
HEMATOCRIT	1	38.000/44.000	35.10L
HEMOGLOBIN	mml/L-Fe	8.502/9.247	7.63L
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.37L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2002
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
ERYTHROCYTE COUNT	TI/L	4.400/5.200	4.15L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.676/1.924	1.96H
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	91H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2012
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 6
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.862	1.89H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2013
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	37.000/44.000	36.70L
HEMOGLOBIN	mml/L-Fe	7.820/9.185	7.70L
ERYTHROCYTE COUNT	TI/L	4.400/5.200	4.14L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2016
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	36.000/44.000	35.80L
HEMOGLOBIN	mml/L-Fe	7.633/9.123	7.39L
ERYTHROCYTE COUNT	TI/L	4.400/5.300	3.97L
MEAN CELL VOLUME (MCV)	fL	78.000/88.000	90H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2017
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MONOCYTES	1	0.000/0.120	0.13H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2019
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 2
Complete Blood Count			
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.34L
RBC DISTRIBUTION WIDTH	1	0.320/0.360	0.13L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2025
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	36.000/44.000		35.60L	
HEMOGLOBIN	mml/L-Fe	7.633/9.123		7.32L	
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.15L	4.01L	4.14L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.862	1.89H		
MEAN CELL VOLUME (MCV)	fL	78.000/88.000	89H	89H	
Blood Chemistry					
AST/SGOT	U/L	7.000/37.000			39.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2026
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
ERYTHROCYTE COUNT	TI/L	4.400/5.300	5.33H	
Blood Chemistry				
AST/SGOT	U/L	7.000/37.000	43.0H	44.0H
LACTIC DEHYDROGENASE	U/L	340.000/770.000		797H
Electrolytes				
SODIUM	mmol/L	135.000/144.000	147H	
CHLORIDE	mmol/L	97.000/104.000	105H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2030
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMATOCRIT	1	38.000/44.000		37.50L
ERYTHROCYTE COUNT	TI/L	4.400/5.300		4.24L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.862		1.92H
NEUTROPHILS, SEGMENTED	1	0.400/0.700		0.71H
LYMPHOCYTES	1	0.250/0.450		0.21L
MEAN CELL VOLUME (MCV)	fL	79.000/89.000	90H	
LYMPHOCYTES, ATYPICAL	1	0.000/0.000	0.01H	
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	340.000/770.000		1025H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2030
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Electrolytes				
CHLORIDE	mmol/L	97.000/104.000	106H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2032
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMATOCRIT	1	36.000/44.000	34.70L	
HEMOGLOBIN	mml/L-Fe	7.633/9.123	7.32L	
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.08L	
Blood Chemistry				
ALKALINE PHOSPHATASE	U/L	80.000/330.000		359H
Electrolytes				
BICARBONATE, HCO3	mmol/L	23.000/27.000	29.0H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2033
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	38.000/44.000	37.90L
LYMPHOCYTES	1	0.250/0.450	0.47H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2038
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 6
Blood Chemistry			
AST/SGOT	U/L	7.000/37.000	40.0H
ALT/SGPT	U/L	8.000/36.000	65.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2040
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	29.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2042
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Blood Chemistry				
ALT/SGPT	U/L	8.000/36.000		37.0H
Electrolytes				
CHLORIDE	mmol/L	98.000/106.000	107H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2050
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
ERYTHROCYTE COUNT	TI/L	4.400/5.200	4.39L
LEUKOCYTE COUNT	GI/L	4.800/10.800	11.0H
NEUTROPHILS, SEGMENTED	1	0.400/0.700	0.81H
LYMPHOCYTES	1	0.250/0.450	0.14L
Blood Chemistry			
ALBUMIN	g/L	34.600/47.800	51H
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	22.0L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2052
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 8
Complete Blood Count				
HEMATOCRIT	1	41.000/50.000	40.10L	
ERYTHROCYTE COUNT	TI/L	4.900/5.800	4.63L	
LYMPHOCYTES	1	0.250/0.450	0.23L	
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	340.000/770.000		791H
Electrolytes				
BICARBONATE, HCO3	mmol/L	23.000/27.000	29.0H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2057
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	38.000/46.000	36.90L
HEMOGLOBIN	mmol/L-Fe	7.944/9.681	7.20L
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mmol/L-Fe	32.000/36.000	31L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.676/1.924	1.41L
LYMPHOCYTES	1	0.250/0.450	0.20L
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	73L
RBC DISTRIBUTION WIDTH	1	0.115/0.145	0.16H
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	22.0L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2060
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
ALKALINE PHOSPHATASE	U/L	80.000/330.000	419H
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	31.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2061
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	38.000/44.000	35.00L
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.57L
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.26L
LEUKOCYTE COUNT	GI/L	4.800/10.800	12.4H
Blood Chemistry			
ALT/SGPT	U/L	8.000/36.000	7.0L
LACTIC DEHYDROGENASE	U/L	340.000/770.000	819H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2064
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	7.820/9.185	7.76L
ERYTHROCYTE COUNT	TI/L	4.400/5.200	4.24L
Electrolytes			
SODIUM	mmol/L	135.000/144.000	145H
BICARBONATE, HCO3	mmol/L	23.000/27.000	29.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2066
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 7
Complete Blood Count				
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.20L	
LEUKOCYTE COUNT	GI/L	4.800/10.800	11.2H	
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	340.000/770.000		789H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2067
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 7	VISIT 10
Complete Blood Count					
LEUKOCYTE COUNT	GI/L	4.800/10.800	12.9H	11.4H	
Blood Chemistry					
ALT/SGPT	U/L	8.000/36.000	39.0H		43.0H
Electrolytes					
BICARBONATE, HCO3	mmol/L	23.000/27.000	28.0H		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2068
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
ERYTHROCYTE COUNT	TI/L	4.300/5.300	4.08L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.552/1.738	1.89H
MEAN CELL VOLUME (MCV)	fL	75.000/83.000	90H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2069
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	36.000/44.000	34.70L
HEMOGLOBIN	mml/L-Fe	7.633/9.123	7.26L
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.07L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2073
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 8
Complete Blood Count				
HEMATOCRIT	1	41.000/50.000	38.50L	40.10L
HEMOGLOBIN	mml/L-Fe	8.688/10.178	8.07L	8.38L
LYMPHOCYTES	1	0.240/0.450	0.46H	
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	470.000/750.000	465L	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2083
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
MEAN CELL VOLUME (MCV)	fL	78.000/88.000	89H		
Blood Chemistry					
AST/SGOT	U/L	7.000/37.000	44.0H	39.0H	38.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2085
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	1	0.250/0.450	0.22L
Blood Chemistry			
ALBUMIN	g/L	34.600/47.800	50H
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	31.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2087
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Blood Chemistry			
LACTIC DEHYDROGENASE	U/L	340.000/770.000	813H
Electrolytes			
CHLORIDE	mmol/L	98.000/106.000	108H
BICARBONATE, HCO3	mmol/L	23.000/27.000	20.0L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2090
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 3
Complete Blood Count			
LYMPHOCYTES	1	0.250/0.450	0.21L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2093
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	38.000/44.000	37.30L
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.39L
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	32.000/36.000	32L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.862	1.61L
LEUKOCYTE COUNT	GI/L	4.800/10.800	4.7L
MONOCYTES	1	0.000/0.120	0.19H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2095
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	36.000/44.000	35.40L
HEMOGLOBIN	mml/L-Fe	7.633/9.123	7.26L
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.15L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2096
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	30.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2102
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
NEUTROPHILS, SEGMENTED	1	0.400/0.700	0.36L
LYMPHOCYTES	1	0.250/0.450	0.53H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2104
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.676/1.924	1.94H
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	92H
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	28.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2107
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	1	0.250/0.450	0.46H
Electrolytes			
BICARBONATE, HCO3	mmol/L	23.000/27.000	28.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2112
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1
Urinalysis			
UA-PH	U	5.000/7.000	8.5H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2114
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 2
Complete Blood Count				
HEMATOCRIT	1	41.000/50.000	50.20H	
HEMOGLOBIN	mml/L-Fe	8.688/10.178	10.74H	
Blood Chemistry				
ALKALINE PHOSPHATASE	U/L	43.000/122.000		129H
Electrolytes				
POTASSIUM	mmol/L	3.500/5.000	5.2H	
CHLORIDE	mmol/L	98.000/106.000	96L	
BICARBONATE, HCO3	mmol/L	23.000/27.000	28.0H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2114
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 2
Urinalysis				
UA-PH	U	5.000/7.000	8.5H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2119
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
HEMATOCRIT	1	38.000/44.000	37.00	L
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.82	L
EOSINOPHILS	1	0.000/0.050	0.10	H
MEAN CELL VOLUME (MCV)	fL	79.000/89.000	79	L
Electrolytes				
SODIUM	mmol/L	135.000/144.000	147	H
BICARBONATE, HCO3	mmol/L	18.000/31.000	33.0	H
Urinalysis				
UA-BACTERIA	NO UNITS		3+	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2119
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2120
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
LEUKOCYTE COUNT	GI/L	4.500/13.000	4.1L		
BANDS	1	0.000/0.060	0.08H		
LYMPHOCYTES	1	0.240/0.450	0.16L		
ELLIPTOCYTES	NO UNITS		1+ A		
Blood Chemistry					
ALT/SGPT	U/L	10.000/30.000			38.0H
LACTIC DEHYDROGENASE	U/L	380.000/770.000		787H	
ALKALINE PHOSPHATASE	U/L	56.000/285.000	339H		316H
Electrolytes					
CHLORIDE	mmol/L	97.000/104.000	96L		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2120
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 6		VISIT 10	
Urinalysis								
UA-BACTERIA	NO UNITS		1+	A				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.1	A				

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2123
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMATOCRIT	1	41.000/50.000	40.40L	
Blood Chemistry				
ALKALINE PHOSPHATASE	U/L	36.000/210.000	246H	251H
Electrolytes				
ANION GAP	mmol/L	8.000/16.000	7.00L	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	1.000/0.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2124
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 6		VISIT 10	
Blood Chemistry								
AST/SGOT	U/L	16.000/38.000			15.0	L		
ALT/SGPT	U/L	5.000/30.000					34.0	H
LACTIC DEHYDROGENASE	U/L	390.000/580.000	596	H	584	H	714	H
Urinalysis								
UA-PH	U	5.000/8.000					8.5	H
UA-BACTERIA	NO UNITS						2+	A
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0	A			1.0	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2125
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 8
Complete Blood Count				
HEMATOCRIT	1	38.000/46.000	36.40L	
HEMOGLOBIN	mml/L-Fe	7.820/9.185	7.76L	
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	78L	
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	380.000/640.000		679H
Electrolytes				
BICARBONATE, HCO3	mmol/L	18.000/31.000	32.0H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2126
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
NEUTROPHILS, SEGMENTED	1	0.400/0.760	0.36	L
LYMPHOCYTES	1	0.240/0.450	0.55	H
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2132
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 2
Complete Blood Count				
ERYTHROCYTE COUNT	TI/L	4.500/5.200	4.39L	
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	26.000/31.000	34H	
Blood Chemistry				
AST/SGOT	U/L	16.000/38.000	9.0L	
Electrolytes				
CHLORIDE	mmol/L	98.000/106.000	1L	
ANION GAP	mmol/L	8.000/16.000	3.00L	
Urinalysis				
UA-BACTERIA	NO UNITS		2+ A	1+ A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2132
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 2	
Urinalysis						
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A	0.1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2133
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	37.000/44.000	36.60L
HEMOGLOBIN	mml/L-Fe	7.820/9.185	7.70L
ERYTHROCYTE COUNT	TI/L	4.500/5.200	4.17L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2136
Treatment Group:

Lab Test	Units	Low/High Reference		VISIT 1
Complete Blood Count				
HEMATOCRIT	1	38.000/46.000		37.20L
NEUTROPHILS, SEGMENTED	1	0.400/0.760		0.38L
EOSINOPHILS	1	0.000/0.050		0.06H
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	380.000/770.000		946H
Electrolytes				
CHLORIDE	mmol/L	97.000/104.000		106H
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.1	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2138
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	41.000/50.000	40.80L
Electrolytes			
ANION GAP	mmol/L	8.000/16.000	18.00H
Urinalysis			
UA-UROBILINOGEN	NO UNITS	1.0	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2142
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	38.000/44.000	36.10L		
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.51L		
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.28L		
Blood Chemistry					
AST/SGOT	U/L	16.000/46.000			49.0H
ALT/SGPT	U/L	10.000/35.000			41.0H
LACTIC DEHYDROGENASE	U/L	420.000/750.000	802H	815H	
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2146
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
LYMPHOCYTES	1	0.240/0.450	0.18L
Blood Chemistry			
LACTIC DEHYDROGENASE	U/L	390.000/580.000	728H
Urinalysis			
UA-UROBILINOGEN	NO UNITS		0.2 A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2147
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
HEMATOCRIT	1	38.000/46.000	36.60L	
HEMOGLOBIN	mml/L-Fe	7.944/9.681	7.76L	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2149
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference		VISIT 1
Complete Blood Count				
ERYTHROCYTE COUNT	TI/L	4.500/5.200		5.26H
LEUKOCYTE COUNT	GI/L	4.500/11.000		12.8H
LYMPHOCYTES	1	0.240/0.450		0.22L
MEAN CELL VOLUME (MCV)	fL	80.000/90.000		77L
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2153
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
HEMOGLOBIN	mml/L-Fe	8.688/10.178	8.63L	
LEUKOCYTE COUNT	GI/L	4.500/11.000	12.0H	
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	470.000/750.000	442L	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2155
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1	
Urinalysis				
UA-BACTERIA	NO UNITS		2+	A
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2162
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 6
Complete Blood Count			
HEMATOCRIT	1	38.000/44.000	37.10L
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.82L
LYMPHOCYTES, ATYPICAL	1	0.000/0.000	0.01H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2163
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	37.000/44.000	36.30L
HEMOGLOBIN	mml/L-Fe	7.820/9.185	7.51L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2166
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	38.000/46.000	37.80L		
Blood Chemistry					
ALT/SGPT	U/L	10.000/30.000		33.0H	36.0H
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2167
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
BASOPHILS	1	0.000/0.020		0.03H	
LYMPHOCYTES, ATYPICAL	1	0.000/0.000			0.01H
Blood Chemistry					
AST/SGOT	U/L	16.000/38.000	44.0H	43.0H	44.0H
ALT/SGPT	U/L	10.000/45.000	143.0H		
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	16.00H		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2169
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 6
Complete Blood Count					
HEMATOCRIT	1	41.000/50.000			40.60L
Blood Chemistry					
ALKALINE PHOSPHATASE	U/L	65.000/260.000			59L
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2172
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 10	
Complete Blood Count						
HEMATOCRIT	1	38.000/46.000	36.30	L		
ERYTHROCYTE COUNT	TI/L	4.400/5.200	4.37	L		
EOSINOPHILS	1	0.000/0.050	0.06	H		
RBC DISTRIBUTION WIDTH	1	0.115/0.145	0.11	L		
Blood Chemistry						
ALT/SGPT	U/L	10.000/30.000			43.0	H
ALKALINE PHOSPHATASE	U/L	130.000/560.000	59	L	58	L
Urinalysis						
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2173
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMATOCRIT	1	38.000/44.000	35.50L	35.50L
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.51L	7.45L
ERYTHROCYTE COUNT	TI/L	4.400/5.300	4.37L	4.32L
Blood Chemistry				
AST/SGOT	U/L	16.000/46.000		56.0H
LACTIC DEHYDROGENASE	U/L	420.000/750.000		922H
ALKALINE PHOSPHATASE	U/L	175.000/420.000	162L	101L
Urinalysis				
UA-PROTEIN	NO UNITS		1+ A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2173
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2174
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
NEUTROPHILS, SEGMENTED	1	0.400/0.760			0.36L
LYMPHOCYTES	1	0.240/0.450	0.56H	0.53H	0.55H
Blood Chemistry					
AST/SGOT	U/L	16.000/46.000	15.0L		
LACTIC DEHYDROGENASE	U/L	470.000/750.000	463L		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2177
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 2	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	38.000/46.000	36.90L		
HEMOGLOBIN	mml/L-Fe	7.820/9.185	7.76L		
MEAN CELL HEMOGLOBIN CONCENTRATION (MCHC	mml/L-Fe	32.000/36.000			32L
MEAN CELL VOLUME (MCV)	fL	80.000/90.000			91H
ELLIPTOCYTES	NO UNITS			1+ A	
Electrolytes					
POTASSIUM	mmol/L	3.500/5.000	3.3L		
ANION GAP	mmol/L	5.000/14.000	15.00H		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2178
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 10
Blood Chemistry			
AST/SGOT	U/L	16.000/38.000	72.0H
ALT/SGPT	U/L	5.000/30.000	59.0H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2179
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
ERYTHROCYTE COUNT	TI/L	4.500/5.200		4.41L	
Blood Chemistry					
LACTIC DEHYDROGENASE	U/L	390.000/580.000	367L	383L	335L
CORTISOL					
CORTISOL	nmol/L	0.000/27.590	69.0H		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2180
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 10
Blood Chemistry			
LACTIC DEHYDROGENASE	U/L	432.000/700.000	351L
ALKALINE PHOSPHATASE	U/L	135.000/520.000	83L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2184
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMOGLOBIN	mml/L-Fe	8.688/10.178			10.43H
LEUKOCYTE COUNT	GI/L	4.500/11.000			4.4L
BASOPHILS	1	0.000/0.020			0.03H
Blood Chemistry					
AST/SGOT	U/L	16.000/38.000			65.0H
ALKALINE PHOSPHATASE	U/L	200.000/495.000	166L	173L	
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	15.00H		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2184
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 6		VISIT 10	
Urinalysis								
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0	A	1.0	A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2185
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 10
Complete Blood Count			
HEMATOCRIT	1	38.000/44.000	35.20L
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.51L
ERYTHROCYTE COUNT	TI/L	4.400/5.200	4.39L
NEUTROPHILS, SEGMENTED	1	0.400/0.760	0.36L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2186
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 6	
Complete Blood Count						
HEMATOCRIT	1	38.000/44.000	32.00	L	33.40	L
HEMOGLOBIN	mml/L-Fe	7.882/9.247	6.89	L	7.01	L
ERYTHROCYTE COUNT	TI/L	4.400/5.300	3.85	L	4.03	L
RBC DISTRIBUTION WIDTH	1	0.115/0.145	0.11	L		
DACROCYTES (TEAR DROP CELLS)	NO UNITS				1+	A
Blood Chemistry						
ALKALINE PHOSPHATASE	U/L	175.000/420.000	112	L	101	L
Urinalysis						
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2187
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMATOCRIT	1	41.000/50.000	39.90L	37.20L
HEMOGLOBIN	mml/L-Fe	8.688/10.178	8.50L	7.94L
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	78L	78L
Electrolytes				
ANION GAP	mmol/L	5.000/14.000	18.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2188
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
LEUKOCYTE COUNT	GI/L	4.500/11.000	14.4	H
Electrolytes				
POTASSIUM	mmol/L	3.500/5.000	3.3	L
Urinalysis				
UA-BACTERIA	NO UNITS		1+	A
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2190
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1	
Electrolytes				
POTASSIUM	mmol/L	3.500/5.000	3.2L	
ANION GAP	mmol/L	5.000/14.000	18.00H	
Urinalysis				
UA-PROTEIN	NO UNITS		1+	A
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2195
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
LYMPHOCYTES	1	0.240/0.450		0.17L
Electrolytes				
ANION GAP	mmol/L	5.000/14.000	15.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2197
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	38.000/46.000			35.60L
HEMOGLOBIN	mml/L-Fe	7.820/9.185			7.45L
ERYTHROCYTE COUNT	TI/L	4.400/5.200			4.23L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.924		1.54L	
BANDS	1	0.000/0.060	0.07H		
LYMPHOCYTES	1	0.240/0.450			0.46H
EOSINOPHILS	1	0.000/0.050		0.08H	
RBC DISTRIBUTION WIDTH	1	0.115/0.145			0.11L
Blood Chemistry					
ALT/SGPT	U/L	10.000/30.000			5.0L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2197
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	17.00H		
Urinalysis					
UA-PH	U	5.000/8.000	8.5H		
UA-BACTERIA	NO UNITS		1+ A		
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2204
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.924	1.97H		
LYMPHOCYTES	1	0.240/0.450	0.22L	0.22L	
EOSINOPHILS	1	0.000/0.050		0.09H	0.07H
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	90H	91H	92H
RBC DISTRIBUTION WIDTH	1	0.115/0.145		0.11L	
Blood Chemistry					
AST/SGOT	U/L	5.000/40.000		42.0H	
ALT/SGPT	U/L	10.000/40.000		41.0H	
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	16.00H		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2204
Treatment Group: Placebo

Lab Test	Units	Low/High Reference			VISIT 1	VISIT 6	VISIT 10
Urinalysis							
UA-UROBILINOGEN	NO UNITS		X/1.000	0.2	A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2207
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMOGLOBIN	mml/L-Fe	7.820/9.185	9.50H
ERYTHROCYTE COUNT	TI/L	4.400/5.200	5.45H
LYMPHOCYTES, ATYPICAL	1	0.000/0.000	0.02H
Blood Chemistry			
ALT/SGPT	U/L	10.000/30.000	46.0H
Electrolytes			
SODIUM	mmol/L	135.000/144.000	145H
CHLORIDE	mmol/L	97.000/104.000	107H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2207
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1
Electrolytes			
ANION GAP	mmol/L	5.000/14.000	21.00H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2210
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	38.000/46.000		35.80L	37.90L
HEMOGLOBIN	mml/L-Fe	7.820/9.185		7.32L	7.70L
ERYTHROCYTE COUNT	TI/L	4.400/5.200		4.30L	
EOSINOPHILS	1	0.000/0.050		0.06H	0.07H
Blood Chemistry					
LACTIC DEHYDROGENASE	U/L	380.000/640.000	745H	670H	
ALBUMIN	g/L	37.000/56.000	36L		
Electrolytes					
CHLORIDE	mmol/L	97.000/104.000	107H		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2210
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	15.00H		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2211
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	38.000/44.000		37.90L	34.30L
HEMOGLOBIN	mml/L-Fe	7.882/9.247			7.14L
ERYTHROCYTE COUNT	TI/L	4.400/5.200			3.96L
LEUKOCYTE COUNT	GI/L	4.500/13.500	4.2L		
Blood Chemistry					
AST/SGOT	U/L	16.000/46.000	49.0H	47.0H	
LACTIC DEHYDROGENASE	U/L	420.000/750.000			760H
ALKALINE PHOSPHATASE	U/L	175.000/420.000	158L		171L
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	16.00H		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2211
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Urinalysis					
UA-PH	U	5.000/8.000	8.5H		
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2212
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 10
Complete Blood Count			
HEMATOCRIT	1	38.000/46.000	37.30L
NEUTROPHILS, SEGMENTED	1	0.400/0.760	0.35L
LYMPHOCYTES	1	0.240/0.450	0.56H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2213
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
LYMPHOCYTES	1	0.240/0.450		0.24L
Blood Chemistry				
ALT/SGPT	U/L	10.000/30.000		4.0L
ALKALINE PHOSPHATASE	U/L	105.000/420.000		95L
Electrolytes				
ANION GAP	mmol/L	5.000/14.000	16.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2214
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMOGLOBIN	mml/L-Fe	7.820/9.185		9.68H
ERYTHROCYTE COUNT	TI/L	4.400/5.200		5.31H
LYMPHOCYTES	1	0.240/0.450	0.50H	
RBC DISTRIBUTION WIDTH	1	0.115/0.145	0.11L	0.11L
Electrolytes				
POTASSIUM	mmol/L	3.500/5.000	3.3L	
ANION GAP	mmol/L	5.000/14.000	15.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1.0 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2215
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 6	
Complete Blood Count						
HEMOGLOBIN	mml/L-Fe	8.688/10.178	10.24H			
Blood Chemistry						
AST/SGOT	U/L	5.000/40.000			47.0H	
HEME						
POLYCHROMIA	NO UNITS			1+		A
Electrolytes						
POTASSIUM	mmol/L	3.500/5.000	3.4L			

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2215
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Electrolytes				
ANION GAP	mmol/L	5.000/14.000	16.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2220
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMATOCRIT	1	37.000/44.000	44.20H	
RBC DISTRIBUTION WIDTH	1	0.115/0.145		0.11L
LYMPHOCYTES, ATYPICAL	1	/0.000		0.01H
Electrolytes				
ANION GAP	mmol/L	5.000/14.000	16.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2221
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1
Complete Blood Count			
HEMATOCRIT	1	37.000/44.000	35.20L
HEMOGLOBIN	mml/L-Fe	7.820/9.185	7.39L
ERYTHROCYTE COUNT	TI/L	4.500/5.200	4.25L
LYMPHOCYTES	1	0.240/0.450	0.47H
Blood Chemistry			
AST/SGOT	U/L	16.000/46.000	11.0L
ALT/SGPT	U/L	10.000/30.000	5.0L
LACTIC DEHYDROGENASE	U/L	380.000/640.000	376L
ALKALINE PHOSPHATASE	U/L	105.000/420.000	75L

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2221
Treatment Group:

Lab Test	Units	Low/High Reference	VISIT 1	
Electrolytes				
POTASSIUM	mmol/L	3.500/5.000	3.3	L
Urinalysis				
UA-PROTEIN	NO UNITS		2+	A
UA-BACTERIA	NO UNITS		3+	A
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2229
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
LEUKOCYTE COUNT	GI/L	4.500/13.000	13.4	H
LYMPHOCYTES	1	0.240/0.450	0.24	L
HEME				
POLYCHROMIA	NO UNITS		1+	A
Electrolytes				
ANION GAP	mmol/L	5.000/14.000	19.00	H
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2230
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 4	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	38.000/46.000		35.90L	36.00L
HEMOGLOBIN	mml/L-Fe	7.820/9.185		7.51L	7.39L
ERYTHROCYTE COUNT	TI/L	4.400/5.200		4.15L	4.09L
LEUKOCYTE COUNT	GI/L	4.500/13.000	4.3L		
NEUTROPHILS, SEGMENTED	1	0.400/0.760	0.26L	0.39L	0.37L
LYMPHOCYTES	1	0.240/0.450	0.55H	0.54H	0.49H
EOSINOPHILS	1	0.000/0.050	0.11H		0.09H
Blood Chemistry					
LACTIC DEHYDROGENASE	U/L	380.000/640.000			736H

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2230
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 4	VISIT 10
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2231
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1		VISIT 6	
Complete Blood Count						
MEAN CELL VOLUME (MCV)	fL	80.000/90.000			80L	
Blood Chemistry						
AST/SGOT	U/L	16.000/46.000			48.0H	
LACTIC DEHYDROGENASE	U/L	432.000/700.000			873H	
HEME						
POLYCHROMIA	NO UNITS				1+	A
Urinalysis						
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2233
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	
Complete Blood Count				
HEMOGLOBIN	mml/L-Fe	7.882/9.247	7.70L	
NEUTROPHILS, SEGMENTED	1	0.400/0.760	0.39L	
LYMPHOCYTES	1	0.300/0.500	0.51H	
Blood Chemistry				
AST/SGOT	U/L	16.000/46.000	82.0H	
LACTIC DEHYDROGENASE	U/L	420.000/750.000	953H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2	A

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2235
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 4	VISIT 6	VISIT 10
Complete Blood Count						
HEMATOCRIT	1	38.000/44.000			36.90L	37.30L
HEMOGLOBIN	mml/L-Fe	7.882/9.247			7.63L	7.45L
ERYTHROCYTE COUNT	TI/L	4.400/5.200			4.10L	4.13L
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.986/2.234			1.86L	
LYMPHOCYTES	1	0.300/0.500				0.23L
MEAN CELL VOLUME (MCV)	fL	79.000/89.000			90H	90H
RBC DISTRIBUTION WIDTH	1	0.115/0.145			0.11L	0.11L
LYMPHOCYTES, ATYPICAL	1	0.000/0.000				0.01H
Blood Chemistry						
AST/SGOT	U/L	16.000/46.000			48.0H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2235
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 4	VISIT 6	VISIT 10
Blood Chemistry						
LACTIC DEHYDROGENASE	U/L	420.000/750.000			413L	406L
ALKALINE PHOSPHATASE	U/L	175.000/420.000	159L		142L	132L
Electrolytes						
ANION GAP	mmol/L	5.000/14.000	15.00H			
Urinalysis						
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2237
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 10
Complete Blood Count				
HEMATOCRIT	1	41.000/50.000	39.40L	
HEMOGLOBIN	mml/L-Fe	8.688/10.178	8.07L	
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.924	1.58L	
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	77L	
Blood Chemistry				
AST/SGOT	U/L	16.000/46.000	113.0H	82.0H
ALKALINE PHOSPHATASE	U/L	200.000/295.000	298H	
Electrolytes				
POTASSIUM	mmol/L	3.500/5.000	3.3L	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2237
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 10
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2238
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Complete Blood Count				
HEMATOCRIT	1	41.000/50.000	37.90L	40.90L
HEMOGLOBIN	mml/L-Fe	8.688/10.178	7.76L	8.56L
MONOCYTES	1	0.000/0.120		0.13H
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	470.000/750.000	409L	363L
ALKALINE PHOSPHATASE	U/L	200.000/495.000	141L	150L
Electrolytes				
CHLORIDE	mmol/L	998.000/106.000	103L	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2238
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6
Electrolytes				
ANION GAP	mmol/L	5.000/14.000	15.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2242
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
ERYTHROCYTE COUNT	TI/L	4.400/5.300		5.35H	
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.924		1.59L	
NEUTROPHILS, SEGMENTED	1	0.400/0.760		0.35L	
LYMPHOCYTES	1	0.300/0.500		0.51H	
EOSINOPHILS	1	0.000/0.050		0.06H	0.08H
MEAN CELL VOLUME (MCV)	fL	80.000/90.000			80L
Blood Chemistry					
AST/SGOT	U/L	16.000/46.000	59.0H		
LACTIC DEHYDROGENASE	U/L	420.000/750.000		773H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2242
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
HEME					
POLYCHROMIA	NO UNITS			1+ A	
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	17.00H		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2244
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 8	VISIT 10
Complete Blood Count					
HEMOGLOBIN	mml/L-Fe	8.688/10.178	8.56L	8.50L	
MEAN CELL HEMOGLOBIN (MCH)	fmol(Fe)	1.614/1.924	1.58L	1.57L	1.57L
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	78L	78L	78L
Blood Chemistry					
AST/SGOT	U/L	16.000/46.000	47.0H		
Electrolytes					
ANION GAP	mmol/L	5.000/14.000	16.00H		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2246
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 4	VISIT 6	VISIT 10
Complete Blood Count						
LYMPHOCYTES	1	0.240/0.450	0.15L			0.49H
ELLIPTOCYTES	NO UNITS				1+ A	1+ A
TOXIC GRANULATION					1+ A	
LYMPHOCYTES, ATYPICAL	1	0.000/0.000				0.01H
Blood Chemistry						
AST/SGOT	U/L	16.000/38.000				42.0H
Urinalysis						
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1 A	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2249
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Complete Blood Count					
HEMATOCRIT	1	37.000/44.000		34.90L	
HEMOGLOBIN	mml/L-Fe	7.820/9.185		7.20L	
ERYTHROCYTE COUNT	TI/L	4.500/5.200	4.47L	3.80L	4.18L
NEUTROPHILS, SEGMENTED	1	0.400/0.760			0.38L
LYMPHOCYTES	1	0.240/0.450			0.50H
MEAN CELL VOLUME (MCV)	fL	80.000/90.000		92H	91H
Blood Chemistry					
AST/SGOT	U/L	16.000/38.000	41.0H	58.0H	
ALT/SGPT	U/L	5.000/30.000		41.0H	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2249
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 10
Blood Chemistry					
LACTIC DEHYDROGENASE	U/L	390.000/580.000			348L
ALKALINE PHOSPHATASE	U/L	70.000/230.000	56L	53L	51L
Electrolytes					
CHLORIDE	mmol/L	98.000/106.000	107H		
ANION GAP	mmol/L	5.000/14.000	16.00H		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2250
Treatment Group: Flx 20mg

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 7
Complete Blood Count					
HEMATOCRIT	1	37.000/44.000			36.30L
HEMOGLOBIN	mml/L-Fe	7.820/9.185		7.57L	7.51L
ERYTHROCYTE COUNT	TI/L	4.500/5.200	4.32L	4.16L	4.03L
MEAN CELL VOLUME (MCV)	fL	80.000/90.000	91H		90H
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	0.2 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2251
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 7
Complete Blood Count					
LYMPHOCYTES	1	0.400/0.700	0.31L		
MEAN CELL VOLUME (MCV)	fL	78.000/88.000	89H		
MEAN CELL VOLUME (MCV)	fL	80.000/90.000			90H
Blood Chemistry					
AST/SGOT	U/L	23.000/58.000	14.0L		
LACTIC DEHYDROGENASE	U/L	470.000/900.000	313L		
ALKALINE PHOSPHATASE	U/L	150.000/380.000	67L		
ALKALINE PHOSPHATASE	U/L	340.000/670.000		67L	
Electrolytes					
CHLORIDE	mmol/L	97.000/104.000	105H		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2251
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 6	VISIT 7
THYROID PANEL					
THYROXINE, TOTAL-T4	nmol/L	51.480/154.440	157H		
Urinalysis					
UA-UROBILINOGEN	NO UNITS	0.000/1.000	1 A		

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (continued)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2252
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 4
Complete Blood Count				
HEMATOCRIT	1	38.000/44.000		36.20L
HEMOGLOBIN	mml/L-Fe	7.882/9.247		7.45L
ERYTHROCYTE COUNT	TI/L	4.400/5.300		4.19L
NEUTROPHILS, SEGMENTED	1	0.400/0.760	0.37L	
LYMPHOCYTES	1	0.300/0.500	0.59H	
BASOPHILS	1	0.000/0.020		0.03H
Blood Chemistry				
AST/SGOT	U/L	16.000/46.000	72.0H	57.0H
ALT/SGPT	U/L	10.000/35.000	3.0L	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

Table 14.13. Abnormal Laboratory Values
All Randomized Patients
B1Y-MC-X065 (concluded)

Protocol: B1Y-MC-X065
Investigator Number: 1
Patient Number: 2252
Treatment Group: Placebo

Lab Test	Units	Low/High Reference	VISIT 1	VISIT 4
Blood Chemistry				
LACTIC DEHYDROGENASE	U/L	420.000/750.000	1248H	
Electrolytes				
POTASSIUM	mmol/L	3.500/5.000	5.4H	
CHLORIDE	mmol/L	97.000/104.000	107H	
BICARBONATE, HCO3	mmol/L	18.000/31.000	17.0L	
ANION GAP	mmol/L	5.000/14.000	18.00H	
Urinalysis				
UA-UROBILINOGEN	NO UNITS		0.2 A	

A=abnormal H=high L=low N=normal NEG=negative POS=positive
RMP.B1YP.JCLLIB2(LAL3EM67)
RMP.B1YO.X065REP(LAL3EM67)
XLAL0003

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16. Appendices

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Protocol

Protocol

SS# 096-60-3122

INTRODUCTION:

This is a revision of R01-MH39188-04 in response to the comments of the reviewers of the last submission. The review was helpful, and it has been possible to change certain features of the study. Since the last submission, the work in the first project period has been completed. We have also obtained funding from [redacted] for one year to follow up the subjects seen in the initial project. Additionally, we have added [redacted] as co-investigator, he is a child psychiatrist and clinical polysomnographer.

Two changes have been made independent of the review. We decided to change to fluoxetine from nortriptyline for several reasons including the publication of [redacted] negative nortriptyline study [redacted]; we have changed our diagnostic process slightly to have two experienced clinicians evaluate the subjects independently. This is now feasible with the addition of [redacted]. We have not highlighted changes as the Progress Report and Methods Section were completely re written.

In response to the critique, the following changes are noted.

1. We have rewritten and expanded the data presented in the Progress Report. We have studied more subjects with MDD (n=72) and fewer with dysthymia (n=33) than planned. We have expanded data on diagnosis, sleep data, and D$T results, we present preliminary information on fluoxetine in this age group. To conform to page limitations, we deleted expanded reviews of others work in these sections.
2. While criterion symptoms in addition to DSMIII-R are collected, they are not used to decide inclusion or exclusion in the study. A rationale for collecting these other symptoms is given (pg. 40).
3. Concurrent attention deficit hyperactivity disorder (ADHD), conduct disorder and anxiety disorder, with MDD are included in the study.
4. Those with eating disorders, Bipolar II (or DSMIII-R Bipolar NOS) and patients with Bipolar I first-degree relatives are excluded. Previous tricyclic nonresponders are included since fluoxetine is now the drug of study (pg. 38).
5. All subjects are drug free for 7 days or more prior to the initial evaluation and all are drug free for at least 14 days prior to the sleep EEG and DST.
6. Normal intelligence is defined as IQ > 80. If there is any concern about the subject being close to this on clinical assessment then formal psychometric testing (using a WISC-R) will be completed. We rarely see such a patient without prior intelligence testing data, with MDD (who is otherwise study eligible) with an IQ $\leq$ 80.
7. The clinical care during the study is delineated (pg. 39) i.e. the only treatment will be weekly assessments during the course of the drug trial. Patients who prefer to try psychosocial treatment first are referred out. It is clear that the weekly meetings have a therapeutic component, but it will be the same for both placebo and active medication groups, i.e. review of symptoms, etc.
8. The initial assessment of family history using the family history RDC will be undertaken by a separate interviewer from the one doing the DICA.
9. Additional precautions to ensure the blind is maintained are specified. None of the clinical or evaluation staff will know whether or not the subject is on active medication as this is decided by the pharmacy. All evaluations during the active treatment phase will be conducted by clinicians who will remain blind to treatment status until all subjects have completed the study. Additionally, the first and last treatment visit, symptom evaluation will also be conducted by an independent clinician, from outside the clinical area, who has not been involved with the ongoing treatment.
10. A discussion of blocking on covariates in random assignment is included in the Data Analyses.
11. The issue of power for the regression analyses is addressed in the data management section.

The human subject concerns have been addressed in the Methods Section and the Human Subjects Section. The subjects will continue to be followed or referred out as clinically appropriate. The clinician treating the subject will have access to treatment information, as clinically indicated, once the acute treatment is completed.

Overall we agree with the reviewers helpful suggestions and believe that the changes outlined will address not only their these concerns but express our own additional thoughts in relation to improving the protocol.

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SS# 096-60-3122

A. SPECIFIC AIMS:

This is a revision of a competitive renewal, grant #1-R01-MH39188-04. The original grant (#1-R01-MH39188-03), which was funded from April 1, 1986 to March 31, 1989. The third year was funded as a competitive renewal (2-R01-MH39188-03). This project has been extended without additional funding through March 31, 1990. This application is an extension of our initial grant to outpatients. Also, we wish to study whether we can predict response to fluoxetine in depressed child and adolescent outpatients.

Our initial study found that:

a) Children and adolescent inpatients with Major Depressive Disorder (MDD) evidence shortened Rapid Eye Movement (REM) Latency and an increased amount of REM sleep (minutes and percent) compared to normal controls.

b) The Dexamethasone Suppression Test (DST) is abnormal in depressed children and adolescents when depressed, but 1 mg dexamethasone is the minimum dose required to perform this test.

The proposed study extends these initial findings to work on sleep polysomnographic findings (PSG) and dexamethasone nonsuppression in outpatients with Major Depressive Disorders (MDD). The extension to outpatients makes possible a placebo controlled study of antidepressant treatment of MDD in children and adolescents. Though antidepressants are used extensively in this population, controlled studies are limited. If antidepressants are effective for some patients, then it would be important to assess which biological, clinical and family history data variables might best predict acute response to treatment.

The following is an extension of the aims of the study to reflect progress to date and the specific aims to be tested in this proposal.

1) To determine whether outpatient children and adolescents with Major Depressive Disorder (MDD) evidence sleep polysomnographic and DST abnormalities like those found in depressed inpatients.

2) To determine the effectiveness of fluoxetine in comparison to placebo in the treatment of MDD in outpatient children and adolescents.

3) To determine whether response to fluoxetine is different between children and adolescents.

4) To determine if pretreatment reduced REM latency and/or DST status predicts acute response to medication treatment.

5) To determine if clinical, demographic, or family history variables predict acute response to treatment.

6) To develop preliminary data on blood levels of fluoxetine using a fixed dose.

B. SIGNIFICANCE:

I. Clinical Significance:

Carlson and Cantwell (1982a) found that severe suicidal ideation increased around puberty and that it correlated with increasingly severe depressive symptomatology. Most but not all suicide attempts were apparently related to depression.

Suicide is the second most common cause of death in children age 8 to 18. In the United States over 12,000 patients under the age of 15 are admitted to psychiatric hospitals following suicidal behavior (Cohen-Sandler et al., 1982). In a recent study (Emslie et al., 1990a), supported by the [redacted] we evaluated the self-report of depressive symptoms in 3,294 high school students of mixed ethnic background in the [redacted] Beck Depression Inventory (BDI) scores of 16 or greater were reported in 18.6% of students and 13% met a modified Weinberg criteria (Weinberg et al., 1973) by self-report. Overlap between these groups was incomplete. Both instruments were positive in 7.9% of the students. What is clear is that a large number of adolescents experience substantial depressive symptoms. How many meet DSM-III-R criteria for MDD and whether those with higher scores are at greater risk for developing Major Depressive Disorder as has been postulated in adults (Weissman et al., 1986) are questions still to be answered. However, depression is a significant disorder in this age group and carries with it significant morbidity and mortality. Improvements in our capacity to recognize, diagnose and treat depression in adolescents has major public health value.

Of concern to clinicians, children and parents alike therefore, are questions of whether treatment will be effective, how long it should continue and whether the depression will recur. To date little, information is available to answer these questions in this age group though there is a suggestion that the risk of recurrence in children with MDD is higher than reported in adults and

higher in those with dysthymia and MDD (double depression). Kovacs reported that 26% of those children who recovered from MDD (well for 2 months) relapsed within one year and 40% in less than 2 years with no additional cases after 2 years until the end of the study. Subjects were excluded who had previous episodes prior to the studied episode (Kovacs et al., 1984a,b).

The identification of biological correlates of depression has potential significance for our understanding of diagnosis, prediction of acute treatment, prediction of relapse, family (genetic) studies, and increased understanding of the basic pathophysiology of this disorder. The ability to utilize biological variables in addition to clinical variables to assist in validating particular subgroups of depression have been well described. From preliminary work in adults we feel that polysomnogram (PSG) and DST have the best potential for further investigation both in diagnosis and outcome.

The recognition of biological abnormalities in adult depressives has spurred research into whether similar abnormalities are seen in children and adolescents. Work by Poznanski (Poznanski et al., 1982, Weller 1984) and others have shown that DST nonsuppression occurs in depressed children and adolescents. Sleep PSG abnormalities were not found in 2 initial studies of depressed children (Puig-Antich 1982, Young 1982). Our own recent data in depressed inpatient children showed reduced REM latency and increased REM time (Emslie et al., 1990b). Depressed adolescents have been reported to show shortened REM latency by 2 groups (Lahmeyer et al., 1983, Emslie et al., 1988) but not in a third (Goetz et al., 1987). Recently Dahl et al., (1990) showed inpatient, suicidal depressed adolescents evidenced a short REM latency.

Possible reasons for differences between groups may be in part due to methodology, severity of illness or particular subgroups of depressives studied (Dahl et al., 1990). Study of outpatients would allow for a potentially less severe group with fewer comorbid diagnoses. The data from both inpatients and outpatients combined may allow for a sizeable enough sample to look at groups of depressed children with different comorbid diagnoses or no comorbid diagnoses (Emslie et al., 1990b).

Antidepressants are widely used in the clinical management of children and adolescents with depression. Yet published studies to date have been equivocal in proving their effectiveness (Kramer, 1981; Puig-Antich, 1987; Preskorn, 1987; Ryan, 1986, 1988; Geller, 1990). Several Studies are ongoing but not published. Problems in design include, limited number of placebo controlled studies, inadequate dosage as compared to blood levels (Geller, 1986; Preskorn, 1987), and an apparently higher placebo response rate (Puig-Antich, 1987).

Clinical predictors of response to acute treatment in adults have been studied with mixed results. However, in adults (Rush et al., 1986, 1989, Giles et al., 1987a) there is evidence that depressed subjects with shortened REM latency show a better response to tricyclics than depressed subjects without shortened REM latency (80% vs 50%). On the other hand in those patients with pretreatment shortened REM latency, 50% relapsed in the first 4 months after medication was discontinued compared with the 0% relapse rate in those with normal REM latency. Therefore, it is possible that REM latency could aid in treatment selection and be a guide towards the need for maintenance treatment.

There is also a suggestion in adults that reduced REM latency depressives show a decreased placebo response (Fairchild et al., 1989). Similarly, in adults (Qualls et al., 1980; Brown et al., 1987) and children (Preskorn et al., 1987) DST nonsuppression predicted higher response to active medication than to placebo. Recently, a study by Robbins et al., (1989) suggested that adolescents with a positive DST were less likely to respond to psychosocial treatment alone. Either placebo response is more likely in DST suppressors and/or in those with normal REM latency, or the presence of positive biological findings is predictive of a better antidepressant response. In either case, the use of such pretreatment measures in child and adolescent depressives are likely to better differentiate placebo vs. medication responders.

Fluoxetine is the first selective serotonin reuptake blocker, nontricyclic antidepressant to receive Food and Drug Administration (FDA) approval. It has been available for 2 years. It has been shown to be equally effective to amitriptyline, imipramine, doxepin, trazodone (Debus, 1988) and mianserin. It would also appear to be safer, with fewer side effects, less risk of completed suicide and high cardiovascular safety (Fisch, 1985, Halper & Mann 1988, Rush & Hendrickse, submitted see Appendix) Open studies have been published in adolescents with depression (Joshi et al., 1989) and children with Tourettes and OCD (Riddle et al., 1990) but no double blind placebo controlled studies have been published in this age group.

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II. Theoretical Significance:

This project should contribute significantly to our understanding of the developmental and familial characteristics of depression. Careful evaluation of family histories will determine whether early expression of genetic vulnerabilities is a function of high genetic loading i.e., is higher loading associated with earlier age of onset. (Weissman et al., 1984, 1986, Puig-Antich et al., 1989). The question of whether PSG abnormalities are trait or state parameters cannot be answered unequivocally by this study as it is not possible to study depressed children prior to the onset of their first episode. However, which variables are present throughout all ages can give an indication of what variables may be more central to the disorder. Such data will establish the ground work for family studies. Preliminary evidence in adults suggest concordance of reduced REM latency in first-degree relatives of unipolar probands (Giles, 1988). Similarities and differences between adult and child data are likely to contribute to our understanding of the basic pathophysiology of depression in both groups.

C. PROGRESS REPORT:

In this section, we report the data, based on work to date, which we feel supports the need for continued work in this area. The focus of the initial grant has been on a cross sectional assessment of depressed child and adolescent inpatients with regards to clinical, family history, and biological measures as compared to normal controls.

The following publications and presentations have resulted totally or in part from this funding since 1986:

Emslie G.J., Roffwarg H.P., Rush A.J., Weinberg W.A., Parkin-Feigenbaum L. Sleep EEG Findings in Depressed Children and Adolescents. Am. J. Psych. 144:668-670, 1987.

Weinberg W.A., Emslie, G.J. Depression and Suicide in Adolescents. Int. Pediatrics 2:154-159, 1987.

Emslie G.J., Rush A.J., Weinberg, W.A., Rintelmann J.W., Roffwarg H.P. Polysomnographic Findings in Depressed Children and Adolescents. Abstract in Sleep Research Vol. 17. (eds.) Chase M.H., McGinty D.J., O'Conner C. Brain Information Service, University of California, Los Angeles, 1988.

Weinberg W.A., Emslie G.J. Weinberg Screening Affective Scales (WSAS and WSAS_SF). J. Child Neurol. 3:294-296, 1988.

Emslie G.J., Rush A.J., Weinberg, W.A., Rintelmann J.W., Roffwarg H.P. Children with Major Depression Evidence Reduced Rapid Eye Movement Latencies. Arch. Gen. Psych. 47:119-124, 1990.

Emslie G.J., Weinberg, W.A., Rush A.J., Adams R.M., Rintelmann J.W. Depressive Symptoms by Self-Report in Adolescence: Phase I of the Development of a Questionnaire for Depression by Self-Report. J. Child Neurol. 5:114-121, 1990.

Emslie, G.J., Rush A.J., Roffwarg H.P., Weinberg W.A., Rintelmann J.W. Sleep EEG Measures in Depressed Prepubertal Children. Presented American Academy of Child and Adolescent Psychiatry, Annual Meeting, Washington, D.C., October 1987.

Emslie, G.J., Rush A.J., Roffwarg H.P., Weinberg W.A., Rintelmann J.W. Sleep EEG Measures in Depressed Prepubertal Children. Presented at American College of Neuropsychopharmacology, Annual Meeting, San Juan, Puerto Rico, October 1987.

Emslie, G.J., Rush A.J., Weinberg W.A., Rintelmann J.W., Roffwarg H.P. Polysomnographic Findings in Depressed Children and Adolescents. Presented at Second Annual Meeting of Association of Professional Sleep Societies, San Diego, California, June 1988.

Emslie, G.J. Biological Correlates of Depression in Children and Adolescents: Developmental and Methodological Issues. 5th India-U.S. Symposium on Child Mental Health, national Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, India, March 1989.

Emslie, G.J. Sleep polysomnography (PSG) in depressed children and adolescents: Developmental and methodological issues. Presented American Academy Child and Adolescent Psychiatry Annual Meeting, New York, 1989.

Emslie, G.J. Dexamethasone nonsuppression in normal children and adolescents. Presented American Academy Child and Adolescent Psychiatry. Annual Meeting, New York. October, 1989.

Patient and normal control subjects studied so far have been cooperative with the study.

The interaction with the sleep laboratory has continued to be optimal. The funding of the [redacted] has strengthened further the core laboratory support for this and other projects by maintaining careful longitudinal quality control for cortisol determinations and for PSG evaluations.

In anticipation of this application, for the past three years we have been operating a Psychopharmacology Clinic at [redacted] to allow for a more systematic follow up of the patients seen. This clinic is staffed by 3 attendings, 3 to 5 psychiatry fellows, 2 psychologists, 2 nurses and 1 research assistant. In the past 24 months, 190 new patients have been seen of whom 48% had major depression. This computes to a flow rate of 3.6 study eligible patients per month. Additionally, [redacted] sees approximately 300 new outpatients per year, of whom 35% have a primary diagnosis of depression. This computes to an average flow rate of 8.4 study eligible patients per month. Assuming no additional recruiting effort, we have 8.4 + 3.6 = 12.0 study eligible patients per month. Assuming only 1/3 will (a) agree to participate, (b) meet all inclusion/exclusion criteria, and (c) complete the evaluation/laboratory phase, we would have 48 patients per year who would enter the single blind placebo phase. We, in fact only need 30 per year. Thus, the patient flow is more than adequate as there are no competing studies. Additionally, further referrals will be obtained from the adult affective disorder program if needed. [redacted] serves a large geographical area and is the only medical school within this area.

Overview of Subjects studied

The initial grant proposed to study 120 inpatients (60 MDD and 60 dysthymic). We have entered 114 subjects, 5 refused to sleep after initial agreement or pulled out after 1 night. Of the 109 subjects completing the study, 72 were MDD, 33 dysthymic and 4 excluded (2 were found on PSG to have a primary sleep disorder and 2 were not depressed). The number of dysthymics was fewer than proposed because inpatient admission was usually precipitated by a recent deterioration. In fact, about 40% of those with MDD had dysthymic disorder as an additional diagnosis but had worsened to MDD prior to admission to the hospital. Thus we have data on more MDD patients but fewer dysthymic subjects than originally planned. With regards to normal controls, 172 were screened by telephone interview, 93 were interviewed, and 71 completed the study of whom 62 were considered normal. Of the 9 excluded after completion of the study, 1 was on medication, 1 became sick during the study, 1 had epilepsy (not initially identified) and 6 had first-degree relatives with affective disorders (omitted in the initial history).

Data on the 72 subjects with MDD will be summarized as this is most relevant to the current proposal. Of the 72 subjects with MDD, 29/72 (40%) were 12 years or younger and 43/72 (60%) were 13 or over. 40/72 (56%) were male and 66/72 (92%) were Caucasian. The mean social class was 2.4 (SD=1.0): social class I, 15 (21%), social class II, 24 (33%), social class III, 21 (29%), social class IV, 12 (16%), social class V, 0%. This is generally a more middle class group than other similar studies and less compounded by environmental and financial factors in those with MDD. 41/72 (57%) came from intact families.

We will review progress in four areas 1) diagnosis, clinical variables and family history, 2) sleep polysomnography, 3) dexamethasone nonsuppression, 4) treatment and outcome.

1. Diagnosis

In adults, specific criteria as found in Research Diagnostic Criteria (RDC) (Spitzer et al., 1978) or in DSM-III (APA, 1980) for diagnosis of mood disorders has increased diagnostic reliability. In addition, the use of structured and semistructured interviews reduce information variance and improve interater reliability in clinical and epidemiologic research.

Clinical criteria for depression in children have been developed based on the RDC for adults (Brumback, 1976; Crytyn and McKnew, 1972; Weinberg, 1973; Hudgens, 1974; Ling et al., 1970; Petti, 1978; Puig-Antich et al., 1978). The development of DSM-III reflected the general acceptance of these sorts of criteria for diagnosing affective disorders in children and adolescents. DSM-III uses the same criteria in children and adolescents as are applied to adults. Accordingly, there are no distinctive or unique diagnostic categories for affective disorders in children and adolescents.

Assessment techniques for evaluating depression in children and adolescents have been reviewed (Kazdin, 1981; 1983). As pointed out by Puig-Antich (1982b) and Weinberg (1973), development of structured psychiatric interviews for use in children is fundamental to the

diagnosis of depression in children and adolescents. Both child and parents must be interviewed to obtain diagnostic data (Herjanic, 1975; Rutter, 1968), and additional information from peers or teachers is also likely of value. The importance of evaluating for presence of criterion symptoms of other disorders in addition to depression has been noted. The significance of associations between depression and conduct disorder (Puig-Antich, 1982a) or school phobia (Agras, 1959; Gittleman-Klein, 1971) or hyperactivity (Brumback, 1976), has yet to be clarified.

In our completed study the research assistant completes a structured DSM-III based interview schedule, the Diagnostic Inventory for Children (DICA) (Herjanic et al., 1983; Welner et al., 1987), with both parents and patients separately. In addition, the patients are interviewed independently by two experienced clinicians who review all DSM-III diagnosis symptoms and complete the Bellevue Index of Depression (BID). The information from the interviews, parent and child self-reports and additional ancillary information are reviewed systematically in a weekly research conference in which a consensus diagnosis is developed and assigned. This has been our operational procedure during the last 4 years. Several issues have become evident repeatedly and have required further definition. We plan to make changes in our diagnostic procedure to deal with the following problems.

(a) Multiple Diagnosis

This is a continuing area of controversy for researchers as well as clinicians. We have addressed this in several ways. Initially, all patients are diagnosed by all criteria that they meet at the time of the evaluation except for those where rules are already clearly defined, i.e. conduct disorder vs. oppositional disorder. Then the clinical information is reviewed with regard to best estimate of the onset of each disorder and its relationship to the depressive episode. Onset of the disorder is the point when the symptoms are sufficient to meet syndromal criteria and are clinically significant i.e. cause dysfunction and affect performance at home, school or play. For example, a child is described as always having been anxious but functioning well, then has a period of worsening leading to dysfunction and is then unable to go to school. This difficulty may or may not be concurrent with an episode of symptoms that meet criteria for a major depressive episode. Additional diagnoses are defined in two ways: (1) as present or not; (2) as whether or not they appear independent and/or concurrent with episodes of major depression.

Although the process of eliciting sufficient information to make these diagnoses is time consuming, we feel that it is essential because it may be important prognostically.

In the 72 children and adolescent inpatients with MDD, that concurrent diagnoses are common. Of the 72 patients, 23 (32%) have MDD as their only diagnosis, 20 (28%) have 2 diagnoses, 20 (28%) have 3 diagnoses and 9 (12%) have 4 diagnoses. The additional diagnoses were dysthymia n=28 (39%), ADD n=21 (29%), anxiety disorders n=21 (29%), conduct disorder n=4 (5%), and other disorders n=15 (21%). The total is greater than 100% because certain subjects have more than 1 additional diagnosis.

(b) Definition of Depressive Symptoms

In our study of severe depression, to date, meeting criteria for either dysthymic disorder or MDD has not presented a significant problem. The primary difficulty has arisen in defining melancholic subtype, particularly the definition of pervasive anhedonia and lack of reactivity to usually pleasurable stimuli. We have scored these as present if the subject has reported a marked change in the reactivity of mood and/or ability to have fun and not required total anhedonia or total unreactivity of mood in this age group. However, further refinements are required for post hoc analysis, and we would propose that our current diagnostic interview used (DICA) is not sufficient. Additionally, it is increasingly important that different research groups around the country can sufficiently characterize their depressed population for comparison between centers. We plan to add the depressive items from the Kiddie-SADS (Puig-Antich, 1987), in further studies. In addition the Children's Depression Rating Scale (CDRS) (Poznanski, 1985) will be used as a severity measure. The CDRS has been used in previous drug trials in this age group (Geller 1985, 1986, 1989) and appears to be a sensitive change measure. Finally, we believe that utilizing an instrument based on behavior and specific to children and adolescents is important to address symptoms that may be specific to this age group. Accordingly we will continue to use the Bellevue Index of Depression.

(c) Family History

Family history has been obtained from both parents when available. The two natural parents have been available in 58.3% of inpatients. Our experience over time has refined what information is necessary. Each 1st and 2nd degree relative is reviewed with regards to presence of

symptoms consistent with affective disorder, suicide, alcohol and substance abuse, criminal behavior, schizophrenia, anxiety disorders, hysteria and other psychiatric disorders. Additional information is obtained about functional impairment caused by the disorder, whether treatment was obtained, and what type. We would plan to systematize data collection in this important area with a modified RDC family history questionnaire (Andreasen et al. 1977, 1986) in the proposed study.

2. Sleep Polysomnographic Data

Previous studies of the sleep EEG in depressed children and adolescents have been published. Puig-Antich (1982, 1983) reported on the sleep EEG in depressed children, both in the depressed state and following symptomatic recovery, compared to normal controls. The symptomatic depressed group did not differ polysomnographically from normal controls or from nondepressed, neurotic children. However, there were significant differences in REM latency, REM time and number of REM periods in the drug-free, recovered depressed subjects. Young et al., (1972) found that no all night sleep EEG measures discriminated significantly between depressed patients and age-matched normal controls. A recent study by Coble et al., (1984) contributed substantially to the normative data base for children 6-16 years of age.

In adolescents, Laymeyer et al., (1983) found a significantly shorter REM latency and increased REM density in 13 depressed adolescents compared to 13 age-matched controls. A negative correlation between REM latency and age was also noted. The same differences were not found in a study by Goetz et al., (1987). Recently it has been suggested that inpatient status or suicidal behavior may be more associated with short REM latency (Dahl et al., 1990).

Data on the PSG variables in a subgroup of the children we have studied have been reported (Emslie et al., 1990), and data on adolescents studied with MDD is being prepared (Appendix A).

Table 1, below, presents select polysomnographic variables from the complete study sample. It appears that depressed children and adolescents evidence a shortened REM latency, increased REM time, and increased sleep latency as compared to normal controls. Dysthymics are intermediate. Stage 4 seems to be relatively protected in the young depressed. In addition, for the whole group, diagnostic group and age predicted REM latency but not pubertal status. These data encourage further study as to whether these exciting PSG discriminations are present in outpatients as in adults and whether REM latency will predict response to treatment in children and adolescents as in older groups.

Table 1
PSG Variables - Means of Nights 2 and 3

	MDD N=72	Dysthymic N=33	Normal Controls N=62	MDD vs. Control t	P
Sleep Latency (min)	23.0 (19.5)	020.3 (14.7)	011.2 (07.2)	4.8	<.001
REM Latency (min)	84.8 (30.6)	106.5 (43.3)	113.1 (37.3)	4.7	<.001
REM Time (%)	19.9 (05.5)	016.7 (05.1)	015.6 (03.3)	5.5	<.001
Stage 4 (%)	8.5 (05.6)	006.4 (06.0)	008.3 (03.5)	0.2	N.S.

Possible reasons for differences between studies include: 1) Differences in the studies with regards to patient populations and severity of illness. 2) Children (even more frequently than adults) often miss their first REM period or only show minor signs of a REM episode which may be overlooked unless more sensitive polysomnographic criteria are used. The impact of different scoring criteria for both sleep onset and for designating a REM period need to be assessed (Emslie et al. 1987; 1990).

Sleep onset is designated in our sleep laboratory [redacted] as occurring at the initial minute of the first ten minute period in which no less than eight minutes are spent in any stage of sleep (including non-REM Stage 1). The first REM period requires only the presence of the

characteristic pattern on EEG, EOG, and EMG of REM sleep during the standard and accepted scoring epoch in many labs (30 seconds) (Rechtschaffen & Kales 1968) with no other duration criteria.

In [redacted] work in adult MDD patients with major depressive disorder, it was observed that 10% of individual sleep night REM latency scores were pushed to the second REM period by requiring 3 minutes of REM (Pittsburgh "3 minute rule") to designate a REM period. This happened equally across each of the 3 nights of study. The mean data for REM latency, scored either way, remained close, but the variation (standard deviation around the mean) was sharply increased by the three minute rule method. This will serve to reduce statistical power in clinical/biological correlation data. In our study population, 14% of the subject nights had first REM latencies of 0.5 - 2.5 minutes, which would have skipped them to the 2nd REM period. The <3.0 min REM latencies occurred almost equally across 3 nights of study.

3. Dexamethasone Suppression Test

Carroll et al., (1982) recognized that the HPA axis activity in depression was less pronounced than in Cushings disease and developed the use of the DST in major depression - particularly endogenous or melancholic depressions. Carroll suggests a 1 mg dexamethasone challenge, and a 5 mcg/dl threshold value in adults. Reports by some (Rush et al., 1982a; Carroll et al., 1981; Carroll et al., 1976b), but not all, suggest that the DST can usefully differentiate endogenous (melancholic) from nonendogenous, nonmelancholic depressions and normal controls. In addition, the DST may be a laboratory index of recovery (Angst, 1980; Schlesser and Rush, 1981; Albala and Greden, 1980; Goldberg, 1980; McLeod, 1972) or an indicator for early relapse, hospitalization, or suicide (Greden et al., 1980; Coryell and Schlesser, 1981; Carroll et al., 1981). Rush et al., (1982b) compared a 1 mg and a 0.75 mg dexamethasone dose in normal controls. The concluded that the 1 mg dose was the lowest effective dose that could be used in diagnostic testing in adults.

Poznanski et al., (1982) reported on the DST in prepubertal children, using a 0.5 mg dexamethasone dose. They found that of nine children diagnosed as having major depressive disorder, five showed nonsuppression, whereas in a group of nine children with other diagnoses only one showed nonsuppression; i.e. the sensitivity and specificity were similar to adults. Extein et al., (1982) and Robbins (1982) reported similar findings with a 1 mg dexamethasone dose in adolescents.

Recently, Doherty et al., (1986) reported 15 out of 34 (44%) patients, as old as 16 years, with MDD evidenced DST nonsuppression with a 1 mg dexamethasone dose compared to 1 out of 34 (3%) of nondepressed subjects. There were no significant differences in the percentage of depressed children who failed to suppress with a high, medium or low dose of dexamethasone per kilogram of body weight when a 1 mg standard dose was used on all children.

The aim of our study to date has been to evaluate the sensitivity and specificity of the 1.0 mg and 0.5 mg dexamethasone suppression test (DST) in children and adolescents. In our inpatients, this was done by performing the DST at both 1 mg and 0.5 mg in random order to those with MDD and dysthymia. In addition, we gave our normal control children 0.5 mg DST's, with the preliminary aim of seeing when developmentally the 0.5mg dose was inappropriate, i.e. too many false positives were present. Our evolving data has led us to revise some of our original suppositions.

With regard to the 72 patients with MDD, 52 received both the 1.0 mg and the 0.5 mg doses separated by one week; 9 received only the 1.0mg dose, and 9 only the 0.5mg (data are missing on two). Of the 61 (52+9) MDD patients with 1.0 mg, DST nonsuppression rate (post dexamethasone cortisol > 5 mcg/dl) was 13/61 (21%). One possibility to explain the low rate is that many subjects, because of the study design had the DST done 1-2 weeks after hospital admission. Sixty-nine percent of the patients had the 1.0 mg DST after 7 days of hospitalization and 30% after 14 days of hospitalization.

With regard to the normal controls, 48/62 received the 0.5mg dose. Of these 26 or 54% evidenced DST nonsuppression. Data on 33 of these 48 normal controls were recently presented (Emslie et al., 1989) (Appendix). DST suppressors and nonsuppressors did not differ by age, sex, developmental stage, height, weight or surface area.

Although not a part of the original design, we also obtained dexamethasone blood levels. No nonsuppressors had 4pm post dexamethasone levels above 0.8 ng/ml. However the number of subjects in this group is small. These findings are consistent with the report by O'Sullivan et al (1989) who suggest that a dexamethasone window would refine the sensitivity and specificity of the DST, i.e. if the dexamethasone levels are too low then false positives will occur but if they are too high then over-suppression occurs. We are in the process of obtaining dexamethasone levels on a larger sample of our subjects, both normals and patients, to assess this further.

Children, inspite of their smaller sizes have a larger proportional liver mass and therefore may metabolize dexamethasone faster than adults. We have completed the 1.0 mg DST in 11 normal controls, none of whom had DST nonsuppression. These data led us to propose to conduct the DST 7

days after the initial appointment (or 14 drug free days). All subjects will receive the 1.0 mg DST (4pm blood sample) and a serum dexamethasone level (4pm). Currently, we have insufficient data to predict an individual's dexamethasone level. So, at this time, we will persist with a fixed level of dexamethasone.

4. Treatment

The efficacy of tricyclic antidepressants (TCA's) for MDD in adults is well established. Currently, there are only four published placebo-controlled studies of TCA's in children (Kashani et al., 1984; Puig-Antich et al., 1987; Preskorn et al., 1987; Geller et al., 1990). These used amitriptyline (Kashani, et al., 1984), imipramine (Puig-Antich, et al., 1987; Preskorn, et al., 1987) and nortriptyline (Geller, et al., 1990) respectively. Only Preskorn's study with imipramine showed a difference between depressed and controls. It has been suggested that a more serotonergic antidepressant may be more effective (Geller, et al., 1989). Nortriptyline has been extensively studied in children and adolescents with regards to its pharmacokinetics, steady state plasma levels, safety and efficacy (Geller, et al., 1984, 1985). In adolescents there is even less available published data. Kramer et al (1981) studied 20 adolescent inpatients in a random assigned placebo controlled double-blind study of 200mg per day of amitriptyline. There was no difference between the active medication and placebo groups. Significant improvement was found in both groups, at 80% and 70%, respectively. In an open protocol with 34 outpatient adolescents, assessing plasma level and response on imipramine, 44% clinically responded (Ryan et al., 1986). Ryan (1988) has also reported on the efficacy of MAOI's in TCA nonresponders. He reports that 74% achieved a good or fair response though concerns were raised about adolescents following the dietary restrictions. In a recent open study (Ambrosini, 1989), adolescents may have taken longer than the usual 6 weeks to respond.

Though studies to date have showed limited results with antidepressant agents, it is too early to suggest that they are not effective in children and adolescents with major depression. There is a growing consensus that it is important to identify which patients stand the best chances of responding to psychopharmacological treatment; it is equally important to ascertain who is likely to respond to placebo. Factors that may influence response to acute treatment may include biological variables, diagnostic and clinical variables, family history variables, and other factors.

The high placebo response rate in children is of particular relevance to our study. As indicated above, preliminary evidence in adults reveals that depressed patients with reduced REM latency (Fairchild et al., 1989) and DST nonsuppression (Qualls et al., 1980; Brown et al., 1987) show a decreased response to placebo. In children there is a report by Preskorn (1987) that dexamethasone nonsuppression predicted differential response to imipramine vs. placebo. In adolescents, Robbins et al., (1989) note that DST nonsuppressors were less likely to respond to psychosocial treatment alone. In our inpatient study population (developed in the prior study) we retrospectively examined response to treatment (i.e. at discharge from hospital of 30 adolescents with MDD). Two raters independently reviewed the charts using the CGI and CGAS at initial evaluation and at discharge.

Sixty percent of the adolescents were treated with only one antidepressant (n=18) during hospitalization. The rest received no medication (n=3) or multiple medications (n=9). Sixty-seven percent of those who were treated with only one medication had a short REM latency, compared to 25% of those who received multiple or no medications. These preliminary retrospective data are consistent with the idea that reduced REM latency is predictive of a positive response to antidepressant medication as in adults.

Our pilot study funded by the [redacted] for follow up all subjects with MDD has begun. We have located 24 adolescents, 50% of whom have had a definite relapse/recurrence. Of these 75% had a short REM latency, compared to 50% without a definite relapse or recurrence. These are also consistent with the adult data suggesting that reduced REM latency predicts relapse/recurrence as well as response to treatment.

Placebo controlled studies are not possible on our inpatient setting without including cost for hospital bed days. The extension of this current study to outpatients would enable us to address the question of effectiveness of fluoxetine versus placebo in the treatment of MDD in children and adolescents and define which variables predict response. We will diminish the placebo response by the length of the evaluation (at least two weeks) and the use of an initial one week placebo run in prior to randomization.

We will use fluoxetine for several reasons: (1) Studies to date with predominantly noradrenergic agents have shown little drug/placebo difference in depressed children and adolescents, (2) fluoxetine is a highly selective serotonergic agent, (3) fluoxetine is well-tolerated in children and adolescents (Riddle et al., 1990; Joshi et al., 1989), (4) in adolescent outpatients the risk from suicide may be less with fluoxetine than with other antidepressants due to its safety in overdose.

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To date we have treated 23 children and adolescents ages 8 to 19 with fluoxetine. They have generally tolerated the drug well. It was discontinued in 3 subjects because of side effects (1 - hypomania, 2 - stomach aches and sleep problems). 17/23 (74%) showed moderate to good clinical response.

Currently no data on serum levels of fluoxetine and its primary metabolite norfluoxetine are available in this age group. We have preliminary data on several patients. There is a suggestion that fluoxetine levels continue to rise after 4 weeks (see Appendix A for graph of fluoxetine level in a 17 year old boy). As a result we propose to use a single dose over an 8 week period without increasing the dose. A dosage decrease is allowed if side effects develop. A recent study in adults suggests that continuing 20mg after 4 weeks is equally effective as increasing to 40mg (Schweizer et al., 1990)

D. EXPERIMENTAL DESIGN and METHODS:

1) Overview of Design:

A total of 120 outpatients, age 8 to 18, all of whom meet DSM-III criteria for MDD will be studied, following the same format previously described for inpatients. Based on referrals in the past 3 years it is expected that about half will be 8 to 12 years of age and half 13 to 18 years. The study is conducted in 2 phases. First, diagnostic evaluation, including PSG and DST, and secondly, treatment, with separate consent forms for each stage. The first phase is two weeks long. It is similar to our previous study except for the use of outpatients and the additional severity measures and other diagnostic modifications noted above.

The second phase consists of a one week placebo wash-out followed by an 8 week randomized double-blind, placebo-controlled, fixed dose study (20mg/day) of fluoxetine. It is expected that 120 patients completing the evaluation phase and still meeting entry criteria, before the single blind placebo wash-out phase, will result in 80 patients completing the drug study. We expect about 10% (12) not to agree to the recommendation for medication, 10% (12) to respond to the placebo run in, and 10% (12) to not complete the minimum time (4 weeks) on drug trial. We expect to treat about 30 patients a year for four years. In the fifth year, the treatment phase will be completed, and, additional patients will be added if necessary, to have 80 completers of the drug trial. In that year we will also analyze data.

The study continues until 80 subjects, (40 children and 40 adolescents) have completed the protocol. The definition of children and adolescents remains somewhat controversial. For this study, children are defined as age 12 years or younger and adolescents as age 13 years or over. The decision to use age as opposed to pubertal status is based on several factors. Preliminary evidence (Coble et al., 1984; Emslie et al., 1988) suggests that PSG variables correlate with age to a greater extent than pubertal status.

In terms of drug metabolism it is clear that children have a larger proportional liver mass than adolescents though there is no clear evidence as to whether the change in this variable is influenced more by age than pubertal status. All subjects are also coded by pubertal status, (Marshall and Tanner 1969, 1970) so secondary analyses can also be conducted based on pubertal status. It is clear that any definition of children and adolescents is arbitrary, and has its drawbacks, but by carefully assessing pubertal status, as well as age the drawbacks are limited.

2) Subjects

Children and adolescents ages 8 to 18 years with a diagnosis of MDD will be recruited from our outpatient services, referrals to our psychopharmacology clinic, [redacted] Pediatric Behavioral Neurology Program, and the adult affective disorders program. The patient flow was discussed above (pg).

Inclusion Criteria:

a. Outpatients with nonpsychotic, major depressive disorder single or recurrent episodes according to DSM-III-R.
b. Ages 8 to 18 years.
c. Normal intelligence as assessed clinically or by psychometric testing if evidence of IQ < 80.
d. Willing and able to provide informed assent (child), consent (parent).

Exclusion Criteria
a. Bipolar I or II disorder
b. Psychotic Depression
c. Bipolar I disorder in one or more first degree relatives
d. Significant previous or concurrent medical illness
e. Prior adequate treatment with fluoxetine
f. Independent sleep disorder
g. Alcohol and substance abuse
h. Anorexia and Bulimia
i. Known allergies to tricyclics
j. If sexually active, inadequate birth control measures.

One aim of the inclusion and exclusion criteria is to exclude subjects where there is evidence antidepressants do not work. However, data are limited in this age group and it would be premature to be overly exclusive. Additionally, the population studied cannot be so restricted that either the results are not generalizable or it is impossible to collect subjects. Bipolarity and psychotic features appear to be factors leading to unresponsivity to antidepressants and increased likelihood of precipitating a manic episode. Excluding subjects with first degree relatives with Bipolar disorder seems appropriate and should not overly hamper the treatment of subjects. We have not excluded previous failures on other antidepressants because of the possibility that fluoxetine may be helpful in this group. Other exclusion criteria are included because of possible confounds with biological variables, e.g. alcohol and substance abuse, sleep disorders, eating disorders, etc.

3) Diagnostic Method

Possible patients for study are scheduled for a full evaluation after telephone screening for appropriateness. The initial evaluation interview will not be scheduled until the patient has been drug free for 7 days (if they are on medication of any sort). In addition to a structured psychiatric interview, the evaluation includes a physical and neurological examination as well as laboratory tests (SMA 20, CBC, UA, thyroid functions tests) to rule out medical disorders that may present as depression.

Prior to the initial interview, the diagnostic phase of the study is explained and written informed consent will be obtained from the parents and assent from the patient. The evaluation will be done over three consecutive weekly visits (See Table 2). At the initial visit, each patient and parent will be interviewed separately, using the Diagnostic Interview for Children and Adolescents (DICA). The parents are interviewed using a modified family history RDC by a separate interviewer. The parents and child are interviewed together to complete the Children's Depression Rating Scale (CDRS). In addition the parents complete the parent form of the Bellevue Index of Depression (BID) and the patients complete the Weinberg Screening Affective Scale (WSAS) as well as the Children's Depression Inventory (CDI) (for children) and the WSAS and Beck Depression Inventory (BDI) (for adolescents). While the child is completing the DICA, the family history (RDC) interview is conducted by a different interviewer who is blind to the DICA results.

If the patient meets inclusion and exclusion criteria, he/she is scheduled for DST and sleep polysomnography and a repeat interview one week later.

At the second interview, the patient and family are interviewed by one of the three primary clinical investigators (GE, WW, RK). The DSM-III-R data from the DICA will be reviewed, the depressive items of the Kiddie-SADS and CDRS will be completed along with the Child Global Assessment Scale (CGAS), BID and Brief Psychiatric Rating Scale for Children (BPRSC). A third interview is scheduled one week later by which time the sleep polysomnography and DST will be completed. This interview will be done by another of the three clinical investigators above and will be independent from the previous psychiatric assessment. Again, the DICA DSM-III data will be reviewed and the K-SADS depressive items and a CDRS completed. At this interview the parent and patient self-report measures will be repeated. The family history is reviewed at each clinical assessment because often more information becomes available with progressive interviews.

If a subject meets inclusion and exclusion criteria on all three interviews and the CDRS-R score is > 40, then he/she proceeds to the treatment phase of the study. The Kiddie-SADS items can be rated for present episode and past week. To be included in the treatment study, the subject must meet criteria for MDD at the time of all three interviews, the 2 clinician interviews being done independently. The interviewers do not need to agree on additional diagnoses at that point unless they are part of the inclusion/exclusion criteria. If at any of the assessments, they do not meet criteria then the data will be reviewed and the patient reassessed by a third clinician.

A final consensus diagnoses to include concurrent diagnoses will be determined in our weekly diagnostic conference with information from all sources available. This process has been ongoing in our group for the past five years. As described in the progress report, all DSM-III criteria symptoms are reviewed, and the subject is diagnosed by all criteria met at the time of the evaluation except where clear hierarchical rules exist, e.g. conduct disorder vs. oppositional disorder. The clinical information is reviewed in reference to the best estimate of onset of each disorder.
Onset is defined as the time at which the disorder becomes clinically significant (i.e. the symptoms of the disorder causes dysfunction and effects performance at home, school or play). Disorders present concurrent with the MDD are then coded as to whether or not, in the past, they are clinically significant when the subject does not meet criteria for MDD.

Sleep polysomnography will be conducted 7-10 days after the initial interview (after at least 14 drug-free days). Prior to the initial interview, the proposed diagnostic procedure will be explained to prospective subjects on the telephone and they will be asked to discontinue all medication and start a caffeine-free diet. After the initial interview and acceptance into the study the subjects visit the sleep laboratory. Their routine bedtimes are determined and they are instructed to maintain a regular sleep schedule for the 5 days prior to the sleep study (full instructions for subjects are in Appendix. G) They keep sleep logs for the five days prior to the sleep study. The sleep studies are scheduled at approximately the same point in the assessment for every subject. Urine for drug screen is obtained if there is any question on interview or from sleep recording of drug use.

Dexamethasone (1mg) is given to the subjects (parents) at the end of the first interview. Directions are provided to take it at 11:00pm on the night before the next interview. The cortisol and dexamethasone levels will be obtained at 4:00pm on the day of the second interview. It is expected that the whole diagnostic process, 3 interviews, sleep and DST will be of the same duration and structure for all subjects.

4) Treatment

At the end of the 2 week Phase I diagnostic evaluation, if the patient meets inclusion and exclusion criteria and has a CDRS-R score > 40, then the treatment part of the study (Phase II) is explained to the patients and parents. (See Table 2) Options for treatment other than medications will be given. If the patient agrees to the treatment study, informed consent is obtained from the patient and parents. Those subjects not wanting to participate in the study are followed in the psychopharmacology clinic or referred to other clinicians for treatment. Those agreeing to participate, begin a one week placebo wash-out followed by an eight week double-blind, randomized placebo controlled study. Study participants are seen weekly for about one hour during the course of Phase II..

Symptoms and progress are reviewed. Standardized assessments and a side effects checklist are used and questions answered. Patients are not in individual or family therapy during this study. If problems occur, advice is given on how to manage the problems (notes will be kept on nonmedication interventions suggested). Compliance is monitored by counting returned pills and new bottles given weekly. Two extra days of pills are given in case emergencies arise and a visit cannot be made on schedule. No adjunctive medication are given during the course of the study.

At entrance to the study, subjects are given a 1 week supply of placebo, the same number of pills as at the beginning of active treatment. At second visit (end of one week of placebo), they are re-evaluated using the CDRS, C-GAS and CGI, side effect checklist, BPRS-C, and an EKG. If their CDRS is < 40 at that point, they are continued on placebo for another week and re-evaluated. If CDRS is still < 40, they are dropped from the study and followed clinically. At week 1, if CDRS is still > 40, they are randomized to placebo or fluoxetine 20mg tablets and given a one week supply (plus 2 days). The pharmacy assures random assignment to condition.

The subjects will take a fixed dose, one pill in the morning for the duration of the study. Blood levels are obtained weekly for the first 4 weeks and again at 8 weeks. Blood levels will be drawn approximately 8 hours after dose (i.e. 4 pm). EKG's will be done at baseline, week 4, and week 9. If side effects develop the clinician can reduce the dosage to 1 tab every other day. If they persist, the subject is discontinued from the study.

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Table 2

Summary of Project

	Evaluation			Treatment										
Week	**-2**	**-1**	**0**	**0**	***1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	***9**
Informed Consent	X			X										
DICA-Child & Parent Versions	X	R	R											
K-SADS Depression Items		X	X	X	X									X
Family History RDC	X	R	R											
Children's Depression Rating Scale	X	X	X	X	X	R	X	X	X	X	X	X	X	X
Bellevue Index of Depression	X	X	X	X	X	a	X	X	X	X	X	X	X	X
Bellevue Index of Depression-Parent	X	X	X	X	X	n	X	X	X	X	X	X	X	X
Weinberg Screening Affective Scale	X		X	X	X	d	X	X	X	X	X	X	X	X
CDI or BDI	X		X	X	X	o	X	X	X	X	X	X	X	X
Clinical Global Improvement Scale	X		X	X	X	m	X	X	X	X	X	X	X	X
Child Global Assessment Scale		X		X	X	i	X	X	X	X	X	X	X	X
Brief Psychiatric Rating Scale		X		X	X	z	X	X	X	X	X	X	X	X
Consensus Diagnosis			X			e								
Side Effects Checklist			X	X	X	d	X	X	X	X	X	X	X	X
Sleep Log	X													
Physical Exam	X													
Laboratory Tests (SMA 20,CBC,UA,TFTs)	X										X			X
3 Nights of Polysomnography		X												
Dexemethasome Suppression Test		X												
Electrocardiogram					X					X				X
Fluoxetine/Norfluoxetine Level							X	X	X		X			X
Additional Blind Rater *					X									X

Note: R = Reviewed by clinician with subject and parents

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5) Assessment of Response

On weeks 1-8, clinical measures will be repeated. On week 9 (8 weeks of active treatment) measures will be repeated with repeat of Kiddie-SADS depressive items. A second clinician not involved in the clinic, will do a CDRS-R, GGI & CGAS on weeks 1 and 9, independent and blind to progress of the patient. An adequate "drug" exposure is defined as at least 4 consecutive weeks of treatment. We feel 4 weeks is the minimum trial necessary to be considered an adequate trial.

For statistical purposes response is assessed by changes in CDRS, C-GAS and CGI. The BID and BPRS-C are included for comparison and to further develop information on those forms. Response is also defined categorically (i.e. responders vs. nonresponders). Responders are defined as subjects with CDRS-R 28. Geller used both unrevised CDRS score of <20 and <25 to categorize response (Geller, 1986, 1989). Poznanski reports that all children rated <25 on the CDRS were rated nondepressed globally and did qualify for research diagnoses of depression (Poznanski et al., 1983). A CDRS score of 25 equates with a CDRS-R score of <28 (Poznanski, 1985).

Responders at the end of the study will continue to be followed monthly on whatever they are taking. At between 6 - 9 months, consideration will be given by the treating clinician to discontinuing treatment. This range allows treatment to be discontinued at a time when relapse or recurrence would have least impact e.g. end of school, summer, etc. Following discontinuation, the patients will continue to be followed monthly with ratings for a minimum of 12 months from the time treatment started. If the subject has a recurrence/relapse (either after discontinuation of the treatment or after the end of the acute treatment), then only the treating clinician will have access as to whether or not they were on placebo or fluoxetine. Similarly non-responders will be treated openly as clinically indicated. The rationale for following subjects after the end of the study, is that it is good medical care and very preliminary hypothesis generating information can be obtained for the development of future studies at no additional cost.

Maintaining the Blind

The weekly assessments during the acute treatment, weeks 1-9, are completed by one of the clinical investigators (RK) who is not involved with the care of the patients after the end of the study and will remain blind to whether they are or are not on active medication until all the subjects have been run. Additionally, an experienced rater from outside the clinical program (CH), completes independent assessments, at week 1 and 9, on each subject. As this only involves subjects who make it to randomization it is not an excessive clinical load to assure "blind" rating of response. The rationale for the additional rating is a check against inadvertent unblinding of the primary evaluator.

Clinical management, initial evaluation, and all repeat evaluations are conducted blind to laboratory data. The sleep laboratory and the chemistry laboratory stores data on PSG variables, cortisol, dexamethasone, and fluoxetine levels, the hospital pharmacy manages the medication and dispense either placebo or active medication. The pharmacy only informs the chemistry labs as to status (active drug vs. placebo) so as to avoid running unnecessary blood levels. The chemistry laboratory will batch cortisol and dexamethasone levels, so they can be run by a technician blind to treatment status at the end of the study.

6) Study Completers

Study completers are defined as those with an adequate drug exposure, as defined above, i.e., 4 weeks of treatment. Those subjects who fail to complete the study are replaced until a total of 80 have been treated in the protocol. This strategy will ensure an adequate sample size to detect drug/placebo differences. The reasons for failing to complete the study will be recorded (missed appointments, side effects, clinical worsening, etc.) The two treatment groups will also be compared using all randomized subjects (completers plus non completers) to determine if there is a disproportionate loss of certain patient types from one cell or another.

7) Clinical and Descriptive Measures

Choice of the clinical instruments that will be used is based on several factors. A structured DSM-III based interview covering all DSM-III child and adolescent disorders is essential. The rationale for choosing the DICA and depression items of the K-SADS are described below. [redacted] who has recently joined the group, has worked extensively with the DICA. The instrument that is supported by the most available data for measuring depressive symptoms in pharmacology trials is the CDRS. The C-GAS and CGI allow for systematic accumulation of general measures of functioning and improvement. Other measures on which we already have substantial data with regard to diagnosis are used to explore further their usefulness in treatment studies.

a. Diagnostic Inventory for Children and Adolescents (DICA). The characteristics of the 5 major structured interviews for children and adolescents has been recently reviewed (Gutterman et al., 1987) The DICA has been compared to the K-SADS-P (Carlson et al., 1987) with strengths and weaknesses of each reviewed. The DICA is a structured interview developed by Herjanic (1975) and was initially based on DSM-III criteria (it has since been revised for DSMIII-R). It consists of two separate interviews with different formats for patients and parents. This instrument was chosen for several reasons: it uses DSM-III criteria; it is fully structured, and we have extensive experience with it. There is a tendency with the DICA to overdiagnose disorders (Carlson et al., 1987) but this can be modified in "best-estimate" consensus diagnostic conference, utilizing data from all available sources. The reliability, validity, and parent-child agreement of the DICA have been recently reviewed and updated (Welner et al., 1987). Studies using this interview schedule show that children/adolescents can provide reliable information as judged by concordance with information given by their mothers (Herjanic et al., 1975). Also disturbed children can be distinguished from nondisturbed children (Herjanic and Campbell, 1977), and adequate interater and intrarater reliability can be obtained (Herjanic, 1982). In addition, agreement between child and parent on individual symptoms and in diagnostic groups has been appraised (Herjanic, 1982; Reich, 1982). From this work a revised interview schedule was developed that will be exploited in this study. Generally, it has been found that children and mothers agree more often about the child's problem when the question concerns concrete, observable, and severe symptoms. Mothers report more behavioral symptoms, whereas children report more subjective symptoms relating to their feelings.

b. Kiddie-Schedule for Affective Disorders and Schizophrenia - Present State (K-SADS-P) - Depressive Symptoms (Appendix B)

We have our greatest experience utilizing the DICA for diagnosis. However a major problem, in the area of depression, is the extent of symptoms is not assessed. We have, therefore, decided to supplement the DICA with the depression items in the Kiddie-SADS. The symptoms are anchored by level of severity. These items also allow for semistructured interviewing. Further difficulties as to when in the episode to rate the symptoms are overcome as this instrument allows for rating at worst part of episode and for the past week, which makes it more useful for repeated assessments.

The K-SADS (Puig-Antich et al., 1978; Chambers et al., 1985) is an adaptation for children and adolescents of the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978). It has undergone extensive revision and is in wide use. The depression items have been used separately as a severity measure in a double-blind, placebo, controlled study of imipramine in children (Puig-Antich, 1978).

c. Children's Depression Rating Scale - Revised (CDRS-R) (Appendix C)

The CDRS-R, developed by Poznanski, is a clinician rated instrument designed to measure the presence and severity of depression in children (Poznanski et al., 1984, 1985, 1987). While it has been designed for 6-12 year old children, we also plan to use it in adolescents to avoid different severity measures in different age groups. It is modeled after the Hamilton Depression Rating Scale for adults but also includes questions about school.

The CDRS-R consists of 17 items. Fourteen of these items are rated on the basis of the subjects' responses to a series of standardized questions. The remaining three are based on the child's nonverbal behavior. Each item is scored on a 1-5 or 1-7 scale with a rating of 1 indicating no abnormality. Accordingly, the minimum score is 17 and the maximum score is 113. In previous pharmacotherapy trials (Geller, 1986; Preskorn, 1987) with the unrevised version of the CDRS, a CDRSR score of 35 has been used for entry into the study and a score of 25 indicated of remission. On the revised form, a CDRS-R score of 40 is usually associated with a diagnosis of depression (Poznanski et al., 1984). An equivalent score for remission would be 28. The CDRS has good interrater reliability and correlates highly with global rating of depression.

d. Children's Global Assessment Scale (C-GAS) (Appendix D)

The C-GAS was adapted from the Global Assessment Scale for Adults by Shaffer (1985). The subject is rated by a single number, equal to the most impaired level of general functioning over the specified time period. The C-GAS is scored on 1-100 continuum. It is included as it can assess the overall level of functioning, not necessarily just that related to depression.

e. Clinical Global Impression (CGI) (Appendix E)

The CGI was developed at the NIMH and has been used in both adult and child populations. Severity is assessed on a 7-point scale and, for this study, will be based on clinicians experience with

depressed children and adolescents. Global improvement is assessed on a 7-point scale. A score of 1 or 2 will be used as an alternate indicator of response.

f. Other Measures (Appendix F)

Other measures will be used to develop additional data concerning their utility and to provide self report (and parent report) data. These are the BID, BPRS-C, WSAS, BDI, CDI, WSAS. There is sufficient overlap between instruments that the additional interview time necessary to complete them is minimal.

The BID (Petti, 1985) can be used as a measure of severity of depressive symptomatology. It was developed by Petti (1978) from the symptoms delineated by Weinberg (1973). It is administered in a semistructured interview to both children and parents or other knowledgeable adults. There are 10 major symptom groups and 40 minor symptoms. Each of the minor symptoms is ranked from absent to severe on a 0-3 scale. The symptoms, to be considered positive, must be of concern to the parent, child, teacher, or referring professional, must be a change from usual self and have been present for more than a month. In this study the BID is used both as a measure of severity and as a criterion measure (Weinberg criteria). The clinician assessment is noted on the BID from all available information and the parents complete a parent version (BID-P). It is to be used in this study because of our familiarity and experience with the forms and to develop further data on its use in a treatment study. The mean BID score of the 72 MDD children and adolescent inpatients studied is 70.82 $\pm$ 13.5 with a range of 37 to 96.

In this study the Brief Psychiatric Rating Scale for Children (BPRS-C) is used initially to assess presence of other symptom clusters in addition to depressive symptoms. It also will be used in conjunction with the BID for follow-up evaluation and response to treatment.

The BPRS-C was developed by Overall and Pfefferbaum (1982) and consists of 21 symptoms rated on a 7 point scale. The symptoms were developed using factor analysis from 63 symptoms found in routine clinical practice. The BPRS-C includes three key variables to represent seven empirically defined factors. The seven factors are: behavior problems, depression, thinking disturbance, psychomotor excitation, withdrawal retardation, anxiety and organicity.

The information for completing the BPRS-C is obtained from interviews with both parents and child though the actual ratings are based on direct clinical observations. Preliminary work for developing this scale has been done but further work is needed to establish interrater and intrarater reliability and the association of various symptom clusters and DSM-III diagnoses.

The Weinberg Screening Affective Scale (WSAS) is a 54 question self-report scale for children and adolescents. The respondents are asked to answer yes or no to a series of questions that operationalize each of the ten major symptom groups that are covered by the BID. The WSAS was developed by [redacted] and has been administered to over 1,000 patients in the past 6 years. The scoring of the measure will allow assessment of where the patient perceives having problems in the 10 major symptom groups and also it is possible to develop a self-report severity score with a maximum total of 54. The WSAS lacks reliability and validity data but is included both to develop that data, and because it utilizes the same symptoms as the BID interview and parent report. Two normal (adolescent) population studies have been completed. We gave the WSAS to 3,294 high school students and preliminary data have been published (Weinberg 1987, 1988; Emslie et al., 1990a).

The Beck Depression Inventory (BDI); (Beck, et al., 1984) has been used extensively with both adults and adolescents in research studies. For this study it will be used in adolescents. It has been evaluated psychometrically within a wide variety of psychiatric and normal populations (Beck & Beamesderfer, 1974). The instrument has been demonstrated to have high internal consistency and test-retest reliability and validity with adolescents (Reynolds, 1985). Ease of administration and strong psychometric properties similar to those demonstrated for adult populations, and validation across clinical and nonclinical populations, make this one of the standards in single point, self-reported depressive state. The 21 items assess the major symptom categories associated with depression while placing each response on an 0-3 scale of severity. The higher the total score (range = 0 to 62), the more severe the rating of depression. The symptoms and attitudes covered are mood, pessimism, sense of failure, lack of satisfaction, guilt feelings, sense of punishment, self-dislike, self-accusations, suicidal wishes, crying, irritability, social withdrawal, indecisiveness, distortion of body image, work inhibition, sleep disturbance, fatigability, loss of appetite, weight loss, somatic preoccupation, and loss of libido. The BDI is developed for self-administration and asks the respondent to describe "how you have been feeling for the past week including today" for each item.

Children's Depression Inventory (CDI) (Kovacs et al., 1985) was developed from the BDI and will be used as a self report measure of severity of depression in children.

A side effect checklist is also completed prior to starting medication and weekly during the

study. This has been in use in our psychopharmacology clinic for the past 3 years and is based on the Subjective Treatment Emergent Symptoms Scale (STESS) (NIMH). This is completed by the patient and parent and reviewed by the clinician.

8) Biological Measures

a. Sleep Polysomnogram Measurements

Three consecutive nights of sleep polysomnographic recordings will be conducted following at least 14 drug free days. About 80% of our inpatients present for evaluation already drug free for at least 14 days. The sleep EEG recordings will be obtained in the Sleep Study Unit, directed by [redacted] This facility has extensive experience in sleep studies in child, adolescent and adult depressed patients. [redacted] has also performed several studies in normal children and adolescents in terms of sleep stage architecture and the neuroendocrinology of sleep. [redacted] in fact, was the first to describe the sleep stage pattern in infants, children and adolescents (1962; 1966). EEG, electrooculogram (EOG) and submental EMG lead placements are used. Extra electrodes are placed noninvasively whenever suspicion of an independent sleep disorder exists. Records are scored according to Rechtschaffen and Kales (1968) criteria. Sleep onset will be recorded when subjects have ten consecutive minutes in Stage 1 or deeper sleep that is interrupted by no more than two minutes of awake time or movement. Stages REM 1, 2, 3, and 4 are scored in half-minute epochs and resented in minutes. REM latency, REM percentage, and actual time spent in stages 3-4 sleep, sleep continuity, and REM density for each REM period will be measured. The methods will be the same as previously used by our group in adults (Rush et al., 1982). In addition, sleep onset will also be recorded using additional criteria (see Appendix G) and REM latency will also be scored for comparison, using the criteria developed by [redacted] in which sleep onset is defined as the beginning of the first ten minutes of sleep that contain which no less than eight minutes are spent in any stage of sleep excluding stage 1, and the first REM period must satisfy a "3 minute duration criterion." Sleep logs for five days prior to lab recording are maintained by the patients. A sleep history is also obtained. (See Methods section of paper for more detail).

Information is obtained from the parents and child as to their usual bedtime and rise times. All attempts are made to keep total sleep times and sleep clock hours similar to the patient's experience.

b. Dexamethasone Suppression Test (DST)

All patients are given dexamethasone 1.0mg at 2300 hours. Cortisol and dexamethasone levels will be drawn at 1600 hours the next day. All patients are weighed the week prior to the DST and the day of the DST, and these weights are recorded.

c. Assays

The method for serum cortisol determinations (using RIA methods) and fluoxetine assay (using high performance liquid chromatography [HPLC]) are described fully in Appendix H.

9. Data Analysis

The data will be computerized and managed using a screen and menu guided application built in PC-SAS AF and FSP. Throughout the study, quality control procedures will be in place to assure accurate and complete data at the end of the five years. Prior to statistical analyses, a thorough review of the data including computerized edit checks and evaluation of all missing data and unusual data points will be carried out. In addition, the univariate features of the data, such as deviations from symmetry or heteroscedasticity, will be checked, and decisions made regarding the need to introduce nonlinear transformations for the purpose of stabilizing variance.

Most of the dependent variables and predictors used in this study can be analyzed either as continuous variables (the form in which they are obtained) or as categorical variables. The choice of level of measurement and associated analytic approaches is somewhat arbitrary, but each alternative does carry with it specific strengths and weaknesses, which must be evaluated once the empirical data are in hand.

Categorization assumes that a good basis for setting a cutpoint exists (which may not be true) but has the potential advantage that unreliability within each group is ignored and a valid distinction between groups may be heightened. However, this is not likely when the cut point is in a dense region of the frequency distribution (e.g., near the mean or median of a bell-shaped distribution), where subjects with very similar values are assigned to different categories, and unreliability in the

continuous measure results in classification errors. Analysis of continuous measures, on the other hand, usually is more powerful as well as allowing more detailed examination of the nature of relationships between variables (e.g., nonlinearity). Both approaches are described below.

In the critique of the previous submission, the reviewers point out that covariates (such as comorbidity, duration of illness, prior episodes) might influence treatment response, and suggest that blocking on these is preferable to posthoc statistical controls. We have weighed carefully the advantages and problems of stratified randomization, and concluded that stratified randomization on age and gender is warranted and feasible. The revised experimental design incorporates a two by two stratification on age (categorized at $\leq$ 12 vs > 12 yrs) and gender.

Stratification on additional variables would be difficult and may not be warranted. First, setting up the strata on potential covariates requires knowledge we do not have. For instance, we do not know which types of comorbidity must be distinguished and which may by combined if we chose to stratify on comorbidity. In fact, a major aim of this trial is to increase empirical knowledge of the factors affecting response to antidepressant medication in children and adolescents.

Second, the study sample proposed here is close to a size at which gains in statistical efficiency resulting from stratification becomes minimal (Meinert, 1986). Third, introduction of additional blocking factors multiplies the number of randomization lists and may actually result in imbalance if blocks on infrequently encountered cells in the design are not completed. For instance, adding 4 strata for comorbidity would produce 16 randomization lists. If a blocksize of, say, 6 is used, it is likely that for several of the 16 cells, there will not be sufficient subjects to complete even the first block. Meinert (1986) notes that "it is unreasonable to expect that all important sources of baseline variation can be controlled via stratification during randomization. Analysis procedures involving post-stratification and multiple regression will be required to adjust treatment comparisons for baseline differences not controlled via stratification." (p. 93; see also Peto et al., 1976, p. 600f.; Fleiss, pp 149ff.).

Finally, differential attrition between treatments in a drug trial can undermine attempts to balance by experimental design. For all of the above reasons, we propose to stand by our previous plan of analyzing and describing the effects of any baseline differences that randomization fails to eliminate or attrition subsequently introduces into the achieved sample.

a. <u>To determine whether outpatient children and adolescents with Major Depressive Disorder (MDD) evidence sleep polysomnographic and DST abnormalities prior to treatment, as compared to normal controls.</u>

PSG variables are known to be related to age but not gender in our normal control sample of children and adolescents, but the relationship of these variables is not known in depressed outpatients. The relative likelihood of depression in each gender varies with age in depressed children and adolescents, and the characteristics of these biological measures may also be conditional on age and gender in this population. Therefore, the effects of these two factors on biological parameters measured prior to treatment will be carefully studied both within the depressed group, and in comparison to the control group. If necessary, these effects will be controlled for statistically in the comparison of depressed outpatients and normal controls on these parameters. If nonlinear (or interaction) effects between age and gender are found, we propose to carry out a thorough analysis and report of these effects.

The overall group difference in the three PSG measures previously found to be different in depressed inpatients (with appropriate statistical control of age and/or gender as needed) will be tested initially using multivariate analysis of variance. If this is significant, post hoc univariate tests will be used to test whether depressed outpatients differ from normal controls on the three PSG parameters, and discriminant function analysis will be used to further study the pattern of group differences.

The outpatients will also be compared to the inpatients, to establish whether they are similar or not on these variables, using analyses that parallel those above.

Similar, univariate analysis will be carried out on the DST. In addition, Receiver Operator Characteristics (ROC) analysis will be used to establish an optimal cutpoint for distinguishing depressed outpatients from control subjects (Kraemer, 1988; [redacted] has provided us with her software developed for this purpose). This cutpoint will be used in analysis of response predictors (see Question d).

b. To determine the relative effectiveness of fluoxetine (versus placebo) in the treatment of MDD in children and adolescents.

The primary outcome variable of this experiment is the proportion of completing subjects in each group (placebo and drug) who recover, where recovery is defined as below 28 on the CDRS-R and a CGI of 1 or 2. The difference in proportions is tested by chi-square. Assuming a 40% recovery rate in the placebo group and a 70% recovery rate in the fluoxetine group, the proposed sample size of 40 in each group is sufficient for a power of .80 to detect this difference between proportions (.05).

A second way to measure outcome is to use the end-of-treatment scores on the weekly CDRS-R and CGAS. Stratified randomization at baseline should assure equivalent groups are assigned to each treatment; however, differential attrition can result in differences between groups in those who complete. Therefore, the differences on baseline measures between dropouts and completers as well as between the two groups of completers will be evaluated, in order to identify possible confounds or limitations to the internal validity of the study (Jurs & Glass, 1971; Cook & Campbell, 1979, pp 50ff).

If the two groups of completers differ, despite stratified randomization, these differences will be controlled for statistically in order to obtain an unbiased test of treatment effects. Assuming the assumption of homogeneity of regression is met, the primary test of this question will be carried out using two-group analysis of covariance where the covariates are baseline symptom measure as well as other characteristics that differ significantly between medication and placebo completers. If the homogeneity assumption is not met, within-group modeling of the effects will be undertaken, in order to understand better the relationships among variables. The results of these analyses would have important implications for the design of future medication trials in this age group.

Two secondary analyses will be used to explore in more depth the pattern of response to fluoxetine vs. placebo. The first is a repeated measures analysis of variance where Weeks is the within factor and Treatment is the between factor. In order to minimize loss of subjects due to a missing week, a single missing value will be interpolated by taking the average of the two framing weeks (before and after the missing week); this will not be attempted when two consecutive weeks are missing (i.e., these subjects will be lost from the analysis). A second approach is to apply life table methods to analyze the time to recovery. This method has the advantage of utilizing data on all subjects who enroll in the protocol and provides information about the relative likelihood of recovery at each week of treatment.

Finally, the relationship of final blood level of fluoxetine to final CDRS-R and CGAS in the active-drug group will be carried out, using endpoint measures for all subjects who are defined as "completers". This will involve correlation and graphical analyses to evaluate whether magnitude of response was related to blood level, whether the relationship is linear or nonlinear, and whether there appears to be a therapeutic threshold.

c. To determine whether response to antidepressant treatment is different between children and adolescents.

Analysis of this question will involve the same methods described for question b, but in this case the main effect of age and the interaction between age group and treatment will be the focus of statistical tests and descriptive modeling.

d. To determine if pretreatment REM latency or DST response predicts acute response to treatment or placebo.

The simultaneous effects of these variables will be evaluated in each treatment cell separately using multiple regression with endpoint measures on the CDRS-R or the CGAS as the dependent variables. A model-comparison strategy will be followed to reduce the regression model to its most parsimonious explanatory form. As before, the effects of possible covariates will be evaluated, described, and controlled for statistically as needed. This approach allows modeling of nonlinear relationships and of exploring interactions between variables. The expected sample of 40 subjects in each cell gives adequate power (.80) to detect a model R^2 of .35 in the population, at = .05, which is equivalent to a medium-size effect (Cohen, 1988).

In addition, a chi-square test will be used to test the relationship between suppression/nonsuppression on the DST (using the cutpoint defined by ROC analyses, see Question 1) to response/nonresponse to fluoxetine.

e. To determine if clinical, demographic, or family history variables predict acute response to treatment or placebo.

Stepwise multiple regression will be used to answer this question. With the greater number of variables, careful selection of a priori of the variables of most interest is needed. The variables of most interest are number of previous episodes, concomitant disorders, age of onset, length of episode,

family history, gender, age, and symptom severity.

The correlational structure of the predictors will be evaluated prior to the analysis, in order to identify and eliminate collinearities that may bias the results. Influence analysis will also be used, to determine whether outliers in the sample have played a disproportionate effect on parameter estimates. Also, the goodness of fit to a linear model, vs nonlinear alternatives (e.g., logistic or quadratic) will be evaluated.

The power of each partial F test in a stepwise regression varies as the number of terms in the model changes. For example, using backward stepwise regression, the size of the true partial multiple R^2 needed to keep a term (vs. removing it from the model), given the number of terms remaining after removing the term, is as follows (for two levels of Type II error), assuming = .05:

R^2 given number of terms remaining in the model

Power	1	2	3	4	5	6	7
.80	.176	.214	.241	.264	.284	.303	.319
.50	.094	.122	.143	.160	.176	.192	.206

The second line (1- = .50) indicates the approximate size of a significant partial R^2 in the stepwise regression. These correlations correspond to medium effect sizes (Cohen, 1988). SAS PROC STEPWISE removes or adds terms based on significant tests with default = .15, which decreases the R^2 needed for significance and increases the power somewhat.

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E. HUMAN SUBJECTS:

Subjects are child and adolescent outpatients (n=120) who are referred for evaluation and treatment of moderate to severe depression. Ages will be from 8 to 18 years, both males and females, English speaking, predominantly Caucasian, though of all ethnic groups and all SES backgrounds. Inclusion criteria are outpatients ages 8 to 18 years with nonpsychotic major depressive disorder, of normal intelligence and will be able to provide informed consent (parents), assent (patients). Subjects will be excluded who have Bipolar Disorder or psychotic depression, significant previous or current medical illness, prior adequate treatment with fluoxetine, independent sleep disorder, alcohol or substance abuse, known allergy to tricyclic antidepressants and if sexually active have inadequate birth control measures. The use of children and adolescents is essential because data available in adults cannot be automatically assumed to be valid in this age group and depression is a significant problem in this age group.

Research material will consist of systematically collected clinical information, data from sleep polysomnography, blood specimens for cortisol and serum tricyclic levels. All the information will be obtained specifically for research purposes though it parallels what would be normally done in safe clinical practice.

Subjects will be recruited from outpatients referred for evaluation and treatment of depression. Informed consent will be obtained separately for the 2 phases of the study. The diagnostic, clinical and biological evaluation will be explained to the child and parent/guardian. Assent will be obtained from the child and written consent obtained from the parent or guardian. At the end of the evaluation, if still significantly depressed, the randomized double blind placebo controlled study will be explained to the child and parents and assent and consent obtained from the child and parent, respectively. Alternative treatment, including non medication treatment will be explained.

Potential risks for the diagnostic phase of the study are minimal. The risks associated with venepuncture are minor bruising, and occasionally scalp electrodes for sleep polysomnography can cause irritation to the scalp. The clinical and medical evaluation are similar to a routine clinical evaluation. The delay in treatment necessitated by two weeks of evaluation are standard practice for outpatients.

The treatment phase of the study poses risks in 3 major areas, non-medication treatment of those subjects on placebo, risks associated with taking antidepressants and risks associated with venepuncture.

The risk associated with non-treatment (i.e. no active medication) will be minimized by careful clinical management, weekly visits, and availability of clinical staff on a 24 hour basis. Subjects will be withdrawn from the study if the evaluating physician feels it is essential.

If a child or adolescent deteriorates and cannot stay in the study, inpatient treatment is available and they will continue to be followed clinically either inpatient or outpatient. Treatment information will be available to the treating clinician, once the subject leaves the study. The ongoing clinical care will be done by a physician who is separate from the physician doing the evaluation during the acute treatment.

Possible side effects of fluoxetine include nausea, vomiting, diarrhea, constipation, urinary retention, dizziness, fatigue, headaches, blurred vision, agitation, sleep disturbance, restlessness, numbness, tingling, tremors, hypotension, hypertension, dry mouth and skin rash. The safe use of the drug during pregnancy has not been established.

Side effects and vital signs will be monitored weekly. EKGs will be done prior to starting the medication, medically ill subjects will be excluded and blood levels will be monitored. Fluoxetine is approved by FDA for use in adolescents but not children, as a result of insufficient studies in this age group. It has been used in open studies in children. We will obtain an FDA IND number for study of fluoxetine in children. The subjects will be seen weekly by a physician during the study and will be followed clinically after the study. With regards to repeated blood samples, they will be kept to a minimum and subjects who have clear needle phobia will not be included in the study. Additionally, staff experienced in dealing with children will be employed for all aspects of the study.

Alternative treatments for subjects are to be treated clinically for their depression, which for this sample would be a recommendation of an open trial of antidepressants. Those where medication is not clinically indicated or who prefer not to be treated with medication will not be entered into this phase of treatment.

Confidentiality of records will be maintained by having separate research charts in addition to standard hospital medical records. Subjects will only be identified in data analyses by ID number and research materials will be kept double locked in the research coordinator's office.

The risk benefit ratio reflects the status of treatment of depression in this age group. Clinically it would be argued that the prevailing practice is to treat severe depression with antidepressants and

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a placebo controlled group would withhold treatment of active medication for those on placebo. However the effectiveness of antidepressant in this age group has not been adequately demonstrated in research studies. Additionally 40 to 70% respond to placebo and treatment with medication causes some risks however carefully monitored. It is expected that about 70% of subjects on active treatment will benefit from the study with improvement in their condition. It is also expected that a proportion of those who are on placebo will improve. It is not possible at this stage to use data from adults in children. Depression in children and adolescents is a common disorder with significant morbidity and mortality. Further understanding of the diagnosis and treatment of this disorder is important.

F. VERTEBRATE ANIMALS - not applicable.

G. CONSULTANTS - none.

H. CONSORTIUM/CONTRACTUAL ARRANGEMENTS - none.

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FLUOXETINE STUDY SUMMARY OF PROJECT 02/02/93

Name: _____

	EVALUATION				PLACEBO			TREATMENT								
WEEK	0	1	2	3	0	1	2	0	1	2	3	4	5	6	7	8
CONSENT	X				X											
DICA	X	R	R	R												
K-SADS	X	X	X	X	X			X				X				X
F H RDC	X	R	R	R												
CDRS-R	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BID	X	X	X	X	X							X				X
BPRS-C	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI/GAS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FAM. CGAS	X	X	X	X	X											X
FLUX S.E.								X	X	X	X	X	X	X	X	X
PBID	X		X		X			X				X				X
S.EFFECTS	X		X		X	X	X	X	X	X	X	X	X	X	X	X
WSAS	X		X		X		X	X	X		X	X		X		X
CDI/BDI	X	X		X		X		X		X		X	X		X	X
CONSENSUS					X											
S.CONSENT		X														
TOUR/LOG 3 NIGHTS		X														
PHYSICAL	X															
DEX		X														
FLUOX									X	X		X		X		X
FULL LAB		X														
PART LAB												X				X
EKG-1999					X							X				X
TANNER	X															
DEMO	X															
History	X															

16.1.2.
Sample Clinical Report Form

Visit 1:

Visit information
Patient demographics
Psychiatric diagnosis
Vitals
Laboratory data collection - scheduled labs
Laboratory data collection - unscheduled labs
Laboratory comments
Electrocardiogram
Children's depression rating scale-revised checklist
Clinical global impression
BDI
CDI
BPRS-C
Side-Effects checklist
Compliance
Visit comments

Visit 2:

Visit information
Vitals
Childhood depression rating scale-revised checklist
Clinical global impression
BDI
CDI
BPRS-C
Side-Effects checklist
Compliance
Laboratory data collection - unscheduled labs
Laboratory comments
Visit comments

Visit 3 = Visit 4 = Visit 5 = Visit 7 = Visit 8 = Visit 9:

Visit information
Vitals
Childhood depression rating scale-revised checklist
Clinical global impression
BDI
CDI
BPRS-C
Side-Effects checklist
Fluoxetine side-effects checklist
Compliance
Laboratory data collection - unscheduled labs
Laboratory comments
Visit comments

Visit 6 = Visit 10:

Visit information
Vitals
Childhood depression rating scale-revised checklist
Clinical global impression
BDI
CDI
BPRS-C
Side-Effects checklist
Fluoxetine side-effects checklist
Compliance
Laboratory data collection - scheduled labs
Laboratory data collection - unscheduled labs
Laboratory comments
Visit comments

Unscheduled Visits:

Visit information
Vitals
Childhood depression rating scale-revised checklist
Clinical global impression
BDI
CDI
BPRS-C
Side-Effects checklist
Fluoxetine side-effects checklist
Compliance
Laboratory data collection - scheduled labs
Laboratory data collection - unscheduled labs
Laboratory comments
Visit comments

Summary Visit:

Patient summary
Visit information
Vitals
Childhood depression rating scale-revised checklist
Clinical global impression
BDI
CDI
BPRS-C
Side-Effects checklist
Fluoxetine side-effects checklist
Compliance
Laboratory data collection - scheduled labs
Laboratory data collection - unscheduled labs
Laboratory comments
Visit comments
Summary comments
Concomitant medications
Pre-existing conditions and study adverse events
Signature page

Visit 1 Discontinuation:

Patient summary
Visit information
Patient demographics
Psychiatric diagnosis
Vitals
Childhood depression rating scale-revised checklist
Clinical global impression
BDI
CDI
BPRS-C
Side-Effects checklist
Fluoxetine side-effects checklist
Compliance
Laboratory data collection - scheduled labs
Laboratory data collection - unscheduled labs
Laboratory comments
Visit comments
Summary comments
Concomitant medications
Pre-existing conditions and study adverse events
Signature page

Visit Information

Page: of

Patient ID:

Visit Number:

Visit Date:
MM/DD/YY

Initials
Date Verified
Initials
Date Keyed

Program Location
Date Printed

Patient:

Patient Demographics

Visit:
Page: of

Study Drug Kit Number: ____

Sex: ___
1=Female
2=Male

Origin: ___
1=Caucasian
2=African Descent
3=Hispanic
99=Other

Patient Initials: ____

Family Structure: ___
0=Both Parents
1=Natural Mother
2=Natural Mother and Step Father
3=Natural Father
4=Natural Father and Step Mother
5=Grandparents
6=Other Relatives
7=Adoptive Parents
8=College
9=Has Own Apartment
10=Other

Date of Birth: _____
MM/DD/YY

Informed Consent Date: _____
MM/DD/YY

Hollingshead Social Position Scale: ___

Date of First Study Drug: _____
MM/DD/YY

Initials
Date Verified
Initials
Date Keyed

Program Location
Date Printed

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Bottom Copy - Investigator

Clinical Report Form

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Patient:

Psychiatric Diagnosis

Visit:
Page: of

DMS-III DIAGNOSES: _____ _____ _____ _____ _____

EPISODE NUMBER: ___

DURATION CURRENT EPISODE: (WEEKS) ___

ONSET AGE OF FIRST EPISODE: (YEARS) ___

LENGTH OF ILLNESS: (MONTHS) ___

1ST DEGREE AXIS 1 PSYCH HISTORY: ___
1=POSITIVE
0=NOT POSITIVE

PREVIOUS TREATMENT THIS EPISODE: ___
0=NO RX
1=ANXIOLYTICS
2=TRICYCLICS
3=ANTIPSYCHOTICS
4=LITHIUM
5=MAOI
6=PSYCHOTHERAPY
7=0THER
8=FLUOXETINE
9=OTHER SSRIs

Initials
Date Verified
Initials
Date Keyed

Program Location
Date Printed

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Clinical Report Form

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Patient:

Vitals

Visit:
Page: of

☐ Information not obtained

Height: ____ (Check one unit) ☐ centimeters ☐ inches

Weight: ____ (Check one unit) ☐ pounds ☐ kilograms

Blood Pressure and Heart Rate

Position	Blood Pressure (mm Hg) Systolic/Diastolic	Heart Rate (bpm)
SI	____ / ____	____

SI=Sitting Position

Initials
Date Verified
Initials
Date Keyed

Program Location
Date Printed

Patient:

Laboratory Data Collection
Scheduled Labs

Visit:
Page: of

☐ Information not obtained

Test Description/(Abbreviation)	Test Result	X if Test Not Done	Units	Reference Range Low	Reference Range High	Collection Date (mm/dd/yy)	Collection Time (hh:mm)
SERUM ELECTROLYTES							
Sodium (SODIUM)							
Potassium (POTAS)							
Chloride (CHLOR)							
Co2(Bicarbonate) (BICARB)							
anion gap (AN-GAP)							
GENERAL CHEMISTRY							
ALB (ALBUM)							
ENZYMES							
ALKPO4 (ALKPH)							
Lactate Dehydrogenas (LDH)							
SGOT (AST)							
SGPT (ALT)							

Initials
Date Verified
Initials
Date Keyed

Program Location
Date Printed

Patient:

Laboratory Data Collection
Scheduled Labs

Visit:
Page: of

Test Description/(Abbreviation)	Test Result	X if Test Not Done	Units	Reference Range Low	Reference Range High	Collection Date (mm/dd/yy)	Collection Time (hh:mm)
COMPLETE BLOOD COUNT AND DIFFERENTIAL							
WBC (WBC)							
RBC (RBC)							
HGB (HGB)							
HCT (HCT)							
Mean Cell Volume (MCV)							
Mean Cell Hemoblobin (MCH)							
Mean Cell Hemoglobin (MCHC)							
RDW (RDW)							
PLATELET (PLTCT)							
mean plt vol (MPV)							
SEGMENT (POLYS)							
BANDS (BANDS)							
Eosinophils (EOSN)							
MONOS (MONOS)							
LYMPHS (LYMPHS)							
morphology (RBCMOR)							
BASOS (BASO)							
atypical lymphs (ATLYMP)							
oval/elliptocyt (ELLIPT)							
tear drops (DACRO)							
glycated hemoglobin (GLYHGB)							
toxic granulation (TOXGR)							

Initials
Date Verified
Initials
Date Keyed
Program Location
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Clinical Report Form

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Patient:

Laboratory Data Collection
Scheduled Labs

Visit:
Page: of

Test Description/(Abbreviation)	Test Result	X if Test Not Done	Units	Reference Range Low	Reference Range High	Collection Date (mm/dd/yy)	Collection Time (hh:mm)
ROUTINE URINALYSIS							
Color (U-COLR)							
Appearance (U-APP)							
SPECGRAV (U-SPGR)							
PH (U-PH)							
protein (U-PROT)							
URIGLU (U-GLUC)							
ketones (U-KET)							
blood (U-BLD)							
bilirubin (bile) (U-BIL)							
urobilinogen (U-UROB)							
nitrite (U-NITR)							
leukocyte ester (U-LEUE)							
URIWBC (M-WBC)							
URIRBC (M-RBC)							
squamous epith (SQEPI)							
CASTS (M-CAST)							
hyaline cast (HYLN)							
Epi (M-EPI)							
bacteria (M-BACT)							
THYROID RESULTS							
T3 uptake (RT3U)							
T4 (T4-RIA)							
TSH (TSH)							
T3 RIA (FT3)							
T3 RIA (T3-TOT)							
T7(=FTI) (FTI)							

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Patient:

Laboratory Data Collection
Unscheduled Labs

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☐ Information not obtained

Test Description/(Abbreviation)	Test Result	X if Test Not Done	Units	Reference Range Low	Reference Range High	Collection Date (mm/dd/yy)	Collection Time (hh:mm)
ENDOCRINE HORMONE-OTHER							
cortisol (CORTSL)							
URINE DRUG SCREEN							
tox screen (UDRUGS)							
TDM							
carbamazepine (CARBAM)							
FERRITIN							
ferritin (FERRTN)							
BILIRUBIN-TOTAL & DIRECT							
uncong bili (I.BILI)							
congugated bili (D.BILI)							
BILIR (T.BILI)							
SPECIAL CHEMISTRY CARBOHYDRATE/CARBOHYDRATE METABOLISM							
B-OH butyrate (BOHB)							
IMMUNOLOGY							
ANA pattern: SPECKLE (ANA-S)							
ANA titer (ANA)							
ANA pattern: HOMOGEN (ANA-H)							
ANA pattern: NUCLEOL (ANA-N)							
ANA pattern: PERIPHE (ANA-P)							
PREGNANCY TEST							
HCG qualitative (PREG.S)							
beta-HCG quant (PREG.S)							

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Test Description/(Abbreviation)	Test Result	X if Test Not Done	Units	Reference Range Low	Reference Range High	Collection Date (mm/dd/yy)	Collection Time (hh:mm)
OTHER TESTS							
BUN (BUN)							
CREAT (CREAT)							
Creatine Phosphokina (CPK)							
Ammonia (AMMON)							
CALCIUM (CALC)							
CHOL (CHOL)							
GGT (GGT)							
HDL (HCL-C)							
Iron (IRON)							
LDL (LDL-C)							
phosphorus (PHOS)							
sed rate (SR-WES)							
TIBC (TIBC)							
TOTPROT (TPROT)							
transferrin (TRANS)							
Trig (TRIG)							
URICACID (UR AC)							
polychromasia (POLYCH)							
Glucose (FGLU)							

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Laboratory Comments

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☐ No comments

Comment Type and Line Number	Comment

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Electrocardiogram

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Electrocardiogram date: _____
MM/DD/YY

Electrocardiogram result: ☐ Normal ☐ Abnormal

Electrocardiogram comment:

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Patient:
Rater:

Childhood Depression Rating Scale-Revised Checklist

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1. SCHOOLWORK: (attitude to school, grades, concentration, difficulty completing tasks)
   1. performance consistent with ability
   2.
   3. decrease in school performance
   4.
   5. major interference most subjects
   6.
   7. no motivation

2. ABILITY TO HAVE FUN: (interest, bored)
   1. appropriate for age
   2.
   3. interests, not enthusiasm
   4.
   5. is easily bored
   6.
   7. no initiative/become involved

3. SOCIAL WITHDRAWAL: (friends, activities)
   1. enjoys friendships
   2.
   3. waits for offers/rejects some
   4.
   5. freq/avoids/refuses
   6.
   7. no relating to others

4. SLEEP: (initial, restless, terminal)
   1. no difficulty
   2.
   3. mild difficulty
   4.
   5. moderate nearly every night
      a. initial, b. middle, c. early

5. APPETITE/EATING PATTERNS: (decreased, increased)
   1. no problems/changes
   2.
   3. mild changes
   4.
   5. decreased/increased

6. EXCESSIVE FATIGUE: (daytime, after school, naps)
   1. no unusual
   2.
   3. somewhat excessive/not related to boredom
   4.
   5. daily complaints
   6.
   7. daily complaints/interferes with activities

7. PHYSICAL COMPLAINTS: (stomach, head ...)
   1. occasional
   2.
   3. mildly excessive
   4.
   5. daily complaints
   6.
   7. preoccupied, interferes w/ activities

8. IRRITABILITY:
   1. rare
   2.
   3. several times/short periods
   4.
   5. several times/longer periods
   6.
   7. constant

9. GUILT: (fault, blame, guilty)
   1. appropriate
   2.
   3. exaggerated guilt
   4.
   5. pathological
   6.
   7. severe delusions of guilt

10. SELF-ESTEEM: (looks, smarts, friends)
    1. positive terms
    2.
    3. one important area feels deficit
    4.
    5. negative terms, bland answers
    6.
    7.

11. DEPRESSED FEELINGS: (unhappy, others know?)
    1. occasionally quickly disappears
    2.
    3. sustained periods/excessive/event
    4.
    5. unhappy most time/no precipitant
    6.
    7. unhappy all/time psychic pain

12. MORBID IDEATION:(pet, friend, relative, worry about)
    1. none
    2.
    3. some morbid thoughts, excessive
    4.
    5. preoccupied several times a week
    6.
    7. death, morbid themes elaborate

13. SUICIDAL IDEATION: (thoughts, threats, attempts)
    1. not apply
    2. sharp denial
    3. thoughts when angry
    4.
    5. recurrent thts suicide
    6.
    7. attempted within last month/actively

14. WEEPING: (crying more than usual for no reason)
    1. normal for age
    2. sug. statements > than peers
    3. cries more than peers
    4.
    5. several times week/no reason
    6.
    7. cries nearly everyday

15. DEPRESSED AFFECT:
    1. not depressed
    2. mild suppression of affect
    3. overall loss spontaneity
    4.
    5. moderate restriction
    6.
    7. severe, looks sad withdrawn

16. TEMPO OF SPEECH:
    1. normal
    2. slow
    3. delays interview
    4.
    5. severe

17. HYPOACTIVITY:
    1. none
    2.
    3. mild
    4.
    5. moderate
    6.
    7. severe

18. LABILITY OF MOOD:
    a. mood appropriate
    b.
    c. moody, abrupt
    d.
    e. extremely moody

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Clinical Global Impression

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CLINICAL GLOBAL IMPRESSION: SEVERITY

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Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0-Not assessed
1-Normal, not at all ill
2-Borderline mentally ill
3-Mildly ill
4-Moderately ill
5-Markedly ill
6-Severely ill
7-Among the most extremely ill patients

☐

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CLINICAL GLOBAL IMPRESSION: IMPROVEMENT

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Rate total improvement, whether or not in your judgement is due entirely to drug treatment. Compared to the patient's condition at Visit 2, how much has s/he changed?

0-Not assessed
1-Very much improved
2-Much improved
3-Minimally improved
4-No change
5-Minimally worse
6-Much worse
7-Very much worse

Note: scored only at visits 3-10

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BDI

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A.
0-I do not feel sad
1-I feel sad
2-I am sad all of the time and I can't snap out of it
3-I am so sad or unhappy that I can't stand it

B.
0-I am not particularly discouraged about the future
1-I feel discouraged about the future
2-I feel I have nothing to look forward to
3-I feel the future is hopeless and that things cannot improve

C.
0-I do not feel like a failure
1-I feel I have failed more than the average person
2-As I look back on my life, all I see is a lot of failure
3-I feel I am a complete failure as a person

D.
0-I get as much satisfaction out of things as I used to
1-I don't enjoy things the way I used to
2-I don't get real satisfaction out of anything anymore
3-I am dissatisfied or bored with everything

E.
0-I don't feel particularly guilty
1-I feel guilty a good part of the time
2-I feel quite guilty most of the time
3-I feel guilty all of the time

F.
0-I don't feel I am being punished
1-I feel I may be punished
2-I expect to be punished
3-I feel I am being punished

G.
0-I don't feel disappointed in myself
1-I am disappointed in myself
2-I am disgusted with myself
3-I hate myself

H.
0-I don't feel I am any worse than anybody else
1-I am critical of myself for my weaknesses or mistakes
2-I blame myself all the time for my faults
3-I blame myself for everything bad that happens

I.
0-I don't have any thoughts of killing myself
1-I have thoughts of killing myself, but I would not carry them out
2-I would like to kill myself
3-I would kill myself if I had the chance

J.
0-I don't cry any more than usual
1-I cry more now than I used to
2-I cry all the time now
3-I used to be able to cry, but now I can't cry even though I want to

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K. 0-I am no more irritated now that I ever am
1-I get annoyed or irritated more easily than I used to
2-I feel irritated all the time now
3-I don't get irritated at all by the things that used to irritate me

L. 0-I have not lost interest in other people
1-I am less interested in other people than I used to be
2-I have lost most of my interest in other people
3-I have lost all of my interest in other people

M. 0-I make decisions about as well as I ever could
1-I put off making decisions at all anymore
2-I have greater difficulty in making decisions than before
3-I can't make decisions at all anymore

N. 0-I don't feel I look any worse than I used to
1-I am worried that I am looking old or unattractive
2-I feel that there are permanent changes in my appearance that make me look unattractive
3-I believe that I look ugly

O. 0-I can work about as well as before
1-It takes extra effort to get started at doing something
2-I have to push myself very hard to do anything
3-I can't do any work at all

P. 0-I can sleep as well as usual
1-I don't sleep as well as I used to
2-I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
3-I wake up several hours earlier than I used to and cannot get back to sleep

Q. 0-I don't get more tired than usual
1-I get tired more easily than I used to
2-I get tired from doing almost anything
3-I am too tired to do anything

R. 0-My appetite is no worse than usual
1-My appetite is not as good as it used to be
2-My appetite is much worse now
3-I have no appetite at all anymore

S. 0-I haven't lost much weight, if any, lately
1-I have lost more than 5 pounds
2-I have lost more than 10 pounds
3-I have lost more than 15 pounds
I am purposely trying to lose weight by eating less Yes___ No___

T. 0-I am no more worried about my health than usual
1-I am worried about physical problems such as aches and pains, upset stomach or constipation
2-I am very worried about physical problems-it's hard to think of much else
3-I am so worried about my physical problems I cannot think of anything else

U. 0-I have not noticed any recent change in my interest in sex
1-I am less interested in sex than I used to be
2-I am much less interested in sex now
3-I have lost interest in sex completely

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Patient: **CDI** Visit:
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Remember, pick out the sentences that best describe your feelings and ideas in the PAST TWO WEEKS

1. ☐ 0-I am sad once in a while
1-I am sad many times
2-I am sad all the time

2. ☐ 2-Nothing will ever work out for me
1-I am not sure if things will work out for me
0-Things will work out for me O.K.

3. ☐ 0-I do most things O.K.
1-I do many things wrong
2-I do everything wrong

4. ☐ 0-I have fun in many things
1-I have fun in some things
2-Nothing is fun at all

5. ☐ 2-I am bad all the time
1-I am bad many times
0-I am bad once in a while

6. ☐ 0-I think about bad things happening to me once in a while
1-I worry that bad things will happen to me
2-I am sure that terrible things will happen to me

7. ☐ 2-I hate myself
1-I do not like myself
0-I like myself

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8. ☐ 0-Bad things are usually not my fault
1-Many bad things are my fault
2-All bad things are my fault

9. ☐ 0-I do not think about killing myself
1-I think about killing myself but I would not do it
2-I want to kill myself

10. ☐ 2-I feel like crying everyday
1-I feel like crying many days
0-I feel like crying once in a while

11. ☐ 2-Things bother me all the time
1-Things bother me many times
0-Things bother me once in a while

12. ☐ 0-I like being with people
1-I do not like being with people many times
2-I do not want to be with people at all

13. ☐ 2-I cannot make up my mind about things
1-It is hard to make up my mind about things
0-I make up my mind about things easily

14. ☐ 0-I look O.K.
1-There are some bad things about my looks
2-I look ugly

15. ☐ 2-I have to push myself all the time to do my schoolwork
1-I have to push myself many times to do my schoolwork
0-Doing schoolwork is not a big problem

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Patient: **CDI** Visit:
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16. ☐ 2-I have trouble sleeping every night
1-I have trouble sleeping many nights
0-I sleep pretty well

17. ☐ 0-I am tired once in a while
1-I am tired many days
2-I am tired all the time

18. ☐ 2-Most days I do not feel like eating
1-Many days I do not feel like eating
0-I eat pretty well

19. ☐ 0-I do not worry about aches and pains
1-I worry about aches and pains many times
2-I worry about aches and pains all the time

20. ☐ 0-I do not feel alone
1-I feel alone many times
2-I feel alone all the time

21. ☐ 2-I never have fun at school
1-I have fun at school only once in a while
0-I have fun at school many times

22. ☐ 0-I have plenty of friends
1-I have some friends but I wish I had more
2-I do not have many friends

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23. ☐ 0-My schoolwork is alright
1-My schoolwork is not as good as before
2-I do very badly in subjects I used to be good in

24. ☐ 2-I can never be as good as other kids
1-I can be as good as other kids if I want to
0-I am just as good as other kids

25. ☐ 2-Nobody really loves me
1-I am not sure if anybody loves me
0-I am sure that somebody loves me

26. ☐ 0-I usually do what I am told
1-I do not do what I am told most times
2-I never do what I am told

27. ☐ 0-I get along with people
1-I get into fights many times
2-I get into fights all the time

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BPRS-C

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	Not Present	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extremely Severe
1. Uncooperativeness-negative, uncooperative resistant, difficult to manage	1	2	3	4	5	6	7
2. Hostility-angry or suspicious affect, belligerence, accusations and verbal condemnations of others	1	2	3	4	5	6	7
3. Manipulativeness-lying, cheating, exploitive of others	1	2	3	4	5	6	7
4. Depressive mood-sad, tearful, depressive demeanor	1	2	3	4	5	6	7
5. Feelings of Inferiority-lacking self-confidence, self-depreciatory, feeling of personal inadequacy	1	2	3	4	5	6	7
6. Suicidal Ideation-thoughts, threats, or attempts of suicide	1	2	3	4	5	6	7
7. Peculiar Fantasies-recurrent, odd, unusual, or autistic ideations	1	2	3	4	5	6	7
8. Delusions-ideas of reference, persecutory or grandiose delusions	1	2	3	4	5	6	7
9. Hallucinations-visual, auditory, or other hallucinatory experiences or perceptions	1	2	3	4	5	6	7
10. Hyperactivity-excess. energy expenditure, freq. changes in posture perpetual motion	1	2	3	4	5	6	7
11. Distractibility-poor concentration, shortened attention span, reactivity to peripheral stimuli	1	2	3	4	5	6	7
12. Speech or Voice Pressure-loud, excessive, or pressured speech	1	2	3	4	5	6	7
13. Underproductive Speech-minimal, sparse inhibited verbal response patterns or weak low voice	1	2	3	4	5	6	7
14. Emotional Withdrawal-unspontaneous relations to examiner, lack of peer interaction, hypoactivity	1	2	3	4	5	6	7
15. Blunted Affect-deficient emotional expression, blankness, flatness of affect	1	2	3	4	5	6	7
16. Tension-nervousness, fidgetiness, nervous movement of hands or feet	1	2	3	4	5	6	7
17. Anxiety-clinging behavior, separation anxiety, preoccupation with anxiety topics, fears or phobias	1	2	3	4	5	6	7
18. Sleep Difficulties-inability to fall asleep, intermittant awakening, shortened sleep time	1	2	3	4	5	6	7
19. Disorientation-confusion over persons, places or things	1	2	3	4	5	6	7
20. Speech Deviance-inferior level of speech development, underdeveloped vocabulary, mispronunciations.	1	2	3	4	5	6	7
21. Stereotypy-rhythmic, repetitive, manneristic movements or posture	1	2	3	4	5	6	7

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Patient:

Side Effects Checklist

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Since last time here,have you had trouble with any item below?
If 1st visit,have you had any of item below in the last week?
Mark the number which best tells how much you were bothered.

Have you had trouble with:	Not At All	Just A Little	Pretty Much	Very Much	Don't Know
1. Eating?	0	1	2	3	4
2. Drinking?	0	1	2	3	4
3. Dry mouth and lips?	0	1	2	3	4
4. Wetness in mouth?	0	1	2	3	4
5. Constipation?	0	1	2	3	4
6. Diarrhea?	0	1	2	3	4
7. Stomachaches?	0	1	2	3	4
8. Muscle cramps?	0	1	2	3	4
9. Being sick to your stomach?	0	1	2	3	4
10. Wetting the bed?	0	1	2	3	4
11. Urinating?	0	1	2	3	4
12. Itchy or scratchy skin?	0	1	2	3	4
13. Rashes?	0	1	2	3	4
14. Cold or sniffles?	0	1	2	3	4
15. Headache?	0	1	2	3	4
16. Dizziness?	0	1	2	3	4
17. Playing sports?	0	1	2	3	4
18. Shakiness?	0	1	2	3	4
19. Pronouncing words?	0	1	2	3	4
20. Doing things with your hands?	0	1	2	3	4
21. Sitting still?	0	1	2	3	4
22. Tiredness?	0	1	2	3	4
23. Feeling sleepy?	0	1	2	3	4
24. Trouble sleeping?	0	1	2	3	4
25. Bad dreams?	0	1	2	3	4
26. Getting along with parents?	0	1	2	3	4
27. Getting along with kids?	0	1	2	3	4
28. Crying?	0	1	2	3	4
29. Getting mad?	0	1	2	3	4
30. Not being happy?	0	1	2	3	4
31. Being sad?	0	1	2	3	4
32. Paying attention?	0	1	2	3	4

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Patient:

Fluoxetine Side Effects Checklist

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	Never		Somewhat		Constantly
1. Trouble sleeping	0	1	2	3	4
2. Heart racing	0	1	2	3	4
3. Heart pounding	0	1	2	3	4
4. Feeling dizzy	0	1	2	3	4
5. Feeling the room spin	0	1	2	3	4
6. Feeling tense inside	0	1	2	3	4
7. Restlessness	0	1	2	3	4
8. Numbness of hands or feet	0	1	2	3	4
9. Tingling in hands or feet	0	1	2	3	4
10. Trouble keeping balance	0	1	2	3	4
11. Dry mouth	0	1	2	3	4
12. Blurry vision	0	1	2	3	4
13. Seeing double	0	1	2	3	4
14. Constipation	0	1	2	3	4
15. Diarrhea	0	1	2	3	4
16. Delays in urinating	0	1	2	3	4
17. Itchiness	0	1	2	3	4
18. Light hurting eyes	0	1	2	3	4
19. Nausea	0	1	2	3	4
20. Vomiting	0	1	2	3	4
21. No appetite	0	1	2	3	4
22. Stomach pains	0	1	2	3	4
23. Drowsy	0	1	2	3	4
24. Leg spasms at night	0	1	2	3	4
25. Sweating	0	1	2	3	4
26. Tremor	0	1	2	3	4
27. Tinnitus	0	1	2	3	4
28. Headache	0	1	2	3	4
29. Nightmares	0	1	2	3	4
30. Weight change	0	1	2	3	4

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Compliance

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Drug Regimen: ___
1=Every Day
2=Every Other Day
96=N/A

Number of Capsules Dispensed: ___

Number of Capsules Returned: ___

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Visit Comments

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☐ No comments

Comment Type and Line Number	Comment

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Summary Comments

☐ No comments

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Patient:

Patient Summary

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Date of discontinuation: _____ MM/DD/YY

Discontinuation visit: _____ MM/DD/YY

- ☐ 011 Protocol completed
- ☐ 081 Adverse event E _____ E_code
- ☐ 021 Lack of efficacy
- ☐ 051 Physician decision
- ☐ 041 Patient decision
- ☐ 062 Entry criteria not met
- ☐ 063 Interim criteria not met
- ☐ 031 Lost to follow-up
- ☐ 004 Noncompliance
- ☐ 091 Death Date of Death: _____ MM/DD/YY
- ☐ 999 Other Specify other:

Date of last study drug dose: _____ MM/DD/YY

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Date Verified
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Date Keyed

Program Location
Date Printed

Eli Lilly and Company
Distribution: Top Copy - Lilly
Bottom Copy - Investigator

Clinical Report Form

B1Y-MC-X065

Confidential

Patient:

Concomitant Medication

Visit:
Page: of

☐ No medications recorded

Continue listing all medications, other than study drug, the patient is taking during the study.

Indication for Use (IFU)
Enter code from patient's Pre-existing Conditions and Adverse Events page

E__ = Pre-existing Condition or Event (e.g. E02)
X01 = Primary or study condition
X02 = Prophylaxis or non-therapeutic use
97 = Unknown

Brand or Trade Name (Use generic if brand or trade name unknown)	Start Date (MM/DD/YY)	Stop Date (MM/DD/YY)	IFU

Initials
Date Verified
Initials
Date Keyed

Program Location
Date Printed

Patient: **Pre-Existing Conditions and Study Adverse Events** Visit:
Page: of

☐ No events recorded

Continue listing all events that occur during the study.
*If Event is serious, notify Lilly immediately.

Is this event or did this event...

Event Code	Description of Condition/Event	Onset Date (MM/DD/YY)	Stop Date (MM/DD/YY)	Related to study drug?	An instance of cancer, result in congenital anomaly; result from drug overdose, or life threatening?	Result in severe or permanent disability?	Require inpatient hospitalization or prolong an existing hospitalization?	Cause death?	Cause discontinuation?

Initials
Date Verified
Initials
Date Keyed
Program Location
Date Printed

Patient:

Signature Page

Visit:
Page: of

All information reported for this patient is accurate and complete.

_____
Signature of INVESTIGATOR who is a PHYSICIAN

_____/_____/_____
MM DD YY

Initials
Date Verified
Initials
Date Keyed

Program Location
Date Printed

16.1.3.
List of Investigators and Other Key Individuals

[redacted]

List of Investigators and Key Individuals

Name	Role
[redacted]	[redacted]

[redacted]

Dear [redacted]

I am unable to locate or obtain copies of CV's for [redacted] or [redacted]
They were both in the Ph.D. psychology program when they were participating as raters in the study. Attached are copies for the following raters:

[redacted]

In the white binder is the Master Drug Supply Inventory:
The first section is a typed list ordered by [redacted] plus a hand written list of those patients that had not been previously entered into the excel database. The second section is the raw data for the drug accountability log (there was no original form or plan to keep track of the drug accountability at the beginning of the study and the drug accountability form was modified as we became increasingly knowledgeable about a better way to track the information (which was used to create the type written log). This was done by the study coordinator who kept track of the medication that was given and returned. The second section is the raw data that was created ,after the fact-by the actual bottles that were stored-prior to disposing of the medication after the study (this was the information used to create the type written list/columns that refers to Drugs recorded by bottle).
I was unable to locate the computerized randomization program that created the randomization tables for the drug randomization that the pharmacy used. I will continue to look for it if I happen to find the program I will send it to you.
Also attached is the original SAE form for the last SAE query.

Sincerely,

[redacted]

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title: [redacted]

Address: [redacted]

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title: [redacted]

Address: [redacted]

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Research and Professional Experience (continued):

[redacted]

Professional Memberships:

Curriculum V

Full Name: [redacted]

Position Title: [redacted]

Address: [redacted]

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

3 January 1994

[redacted]

Research and Professional Experience (continued):

[redacted]

Professional Memberships:

Curriculum Vitae

Full Name: [redacted]

Position Title: [redacted]

Address: [redacted]

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Membership:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title: [redacted]

Address: [redacted]

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title: [redacted]

Address: [redacted]

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title: [redacted]

Address:

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

Curriculum Vitae

Full Name:

Position Title:

Address:

Telephone number:

[redacted]

Education:

[redacted]

Research and Professional Experience:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title:

Address:

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title:

Address:

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title:

Address:

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title:

Address:

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

Curriculum Vitae

Full Name: [redacted]

Position Title:

Address:

Telephone number:

Education:

[redacted]

Research and Professional Experience:

[redacted]

Professional Memberships:

[redacted]

16.1.4.
Signature of Investigator or Sponsor's Responsible Medical Officer

Principal or Coordinating Investigator(s) Signature(s) or Sponsor's Responsible Medical Officer

Study Title: Fluoxetine Versus Placebo in the Acute Treatment of Major Depressive Disorder in Children and Adolescents

Study Author(s): [redacted]

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

[redacted]

21.3.02

Date

Eli Lilly and Company

16.1.5.
Randomization Scheme and Codes

Randomization Codes
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065

Inv	Pat	Therapy Group	-
1	2001	Placebo	
	2002	Placebo	
	2007	Placebo	
	2010	Flx 20mg	
	2012	Flx 20mg	
	2013	Placebo	
	2014	Flx 20mg	
	2017	Placebo	
	2019	Flx 20mg	
	2025	Placebo	
	2026	Placebo	
	2029	Flx 20mg	
	2030	Flx 20mg	
	2032	Placebo	
	2033	Flx 20mg	
	2038	Placebo	
	2040	Flx 20mg	
	2042	Flx 20mg	
	2047	Flx 20mg	
	2050	Placebo	

RMP.B1YP.JCLLIB2(MIL1E42A)
RMP.B1Y0.X065REP(MIL1E42A)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065

Inv	Pat	Therapy Group	-
1	2051	Flx 20mg	
	2052	Placebo	
	2057	Placebo	
	2061	Placebo	
	2064	Placebo	
	2066	Placebo	
	2067	Flx 20mg	
	2068	Placebo	
	2069	Placebo	
	2073	Flx 20mg	
	2075	Flx 20mg	
	2083	Flx 20mg	
	2085	Flx 20mg	
	2087	Placebo	
	2090	Flx 20mg	
	2093	Placebo	
	2095	Placebo	
	2096	Placebo	
	2098	Placebo	
	2100	Placebo	

RMP.B1YP.JCLLIB2(MIL1E42A)
RMP.B1Y0.X065REP(MIL1E42A)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065

Inv	Pat	Therapy Group	-
1	2102	Placebo	
	2107	Placebo	
	2114	Placebo	
	2115	Placebo	
	2119	Flx 20mg	
	2120	Flx 20mg	
	2123	Flx 20mg	
	2124	Flx 20mg	
	2125	Flx 20mg	
	2126	Flx 20mg	
	2133	Placebo	
	2142	Flx 20mg	
	2147	Placebo	
	2149	Flx 20mg	
	2153	Flx 20mg	
	2162	Flx 20mg	
	2163	Flx 20mg	
	2166	Placebo	
	2167	Placebo	
	2169	Flx 20mg	

RMP.B1YP.JCLLIB2(MIL1E42A)
RMP.B1Y0.X065REP(MIL1E42A)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065

Inv	Pat	Therapy Group	-
1	2172	Placebo	
	2173	Flx 20mg	
	2174	Flx 20mg	
	2177	Placebo	
	2178	Flx 20mg	
	2179	Placebo	
	2180	Placebo	
	2184	Flx 20mg	
	2185	Flx 20mg	
	2186	Flx 20mg	
	2187	Placebo	
	2195	Flx 20mg	
	2197	Flx 20mg	
	2204	Placebo	
	2207	Placebo	
	2210	Flx 20mg	
	2211	Placebo	
	2212	Flx 20mg	
	2213	Placebo	
	2214	Flx 20mg	

RMP.B1YP.JCLLIB2(MIL1E42A)
RMP.B1Y0.X065REP(MIL1E42A)
XMIL0001

Randomization Codes
All Randomized Patients
B1Y-MC-X065

Protocol: B1Y-MC-X065

Inv	Pat	Therapy Group	-
1	2215	Placebo	
	2220	Placebo	
	2229	Placebo	
	2230	Flx 20mg	
	2231	Flx 20mg	
	2233	Placebo	
	2235	Flx 20mg	
	2237	Flx 20mg	
	2238	Placebo	
	2242	Flx 20mg	
	2244	Flx 20mg	
	2246	Placebo	
	2249	Flx 20mg	
	2250	Flx 20mg	
	2251	Placebo	
	2252	Placebo	

RMP.B1YP.JCLLIB2(MIL1E42A)
RMP.B1Y0.X065REP(MIL1E42A)
XMIL0001

16.1.6.
Documentation of Statistical Methods

General Considerations

All tests of hypotheses will be tested at a two-sided, 0.05 significance level. All total and subtotal scores from rating scales will be derived from individual items. If any of the individual items are missing, the total or subtotal will be treated as missing.

For analyses of continuous data, treatment groups will be compared using Type III sums of squares from an analysis of variance (ANOVA) with treatment in the model (SAS PROC GLM). The analyses will be performed on the original scale data unless the assumptions of the ANOVA appeared to be violated. In these instances, the analyses will be performed on the rank-transformed data.

For analyses of categorical efficacy and safety (a response, remission, recovery or event), Fisher's exact test will be used. The analyses of demographic variables will also be performed using Fisher's exact test.

Supplemental analyses of the data will be conducted as deemed appropriate.

Data to be Analyzed

All analyses will be performed on an intent-to-treat basis. An intent-to-treat analysis is an analysis of data by treatment group assignment, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol.

Only patients with baseline and postbaseline measurements for the primary efficacy analysis will be included in the analyses of all efficacy scales. Patients who are excluded from the efficacy analyses will be documented. Patients who had their daily dose reduced by switching to alternate day dosing will be included in all analyses. Patients who switched to alternate day dosing will be documented.

Patient Disposition

Reasons for discontinuation for all randomized patients will be compared between treatment groups using Fisher's exact test.

Patient Characteristics

Baseline characteristics of origin, age, age category (preadolescent and adolescent), gender, height, weight, socioeconomic status, and family structure will be compared between treatment groups. Frequencies will be compared using Fisher's exact test and means will be compared using an ANOVA with treatment in the model.

Psychiatric History

Psychiatric history, including comorbid Axis I diagnoses, duration of current episode, number of depressive episodes, length of illness, age of illness onset, and positive family history will be summarized for each treatment group for all randomized patients.

Categorical data will be compared across treatment groups using Fisher's exact test and continuous data will be compared across groups using an ANOVA with treatment group as the independent variable in the model.

Previous Treatment Current Episode

The use of previous treatments for the current episode of illness will be summarized for each treatment group. The frequency of the previous treatments used along with the number of patients using any previous treatment will be reported.

Concomitant Medications

Concomitant medications will be summarized for each treatment group. Incidence rates of concomitant medications will be analyzed by Fisher's exact test.

Compliance

Compliance with study medication was determined post-hoc. A patient will be considered noncompliant if he/she failed to take study drug for more than two days within a visit interval (approximately a week). If the patient's dosage had been reduced to alternate day therapy (average of 10 mg/day), noncompliance will be defined as failing to take study drug for more than one day within a visit interval. The percentage of compliant patients for each treatment group will be summarized by visit.

Baseline Psychiatric Evaluation

Baseline scores for the CDRS-R total, CGI-Severity, and BPRS-C total scales will be summarized for each treatment group. Baseline will be defined as the last available measure for each scale of Visits 1 and 2. Each scale will be compared across treatment groups using an ANOVA with treatment in the model.

Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy variable will be the CDRS-R total score. The primary analysis will be the comparison of the proportion of patients responding between treatment groups. A patient will be considered a responder if his/her CDRS-R total score decreased by at least 30% from baseline (last available measure from Visits 1 and 2) to endpoint (last available measure from Visits 3-10). Two analyses to augment the primary analyses will also be performed: 1) The CDRS-R total response rate using a reduction of at least 50% from baseline, and 2) CDRS-R total response rate on all patients completing at least 4 weeks of treatment. The proportion of patients who responded will be compared across treatment groups using Fisher's exact test.

Secondary Efficacy Analysis

Mean change in CDRS-R total score from baseline (last available measure from Visits 1 and 2) to endpoint (last available measure from Visits 3-10) will be compared across treatment groups using an ANOVA with treatment in the model. The following secondary variables will be analyzed in a similar manner:

- CDRS-R Mood Subtotal – sum of Items 8, 11, 14, 15
- CDRS-R Somatic Subtotal – sum of Items 4, 5, 6, 7, 16, 17
- CDRS-R Subjective Subtotal – sum of Items 9, 10, 12, 13
- CDRS-R Behavior Subtotal – sum of Items 1, 2, 3
- CGI-Severity
- BPRS-C Total
- CDI Total
- BDI Total.

For the analysis of CGI-Improvement, an ANOVA will be performed only on endpoint values, since this scale measures total improvement in direct comparison to the patient's condition at baseline.

Three different longitudinal analyses will be conducted to assess the temporal change in the CDRS-R scale data. The first two analyses will assess mean change in CDRS-R total scores from baseline (last available of Visits 1 and 2) to each subsequent visit (Visits 3-10) will be compared across treatment groups. Two by-visit analyses will be performed: 1) one that includes patients active in the study at the visit of interest, and 2) one that includes all patients with at least one postbaseline measure using a last-observation-carried-forward (LOCF) approach.

The third analysis to assess the temporal change over time of the CDRS-R total score will be a repeated measures analysis of variance. The dependent variable will be the baseline and postbaseline CDRS-R total score. The model will use an unstructured covariance matrix with visit as the within-patient factor, treatment as the between-patient factor, and a treatment-by-visit interaction. The change from baseline to visit 10 will be compared across treatments by assessing this single degree of freedom contrast of the treatment-by-visit interaction. All main effects and interaction tests will be made using the approximate F-tests reported by SAS PROC MIXED.

The proportion of patients meeting definitions of response, remission and recovery will be compared between treatment groups as secondary categorical analyses. All frequencies will be analyzed using a Fisher's exact test. The following categorical definitions will be analyzed:

- **Remission**: A remitter will be defined as a patient who has an endpoint CDRS-R total score ≤28. Endpoint is the last available measurement from Visits 3-10. This analysis will also be performed on all patients completing at least 4 weeks of treatment (endpoint will be the last measurement from Visits 6-10).
- **CGI-Improvement Response**: A patient will be defined as a CGI-Improvement responder if their last available treatment CGI-Improvement score is 1 or 2 (endpoint is the last available measurement from Visits 3-10).
- **Recovery**: Patients with a CDRS-R total endpoint score ≤28 and a CGI-Improvement endpoint score of 1 or 2 will be defined as recovered. Endpoint is the last available measurement from Visits 3-10.

Safety Analyses

Extent of Exposure

The length of exposure (measured in days) for each patient will be summarized by treatment group. Exposure will be defined as the last dose date minus the first dose date plus one. Those patients that switched to alternate day dosing will have their exposure calculation adjusted accordingly.

Adverse Events

Adverse events will be summarized and analyzed using three sources of data: The Side-Effect Checklist, non-solicited adverse events, and the Fluoxetine Side-Effect Checklist. All randomized patients will be included in the analyses and Fisher's exact test will be used for comparing incidence of events.

The frequency of treatment-emergent solicited adverse events as defined by the items on the Side-Effects Checklist will be analyzed. An event will be considered to be treatment-emergent solicited if the Checklist item is present at baseline and worsened as defined by an increase in the score, or if the Checklist item first occurred after baseline. The analysis of the Side-Effects Checklist will be considered the primary analysis of safety as it is the most complete and impartial source of adverse event reporting in this study.

Non-solicited adverse events occurring during treatment will also be summarized by incidence and frequencies will be compared between treatment groups.

All adverse events reported on the Fluoxetine Side-Effects Checklist will be summarized and reported. No statistical tests will be performed on these data because these data are not considered to be a complete source of information. The Fluoxetine Side-Effects Checklist was administered to only a subset of the patients in the study.

Serious adverse events will be summarized and discussed in text.

Laboratory Evaluation

The treatment effect on change from baseline (last measurement from Visits 1 and 2) to endpoint (last measurement from Visits 3-10) for continuous laboratory values will be assessed using an ANOVA with treatment as the independent factor in the model. All patients with a baseline and endpoint score will be included in the analysis. The proportion of patients with abnormal laboratory values will be summarized and compared across treatment groups by Fisher's exact test. Laboratory results include hematology, urinalysis, and serum concentrations.

Vital Signs

Mean change from baseline (last measurement from Visits 1 and 2) to endpoint (last measurement from Visits 3-10) in vital signs will be compared across treatment groups using ANOVA with treatment in the model. All patients with a baseline and endpoint score will be included in the analysis. Vital signs included height, weight, heart rate, and blood pressure.

Subgroup Analyses

The primary efficacy analysis, CDRS-R total response rate, will be assessed for differential treatment effects across two subgroups, gender and age category (8-<13, 13-≤18). Frequency of response for each subgroup will be presented along with the Breslow-Day test for the homogeneity of odds ratio results comparing between-strata differences in the response frequency between treatment groups.

Mean changes in CDRS-R total score from baseline to endpoint will also be compared across treatment groups for the subgroups gender and age category. For each subgroup, the statistical evaluation of both the change from baseline while accounting for subgroup effect and the change from baseline within subgroup strata will be performed. An analysis of covariance will be conducted with treatment, subgroup, and treatment-by-subgroup interaction as the independent factors in the model. The test of the treatment-by-subgroup interaction will be the primary assessment of possible differential treatment effects across subgroups. Tests of interactions will be at a 0.10 significance level.

Treatment-emergent solicited adverse events from the Side-Effects Checklist will be analyzed by the subgroups age category and gender. Specific adverse events of interest may also be analyzed by a Breslow-Day test for homogeneity of odds ratio across subgroups.

16.1.7.
Publications Based on the Study

ORIGINAL ARTICLE

A Double-blind, Randomized, Placebo-Controlled Trial of Fluoxetine in Children and Adolescents With Depression

Graham J. Emslie, MD; A. John Rush, MD; Warren A. Weinberg, MD; Robert A. Kowatch, MD; Carroll W. Hughes, PhD; Tom Carmody, PhD; Jeanne Rintelmann

Background: Depression is a major cause of morbidity and mortality in children and adolescents. To date, randomized, controlled, double-blind trials of antidepressants (largely tricyclic agents) have yet to reveal that any antidepressant is more effective than placebo. This article is of a randomized, double-blind, placebo-controlled trial of fluoxetine in children and adolescents with depression

Method: Ninety-six child and adolescent outpatients (aged 7-17 years) with nonpsychotic major depressive disorder were randomized (stratified for age and sex) to 20 mg of fluoxetine or placebo and seen weekly for 8 consecutive weeks. Randomization was preceded by 3 evaluation visits that included structured diagnostic interviews during 2 weeks, followed 1 week later by a 1-week, single-blind placebo run-in. Primary outcome measurements were the global improvement of the Clinical Global Impressions scale and the Children's Depression Rating Scale—Revised, a measure of the severity depressive symptoms.

Results: Of the 96 patients, 48 were randomized to fluoxetine treatment and 48 to placebo. Using the intent to treat sample, 27 (56%) of those receiving fluoxetine and 16 (33%) receiving placebo were rated "much" or "very much" improved on the Clinical Global Impressions scale at study exit (χ^2=5.1, *df*=1, *P*=.02). Significant differences were also noted in weekly ratings of the Children's Depression Rating Scale—Revised after 5 weeks of treatment (using last observation carried forward). Equivalent response rates were found for patients aged 12 years and younger (n=48) and those aged 13 years and older (n=48). However, complete symptom remission (Children's Depression Rating Scale—Revised ≤28) occurred in only 31% of the fluoxetine-treated patients and 23% of the placebo patients.

Conclusion: Fluoxetine was superior to placebo in the acute phase treatment of major depressive disorder in child and adolescent outpatients with severe, persistent depression. Complete remission of symptoms was rare.

Arch Gen Psychiatry. 1997;54:1031-1037

DEPRESSION IS a major cause of morbidity and mortality in children and adolescents.[1] School failure and school dropout are common outcomes for children and adolescents with depression,[2,3] and suicide remains one of the leading causes of death in adolescents.[4-6] The age of onset of depression is decreasing in those more recently born,[7] with the result that many individuals will experience their first episodes of depression during their adolescent years. Puberty marks a substantial rise in the overall prevalence of depression and is associated with a shift in the sex ratio, with a preponderance of females.

A meta-analysis of all available placebo-controlled trials (n=12) of tricyclic antidepressants (TCAs) in patients between the ages 6 and 18 years concluded that the difference between active treatment and placebo is too small to be clinically significant.[8] This lack of efficacy, as well as the prevalence of side effects of more noradrenergic antidepressants, has led to an increased interest in selective serotonin reuptake inhibitors.[8] Published articles about selective serotonin reuptake inhibitors in adolescent depression include 2 studies of "treatment-resistant" depression with fluoxetine[9,10]; 2 retrospective medical record reviews with fluoxetine[11] and sertraline treatment[12]; and 1 negative, double-blind, placebo-controlled study of fluoxetine.[13] Despite the lack of evidence of effectiveness in randomized control trials, antidepressant medications continue to be prescribed widely in this age group primarily based on adult data. For adults, the efficacy of antidepressant medications for major depressive disorder (MDD) is well established.[14,15] No one antidepressant is clearly more effective than another, except that monoamine oxidase inhibitors are more effective than TCAs for depression with atypical features.[16,17]

From the Departments of Psychiatry (Drs Emslie, Rush, and Kowatch and Ms Rintelmann), Neurology (Dr Weinberg), and Academic Computing (Dr Carmody), University of Texas Southwestern Medical Center at Dallas, and Terrell State Hospital (Dr Hughes), Terrell, Tex.

PATIENTS AND METHODS

PATIENTS

Child and adolescent outpatients (aged 7-17 years) who were self-referred or referred by other practitioners to our mood disorders program and who met *DSM-III-R* criteria for nonpsychotic MDD, single and recurrent. They were in good general medical health and of normal intelligence. Patients with bipolar I and II disorder, psychotic depression (lifetime), independent sleep-wake disorder, alcohol and other substance abuse (within the last year), anorexia nervosa or bulimia (lifetime), or previous adequate treatment with fluoxetine (20 mg/d for at least 3 weeks) were excluded. Any patient with at least 1 first-degree relative with bipolar I disorder (based on family history by a parent) was also excluded.

Possible patients for study were scheduled for a full evaluation after telephone screening for inclusion and exclusion criteria. Prior to the initial interview, the study was explained and written informed consent was obtained from the parent(s) and assent from the patient. The study was approved by the institutional review board at the University of Texas Southwestern Medical Center at Dallas. In addition to a structured psychiatric interview, the initial evaluation included a medical review of systems, a physical and neurological examination, and laboratory tests (blood chemistry study using an automated multiple analysis system, complete blood cell and differential cell counts, urinalysis, thyroid panel, and electrocardiogram). The evaluation was completed during a 3-week period.

METHODS

At the initial visit, each patient and parent(s) were interviewed separately using the Diagnostic Interview for Children and Adolescents,[25,26] a semistructured *DSM-III-R*–based diagnostic interview to establish that the patient met *DSM-III-R* criteria for MDD and to identify other concurrent and lifetime psychiatric disorders. The final diagnoses were based on information from interviews of the parent(s) and child. Additionally, criterion depressive symptoms and depressive symptom severity were assessed using the depressive items of the Kiddie Schedule for Affective Disorders and Schizophrenia[27] and the Children's Depression Rating Scale–Revised (CDRS-R),[28] respectively. Patients completed 2 self-report scales for depression, either the Children's Depression Inventory[29] (all patients ≤12 years) or the 21-item Beck Depression Inventory[30] (all patients ≥13 years) and the Weinberg Screening Affective Scale.[31] Overall functioning was assessed using the Children's Global Assessment Scale (CGAS).[32]

Following the initial diagnostic interview, the patients were seen for 2 additional follow-up interviews, 1 at visit 2 and 1 at visit 3. During the follow-up interviews, the patient and parent(s) were interviewed separately by 1 of 3 of us experienced in evaluating children and adolescents (G.J.E., W.A.W., and R.A.K.). The Diagnostic Interview for Children and Adolescents was reviewed. The Kiddie Schedule for Affective Disorders and Schizophrenia depressive items were scored for the past week and for the nadir of the present episode and were used primarily as a criteria measure at baseline. The CDRS-R and Brief Psychiatric Rating Scale–Children (BPRS-C),[33] a clinician-rated measure of general psychopathologic characteristics, were also completed. The course of illness, including the number, length, and timing of prior and current episodes, was established and the family history was reviewed.

Final consensus diagnoses were determined following visit 3 in a research conference that has been meeting weekly for the past 10 years. To enroll in the 1-week, single-blind, placebo run-in at visit 4 (3 weeks from initial interview), all patients had to continue to meet criteria for MDD, have a CDRS-R score greater than 40, and meet the previous inclusion-exclusion criteria. At the end of the placebo run-in week, the patients were randomized to either fluoxetine treatment or placebo if they still met all of the enrollment criteria, including a CDRS-R score greater than 40 the preceding week. Randomization was by a table of random numbers stratified for age and sex. Randomization was conducted by the pharmacy and clinicians, who remained blind to assignment until the end of the study. Those patients whose conditions improved (n=7) during the 1-week placebo run-in period continued to receive placebo for an additional week to determine if the symptoms returned. If the patients' conditions still improved, they were withdrawn from the study (n=7).

The possible reasons for the differences between adults and adolescents have been reviewed.[18,19] Ryan[19] noted that medications studied to date have been primarily noradrenergic or were metabolized quickly to noradrenergic metabolites. Based on limited animal studies, it is suggested that the noradrenergic system does not develop fully until early adulthood,[20,21] suggesting that serotonergic agents may be more effective in this age group.[19] Alternatively, high levels of hormones during puberty may decrease the effectiveness of TCAs.[18] Several articles have also commented on design issues,[22-24] small sample sizes, definitions of response, comorbidity, length of treatment, and large placebo response in children and adolescents. A primary concern is whether the populations studied are sufficiently homogeneous to allow a study of the efficacy of medication. The major concerns are that (1) the populations studied are abnormally treatment resistant (incipient bipolar, subjects with atypical depression, and substantial comorbidity), (2) the populations are overly treatment responsive, (3) the samples are too heterogeneous to detect medication effects, or (4) the wrong medications have been evaluated.

Our study was undertaken to evaluate the comparative efficacy, safety, and tolerability of fluoxetine treatment compared with placebo in child and adolescent outpatients with nonpsychotic MDD.

RESULTS

Five hundred eighty-three patients were screened by telephone during the course of the study (April 1, 1991 to January 31, 1995), 256 of whom were interviewed at least once. Of these, 106 patients completed the initial evaluation visits and enrolled in the placebo run-in period. Of the 150 ineligible patients, 34 (23%) refused to participate in the treatment study, 55 (37%) did not meet in-

OUTCOME MEASURES

Outcome was measured weekly. The Clinical Global Impressions (CGI) scale improvement rating and the CDRS-R were selected, a priori, as the major outcome measures. Additionally, the clinician completed the CGAS and the BPRS-C weekly. The patient completed the Beck Depression Inventory or Children's Depression Inventory and the Weinberg Screening Affective Scale at the beginning and the end of treatment. All subjects continued in the study for 8 weeks unless continued nonresponsiveness or adverse events dictated a change in treatment.

Following randomization, each patient was given 1 capsule of placebo or 20 mg of fluoxetine every morning. All patients were seen weekly for 8 consecutive weeks; serum levels were collected on all patients at weeks 1, 2, 4, 6, and 8, approximately 8 hours after the last dose; however, results of blood chemistry levels were not provided to clinicians. Compliance was monitored by counting returned pills. New bottles were provided weekly, with 2 extra pills in the event of scheduling difficulties for the next visit. The pharmacy provided blinded medication based on the random assignment. Electrocardiograms and routine laboratory work (repeat of baseline studies) were repeated at weeks 4 and 8 (or at last visit) of the study.

STATISTICAL ANALYSIS

The data were computerized and managed using screen- and menu-guided Statistical Analysis System software (SAS, Cary, NC). Throughout our study, quality control procedures were in place to ensure accurate and complete data (eg, dual entry and multiple manual comparisons).

To assess interrater reliability specific for our study, the CGI scale and CDRS-R scores were assessed in the same interviews by 2 experienced clinicians during various stages of the evaluation and treatment phases of the study. Patients receiving dual assessments were selected solely on the availability of clinicians at the time of appointment, though patients were seen by 2 clinicians on completion of the study if at all possible. As the CGI scale improvement score is not completed during evaluation, paired scores are available for 48 patients for the CDRS-R and 41 patients for the CGI scale, 35 of which were performed at visit 8. The intraclass correlation[34] for the CDRS-R was 0.95 and the CGI improvement rating was 0.93. If the CGI scale improvement rating is used as a categorical variable (ie, responder vs nonresponder), then $\kappa = 0.951$.

The primary outcome measures for the study were categorical. The proportion of patients who were randomized (intent to treat) who responded in each group (drug and placebo) as defined by a CGI scale improvement rating of 1 or 2 ("very much" or "much" improved, respectively) and dimensional (the group mean weekly) CDRS-R scores. Secondary analyses to explore in more depth the pattern of response to fluoxetine treatment and placebo included a survival analysis of time to remission (defined as the first of 2 consecutive weekly CGI scale ratings of 1 or 2) and repeated-measures analyses of variance using weekly CDRS-R scores with the last observation carried forward (LOCF).

However, the results of the LOCF method are not always reliable owing to the creation of "carried forward" data for weeks after discontinuation. This could bias the between-group comparison depending on how the pattern of dropouts varies between groups. Therefore, an additional method of analysis was used to obtain results based on all of the data but without the bias inherent in the LOCF method. For this analysis, the rate of change in the CDRS-R score was estimated for each patient (fluoxetine-treated or placebo) individually using all data available for that patient. The rates of change for all patients in each group (fluoxetine-treated or placebo) were averaged together. The averages for these 2 groups were then compared using a t test. The rate of change (or slope) was first estimated using linear regression (which also produces an estimated baseline CDRS-R score). Kraemer and Thieman[35] recommend analysis of linear regression slopes as an efficient method for use with "soft" data. As a check on the validity of this method, the average slope in each group and the variability of the average was estimated using the more sophisticated empirical Bayesian analysis described by Mori et al.[35] The empirical Bayesian analysis was selected because it adjusts for the correlation between the probability of dropout and the true unobservable rate of change (ie, informative right censoring). Such correlation can be tested[17] and was significant in our data ($P = .02$). Secondary outcome measures were compared based on the last available measurement using analysis of covariance with the baseline measurement as the covariate. All tests were 2-sided with $P < .05$ used for significance. Means are presented as ±SD.

clusionary criteria; 24 (16%) met exclusionary criteria; the condition of 22 (15%) improved during the evaluation, thereby, becoming ineligible; and 15 (10%) needed immediate treatment. Of the 106 patients enrolled in the placebo run-in period, 96 were randomized. Of the 10 not randomized, the condition of 7 improved, 2 refused further study, and 1 had significant side effects while receiving placebo. Of the 96 patients randomized, 48 received fluoxetine treatment and 48 received placebo.

As mentioned previously, the sample was stratified by age (≤12 years and and ≥13 years) and by sex. Of the 48 patients randomized to fluoxetine treatment, 24 were aged 12 years and younger and 24 were aged 13 years and older. Of those randomized to placebo, 24 were aged 12 years and younger and 24 were aged 13 years and older. The 2 groups, fluoxetine-treated and placebo, were not different in any demographic or clinical features, except that those assigned to fluoxetine treatment had a greater lifetime incidence of comorbid anxiety disorders ($\chi^2 = 4.2$, $df = 1$, $P = .04$). **Table 1** lists the demographic and clinical characteristics of these 2 groups (fluoxetine treatment and placebo).

Table 2 lists the timing and basis for patients not completing the 8-week trial. The most common reason for discontinuation was continued nonresponse (19 patients who were receiving placebo and 7 who were receiving fluoxetine). Side effects, as a reason for discontinuation, were minimal, affecting only 4 patients who were receiving fluoxetine and 1 who was receiving placebo. The side effects leading to discontinuation of fluoxetine treatment were in 3 patients in whom manic symptoms developed and 1 patient who developed a severe rash.

Based on a CGI scale improvement rating of 1 or 2 (very much or much improved) to define response, 27 (56%) of 48 patients receiving fluoxetine treatment and 16 (33%) of 48 patients on placebo responded to treatment at exit from the study ($\chi^2 = 5.097$, $df = 1$, $P = .02$). On the other hand, of

Table 1. Clinical and Demographic Characteristics

Features	Patient Group* Fluoxetine-Treated	Placebo
Demographics		
Age, y	12.2±2.7	12.5±2.6
(Range)	(7-17)	(8-17)
Female, No. (%)	22 (46)	22 (46)
White, No. (%)	35 (72.9)	41 (85.4)
Socioeconomic status, No. (%)†		
1-2	14 (29.2)	16 (33.3)
3	16 (33.3)	18 (37.5)
4-5	18 (37.5)	14 (29.2)
Clinical characteristics		
CDRS-R score‡	58.5±10.5	57.6±10.4
(Range)	(42-90)	(42-82)
Melancholic, *DSM-III-R* (%)	7 (14.6)	12 (25)
First episode, No. (%)	23 (47.9)	23 (47.9)
No. of episodes	1.7±0.7	1.8±0.8
(Range)	(1-3)	(1-4)
Duration, current episode, wk	14.6±9.7	13.7±7.5
(Range)	(4-56)	(4-32)
Length of illness, mo	18.8±20.9	18.0±19.7
(Range)	(1-84)	(1-72)
Age at onset, y	10.6±2.7	11.0±2.6
(Range)	(6-16)	(5-17)
Positive family history, No. (%)§	25 (52.1)	29 (60.4)
CGAS score‖	47.9±8.3	48.4±7.8
(Range)	(25-65)	(35-80)
Comorbid diagnoses, lifetime, No. (%)		
None	7 (14.6)	11 (22.9)
Dysthymia	20 (41.7)	14 (29.2)
Anxiety disorders	32 (66.7)	22 (45.8)
ADHD	16 (33.3)	13 (27.1)
Oppositional/conduct	13 (27.1)	16 (33.3)

*There were 48 patients enrolled in each group (mean±SD).
†Two-factor index (A. B. Hollingshead, unpublished data, 1975).
‡CDRS-R indicates Children's Depression Rating Scale–Revised; CGAS, Children's Global Assessment Scale; and ADHD, attention deficit hyperactivity disorder.
§A first-degree relative with affective disorder treated with either hospitalization or medication.
‖Based on average of scores during evaluation.

Table 2. Reasons for Discontinuation Following Randomization

Patient Group	Week 1	2	3	4	5	6	7	8	Total
Fluoxetine-treated									
Lack of efficacy	.	.	.	.	1	3	2	1	7
Side effects	.	.	.	1	2	.	1	.	4
Protocol violation*	.	.	1	.	1	1	.	.	3
Placebo									
Lack of efficacy	.	1	1	1	5	5	5	1	19
Side effects	.	.	.	1	.	.	.	.	1
Protocol violation	1	.	.	1	.	.	.	.	2
Total	1	1	2	4	9	9	8	2	36

*Protocol violations included taking nonstudy medications and missing appointments. Ellipses indicate no patients discontinued.

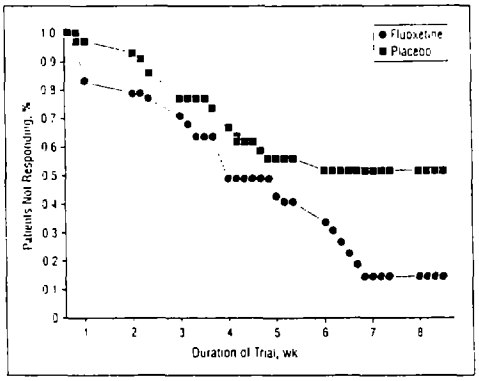

Figure 1. *Survival curve for time to response comparing fluoxetine and placebo. Response is Clinical Global Impressions scale (improvement) rating of 2 or less for 2 consecutive weeks.*

those who completed the entire 8 weeks of treatment 25 (74%) of 34 patients responded to fluoxetine treatment and 15 (58%) of 26 patients responded to placebo (χ^2=1.663, *df*=1, *P*=.20). This result is influenced by the differential dropout of nonresponders in the placebo group. While the condition of many patients improved during the study, only 15 (31%) of 48 patients of the fluoxetine-treated group and 11 (23%) of 48 patients of the placebo group had minimal symptoms (ie, a CDRS-R score ≤28) by end of the study.

To examine the pattern of change in the 2 groups, time to response was defined categorically as the first of 2 consecutive weeks when the CGI scale rating was a 1 or a 2 (much or very much improved). Kaplan-Meier survival curves[36] were compared using the log-rank test and were found significantly different (χ^2=5.66, *df*=1, *P*=.017) (**Figure 1**).

The other primary outcome measure, the weekly CDRS-R score, was examined as a continuous variable. **Figure 2** shows the traditional method of dealing with patient attrition during the course of the treatment (ie, weekly CDRS-R scores for each group are presented with the LOCF). The last available observation is filled in for the values for patients who discontinued study participation before 8 weeks. A repeated measure (analysis of variance) using all 96 patients showed a significant drug by time interaction (F=3.66; *df*=8, 752; *P*=.01). Age group by treatment interaction was also examined but was not significant (*P*=.76). Comparing the weekly CDRS-R scores for each treatment group using *t* tests, the first week that the groups were significantly different was week 5. At week 5, the mean CDRS-R score for the fluoxetine-treated group (39.8±13.2) was lower than the placebo group (46.8±16.6) (*t*=−2.28, *df*=94, *P*=.03).

To make the most efficient use of the available data[36] without resorting to a completion analysis or LOCF analysis, the rate of change (slope) and baseline CDRS-R score (intercept) were estimated from linear regressions on each patient and for each group. The estimated baselines were similar (54.2 for the fluoxetine-treated group vs 53.8 for the placebo group). However, the fluoxetine-treated group slope of −2.75±−2.52 was significantly different from the placebo group slope of −1.27±−2.86 (*t*=2.68, *df*=94, *P*<.001).

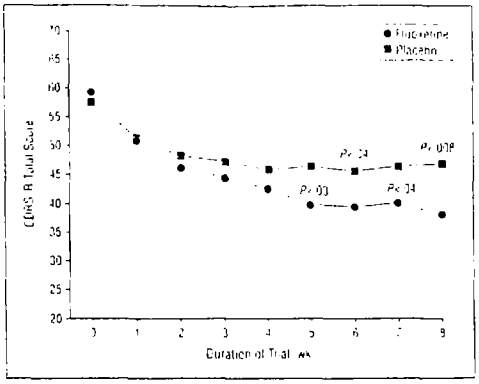

Figure 2. *Weekly Children's Depressive Rating Scale—Revised (CDRS-R) scores (last observation carried forward) for fluoxetine and placebo.*

These results may be interpreted as follows. The fluoxetine-treated group began with an average CDRS-R score of 54.2 and their scores improved by 2.75 U per week to end with an estimated week 8 score of 32.2. While placebo patients began with a similar average CDRS-R score (53.8), their score improved only 1.27 U per week to the end of the study with an estimated exit score of 43.6. Using the empirical Bayesian analysis of estimating slopes (intercept estimates were unavailable) gives an estimated slope of −2.60±2.36 for the fluoxetine-treated group and a significantly smaller slope of −1.32±3.56 for the placebo group (t=2.08, df=94, P=.04).

To further evaluate the effect of age and sex on response, regression lines were calculated for patients aged 12 years and younger and 13 years and older in each group. There were no significant drug by age interactions (F=0.12, df=1, 92, P=.73), though the younger patients independent of the treatment group started with lower CDRS-R scores (F=8.77, df=1, 92, P=.004). Similarly, if the sample is divided by sex, using the same analyses, there was no drug by sex interaction (F=.001; df=1, 92; P=.96).

Finally, for descriptive purposes, **Table 3** lists the initial and last available scores for all 96 patients on the clinician measures and self-report depression scales by groups. Fluoxetine treatment and placebo were associated with significant decreases between baseline and exit scores on these measures. As noted previously, improvement in the CDRS-R scores were greater in the fluoxetine-treated group (final CDRS-R score, 38.4±14.8) than in the placebo group (final CDRS-R score, 47.1±17.0) and the analysis of covariance (F=10.58; df=1, 93; P=.002). However, on measurements of general psychiatric symptoms (BPRS-C) and global functioning (CGAS), there were significant improvements in the condition of the patients in both groups during the course of the study, but the improvement in the fluoxetine-treated group was not significantly superior to the placebo group. Furthermore, self-reported depressive symptom measurements also showed improvement in both groups, but the between-group differences were not significant. However, given the wide variability of initial child self-reports, these findings are difficult to interpret.

Table 3. Baseline to Exit Outcomes

	Patient Group Scores*			
	Fluoxetine-Treated		Placebo	
Scale†	Baseline	Final	Baseline	Final
CDRS-R	58.5±10.5	38.4±14.8	57.6±10.4	47.1±17.0
(Range)	(42-90)	(19-71)	(42-82)	(17-78)
CDI/BDI	15.8±10.6	9.9±12.0	15.3±11.9	11.2±10.8
(Range)	(0-41)	(0-56)	(0-54)	(0-42)
WSAS	20.6±11.8	13.1±12.0	20.6±12.8	16.7±13.5
(Range)	(1-45)	(0-42)	(0-47)	(0-46)
BPRS-C	47.3±7.7	38.9±10.0	46.2±8.9	41.0±10.4
(Range)	(34-65)	(21-58)	(24-69)	(21-67)
CGAS	47.9±8.3	63.9±12.9	48.4±7.8	60.1±14.8
(Range)	(25-65)	(40-89)	(35-80)	(40-95)

*There were 48 patients enrolled in each group (mean±SD).
†CDRS-R indicates Children's Depression Rating Scale–Revised. CDI, Children's Depression Inventory; BDI, Beck Depression Inventory; WSAS, Weinberg Screening Affective Scale; BPRS-C, Brief Psychiatric Rating Scale–Children; and CGAS, Children's Global Assessment Scale.

COMMENT

Fluoxetine treatment was superior to placebo in relieving depressive symptoms. The difference between fluoxetine treatment and placebo was evident in clinician assessment of clinical global improvement (the CGI scale) and in weekly clinician depressive symptom severity ratings (the CDRS-R). Differences between fluoxetine treatment and placebo became statistically significant after 5 weeks.

There was no clear difference in patient responsiveness to either fluoxetine treatment or placebo based on age or sex. The overall rates of response were similar to those reported in adults for fluoxetine treatment and placebo using comparable analyses. For example, the Depression Guideline Panel[11] reports that a meta-analysis of all available double-blind studies of fluoxetine treatment, with intent-to-treat samples, reveals a 46% response rate to fluoxetine treatment and a 22% difference between fluoxetine treatment and placebo.

Despite improvements in depressive symptoms, relatively complete remission of depressive symptoms (a CDRS-R score ≤28) was uncommon, which is not dissimilar to adult data in 6- to 8-week efficacy trials. Differences between the fluoxetine-treated group and the placebo group were less evident in self-report scales (Children's Depression Inventory, Beck Depression Inventory, and Weinberg Screening Affective Scale) and in clinician ratings of general psychiatric symptoms (the BPRS-C) and global functioning (the CGAS).

COMPARISON WITH FINDINGS FROM PREVIOUS STUDIES OF CHILDREN AND ADOLESCENTS

Several factors may explain a positive result in our study compared with previous studies of children and adolescents. While depressed at baseline evaluation, as evidenced by CDRS-R scores, the sample as a whole was neither overly responsive (ie, the placebo response rate of 33%) nor treatment resistant (ie, the fluoxetine-treated group response rate of 56%).

In the study of 38 children by Puig-Antich et al,[39] 56% (9/16) of the children responded to imipramine therapy and 68% (15/22) responded to placebo. Four patients in the imipramine-treated group, but none in the placebo group, failed to complete the 5-week protocol. An open extension of this study suggested that in addition to the high placebo response rate, failure to achieve therapeutic levels of imipramine limited effectiveness.[40]

In part, as a result of this study, Geller et al[41] designed their study of nortriptyline in children to be longer (8 weeks) and controlled for blood chemistry levels. The randomization was preceded by a 2-week placebo washout phase. The patients had severe depression, had a chronic course, and had a high rate of comorbidity including family histories of bipolar disorder. Of the 50 children randomized, 30.8% responded to active treatment and 16.7% responded to placebo based on an earlier version of the CDRS. The mean unrevised CDRS scores at the end of the study for active and placebo were 32.9±11.4 and 32.0±9.8, respectively.

In adolescents, using the same design as for children, Geller et al[42] enrolled 52 patients, 35 of whom were randomized. Response was defined as a CDRS score of less than 25 and a Kiddie Schedule for Affective Disorders and Schizophrenia depressive items score of 2 or less, except concentration. One active treatment patient and 4 placebo patients responded despite mean nortriptyline levels for the active treatment group of 350±70 nmol/L. Kutcher et al[34] reported on a randomized, double-blind, placebo-controlled study of 750 nmol/L of desipramine per day in adolescent outpatients, which was an extension of an earlier report. Of 60 adolescents randomized, 18 dropped out before 6 weeks, 13 of whom were receiving desipramine. With response defined as a 50% or greater decrease in the Hamilton Depression Rating Scale, 48% responded to desipramine treatment compared with 35% to placebo, a difference that failed to reach significance.

Simeon et al[13] described 40 adolescent outpatients with MDD in a double-blind, placebo-controlled study of fluoxetine. All of the patients completed a 1-week, single-blind placebo run-in prior to randomization, though the length of time prior to enrolling in the single-blind placebo run-in was not described. Patients' dosages were titrated to 60 mg of fluoxetine by week 2 and studied for 6 weeks. Fifteen patients in each group completed the study. Simeon et al reported that 2 of every 3 patients showed mild to moderate improvement with either fluoxetine treatment or placebo. All clinical measures showed a greater improvement with fluoxetine treatment than placebo except sleep although none were statistically significant, perhaps owing to the relatively few patients tested. Similar to the study by Puig-Antich et al,[39] the placebo response rate was high.

The design of our study benefited from the experience of previous studies. Factors possibly contributing to a positive result included sample characteristics such as a relatively large sample, the exclusion of patients with psychotic depression, bipolar symptoms or a family history of bipolar disorder, and the recruitment of patients from a range of socioeconomic backgrounds, including those who were able to pay for treatment. All patients were self-identified patients. None were recruited by media methods. Methodologic issues included an extensive evaluation period (3 weeks) and a single-blind placebo period (1 week) prior to randomization.

The choice of the drug studied resulted in the ability to attain adequate levels of medication with few side effects. Also, previous studies, apart from Simeon et al,[13] have used medications that are more noradrenergic or metabolized to noradrenergic metabolites.

To our knowledge, there have been no studies in this age group comparing selective serotonin reuptake inhibitors and TCAs directly. However, in an open trial of 15 adolescents and young adults (aged 16-24 years) who had failed to respond to a TCA, Boulos et al[3] found a 64% response rate to fluoxetine treatment during a 6- to 7-week trial. Also, it has been proposed theoretically that differences in the rate of development of neurotransmitter systems could contribute to differences in response to antidepressants. Data from studies of nonprimates[20] and rhesus monkeys[21] suggest that the development of monoaminergic storage capacity and synthesis continues through childhood and is generally more rapid for serotonin than for catecholamines.

STUDY LIMITATIONS

The patients recruited evidenced relatively severe and persistent symptoms of depression and would not be representative of all children and adolescents with MDD. Of 150 patients who did not enroll in the treatment phase of the study following the initial interview, only 55 (37%) had not met MDD criteria initially. The rest improved, met exclusionary criteria, or refused enrollment in the study. Twenty-nine patients responded to the evaluation or single-blind placebo.

Following randomization, attrition during the study resulted in greater attrition from the placebo group because of failure to respond. Most patients had been seen weekly for at least 8 visits and discontinuation from the study came at the patient's or parent's request and it would have been unethical to continue studying these patients. Every effort was made to have the patients continue with the study as long as possible. It is impossible to know whether nonresponders at week 4 or later would have become responders if they had continued longer in the study in either group, which would effect the result of the χ^2 test of the CGI scale at exit. However, data in adults suggest that placebo responders are more likely to occur early in treatment and the placebo response rate in this study parallels adult findings and is not excessively low. Additionally, the analysis of the CDRS-R using slopes from individual regressions should not be effected much by attrition. Several simulation studies have shown that an unweighted average of individual slopes is subject to little bias owing to dropouts.[37,38] Also, an additional slopes analysis was performed using the procedure of Mori et al[37] that was designed specifically to adjust for nonrandom dropouts. Both of these analyses showed significant treatment effect.

Finally, the study may have been too short to demonstrate significant differences between the groups in global functioning (the CGAS) and, as comorbid disorders were frequent, measurements assessing other symptoms, not only depression (the BPRS-C), might change differentially as a function of treatment, although both

groups improved on both measurements. Self-report measurements for children and adolescents, as mentioned previously, did not significantly differentiate the 2 groups, presumably in part because of relatively poor reliability. For example, some patients rated themselves on self-report as having minimal or no symptoms, whereas on clinical interview, they met criteria for MDD.

CONCLUSION

These data indicate that fluoxetine at 20 mg/d is safe and effective in children and adolescents with MDD. Replication is needed to evaluate the certainty of this finding. In addition, whether long-term treatment would result in the amelioration of school, general functioning, or concurrent comorbidities is unknown. How long to continue fluoxetine treatment, assuming it is effective, deserves study. Subsequent analyses to evaluate predictors of response are planned.

Accepted for publication August 20, 1996.

This study was supported by grants MH-39188 (Dr Emslie) and MH-41115 (Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas) from the National Institute of Mental Health, National Institutes of Health, Bethesda, Md.

Presented in part at the annual New Clinical Drug Evaluation Unit Meeting, Orlando, Fla, June 2, 1995, and the Annual Meeting of the American Academy of Child & Adolescent Psychiatry, New Orleans, La, October 19, 1995.

We thank Kenneth Z. Altshuler, MD, Stanton Sharp Distinguished Chair and Chairman, Department of Psychiatry, for his administrative support, the staff of the Child and Adolescent Psychiatry Service at Children's Medical Center for their clinical assistance; Melody Brunmett, for her secretarial support, and Christina Gullion, PhD, for design, management of the randomization procedures, and data management advice.

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DEPRESSION AND ANXIETY 7:32–39 (1998)

FLUOXETINE IN CHILD AND ADOLESCENT DEPRESSION: ACUTE AND MAINTENANCE TREATMENT

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The objective was to present naturalistic 1-year follow-up information of 96 child and adolescent outpatients with major depressive disorder who had been randomized in an 8-week double-blind, placebo-controlled trial of fluoxetine.

Subjects were children and adolescents, ages 8–18 years, who were entered in a randomized clinical trial of fluoxetine. Following the acute treatment trial, treatment was not controlled. At 6 months and 1 year, the subjects and parents were interviewed using the Kiddie Longitudinal Interval Follow-up Evaluation (K-LIFE) for course of depression.

Eighty-seven of the 96 subjects were followed for 1 year. Of these, 74 (85%) recovered from the depressive episode during that time (47 on fluoxetine, 22 on no medication, and 5 on other antidepressants or lithium). Twenty-nine of the subjects (39%) who recovered had a recurrence of depression during the 1-year follow-up, with 55% of these occurring within 6 months.

Results of this study are similar to adult studies, with respect to response and recovery of depressive episodes. Most patients (85%) recover from the episode within 1 year, but approximately 40% have a recurrence within 12 months, which is a higher recurrence rate than in adults. Recovery was associated with younger age, lower severity of depressive symptoms, higher family functioning, and fewer comorbid diagnoses. Recurrence, which occurs both on and off medication, was difficult to predict, as there was little clinical data associated with recurrence in this population. Depression and Anxiety 7:32–39, 1998. © *1998 Wiley-Liss, Inc.*

Key words: *depression; children; adolescents; fluoxetine; recovery; recurrence*

INTRODUCTION

Depressive disorders are a leading cause of morbidity and mortality in the pediatric age group (Fleming and Offord, 1990; Brent, 1987; Pfeffer et al., 1991). The prevalence of depressive disorders in children and adolescents ranges from 0.4% to 8.3% (Burke et al., 1991; Fleming and Offord, 1990; Kashani et al., 1987a,b; Lewinshon et al., 1986, 1993, 1994), and is greater in adolescents than in children. A recent paper reports on the results of structured diagnostic interviews of 1,285 children and adolescents in the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) study. Shaffer et al. (1996) highlight some of the reasons for differences in reported prevalence rates of depression and other disorders. In the MECA study, the prevalence rates for Major Depressive Disorder (MDD) and any depressive disorder ascertained by structured interview ranged from 1.1% to 7.1% and 1.2% to 8.8%, respectively. These differences reflected a variety of information sources (parent, child, or both) and differing levels of impairment required to make the diagnosis. In the MECA study, requiring the child to meet diagnostic criteria based on structured interviews of both

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Contract grant sponsor: NIMH; Contract grant numbers: MH39188, K07-MH01057-01A2; Contract grant sponsor: Celeb C. and Julia W. Dula Education and Charitable Foundations; Contract Grant Sponsor: Mr. and Mrs. Woody Hunt; Contract Grant Sponsor: Cimmaron Foundation; Contract Grant Sponsor: Mr. and Mrs. Morton Myerson; Contract Grant Sponsor: Azoulay Family

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Received for publication 16 December 1997; Accepted 17 December 1997

parent and child and have diagnosis specific impairment, and a Children's Global Assessment Scale (CGAS) score ≤ 70 led to a prevalence of MDD and any depressive disorder of 4.9% and 6.2%, respectively. This prevalence compares with adults (Kessler et al., 1994) where 12-month prevalence of MDD is reported to be 10.3% ± 0.8% (12.9% ± 0.8% females and 7.7% ± 0.8% males).This finding also highlights the gender differences. MDD in children appears to occur at approximately the same rate in girls and boys with the approximately 2:1 ratio becoming evident in adolescents (Emslie et al., 1990).

For adults, the efficacy of antidepressant medications for MDD is well established (Baldessarini, 1989; Depression Guideline Panel, 1993). No one antidepressant is clearly more effective than another, except that MAOIs are more effective than TCAs for depression with atypical features (Thase et al., 1995; Depression Guideline Panel, 1993). A meta-analysis of all available placebo-controlled trials (n = 12) of TCAs in patients between 6-18 years concluded that the difference between active treatment and placebo is too small to be clinically significant (Hazell et al., 1995). This lack of efficacy, as well as the prevalence of side effects of more noradrenergic antidepressants, has led to an increased interest in the selective serotonin reuptake inhibitors (SSRIs) in children and adolescents.

Fluoxetine is the best studied of SSRIs in depressed children and adolescents, though studies with sertraline and paroxetine are ongoing. Reports of SSRIs for depression in this age group include two double-blind placebo-controlled studies (Simeon et al., 1990, Emslie et al., 1998), two studies of "treatment-resistant" depression with fluoxetine (Boulos et al., 1992; Ghazuiddin et al., 1995), two retrospective chart reviews (Jain et al., 1992; Tierney et al., 1995), one with fluoxetine and one with sertraline, and one open study of depressed inpatients with sertraline (McConville et al., 1996). In these uncontrolled studies, response rates varied from 64% to 74%.

In a placebo-controlled double-blind study of fluoxetine (20-60 mg/day), Simeon et al. (1990) found no difference between fluoxetine and placebo in overall response rate. A full description of the methodology has not been published, however, making it difficult to interpret the results. Of the 40 (20/20) subjects randomized, 15/20 in each group completed the study; 10/15 of the subjects in each group, active drug and placebo, showed mild to moderate improvement, i.e., 50% (20/40) of those randomized responded. Fluoxetine was superior to placebo in all clinical measures except sleep by 5 weeks, but the differences were not statistically significant. Perhaps with a larger sample, and a longer period to wash out responders to nonspecific interventions, the study would have been positive.

Recently, Emslie et al. (1997a) reported the results of a double-blind placebo-controlled study of fluoxetine. Subjects were 96 outpatients (age 8 to 18 years) with MDD, who were randomized to fluoxetine 20 mg or placebo following a four-visit, 3-week evaluation. Of the 96 subjects randomized, 27/48 (56%) were rated as much or very much improved on fluoxetine as compared to 16/48 (33%) on placebo ($P = 0.02$). Weekly measures of depression severity (CDRS-R) were statistically different between the groups by week 5.

Response to acute treatment alone does not necessarily mean patients are asymptomatic. Full or partial recovery from the episode is also an important outcome. Recovery from an index episode of major depression is remarkably consistent across samples, independent of treatment, with over 90% of depressed child and adolescent outpatients (Kovacs et al., 1984a; McCauley et al., 1993), child and adolescent inpatients (Strober et al., 1993; Emslie et al., 1997), and 1 to 2 years. In two of these samples (Keller et al., 1991; Kovacs et al., 1984a), recovery occurred with minimal treatment in the majority of subjects.

Once recovered, however, depressed children and adolescents have a high rate of recurrence of their depression. Earlier studies assessed outcome primarily cross-sectionally. When reevaluated 6 to 7 years later, depression remained a problem in 40% to 50% of clinical patients (Asarnow et al., 1988; Eastgate and Gilmore 1984; Goodyer et al., 1991; Poznanski et al., 1976) and around 25% of nonreferred community samples (Fleming et al., 1993; McGee and Williams, 1988). Recurrences (new episodes of depression) are reported in 54-72% of depressed children and adolescents followed for 3-8 years, with similar rates in inpatients (Garber et al., 1988; Emslie et al., 1997) and outpatients (Kovacs et al., 1984b; McCauley et al., 1993; Rao et al., 1995).

In adults, Keller et al. (1992), in a 5-year prospective follow-up of 431 subjects, found 88% had recovered by 5 years. Fifty percent of the subjects recovered within the first 6 months, and after 6 months, the rate of recovery declined markedly. Similarly, Coryell et al. (1994) noted recovery occurring in 60% by 6 months and 80% by 1 year. Keller et al. (1982) reported on recurrences in 75 adults with MDD who had recovered from their index episode. Within one year, 16 (21%) met RDC criterion for a subsequent major depressive episode.

Factors predicting recurrence in adults include three or more previous episodes (Keller et al., 1982; Maj et al., 1992), severity of index episode (Gonzales et al., 1985), psychotic features (Schatzberg and Rothschild, 1992; Copeland, 1983), psychosocial factors, early age of onset of illness, and double depression (defined as a major depressive disorder superimposed on dysthymic disorder; Gonzales et al., 1985; Keller et al., 1983). In children, older age, race, psychotic disorder, and severity of symptoms predicted recurrence (Emslie et al., 1997).

As a result of the episodic nature of depression, studies of continuation and maintenance treatment for depressive disorders in adults have been conducted over the last several years. In adults, prophylactic drug treatment reduces the risk of relapse and recurrence of depressive episodes compared to no treatment (Frank

et al., 1990). Further, continued treatment appears to reduce the severity of subsequent episodes (Maj et al., 1992). Whether this is the same for children and adolescents is not known. The general consensus has been to continue treatment for at least 4 to 6 months (Cook et al., 1986; Montgomery, 1994a,b, 1996; Montgomery et al., 1991) following acute treatment response. Most (Depression Guidelines Panel, 1993; Stokes, 1993) suggest that patients should continue full-dose continuation therapy for 6 to 9 months following complete remission to prevent relapse. Other studies suggest as long as 1 to 5 years of continued treatment (Nemeroff, 1994; Kupfer, 1993; Kupfer et al., 1992). Unfortunately, as most acute treatment studies with depressed children and adolescents have been negative, no long-term continuation treatment studies have been reported on this age group.

This paper reports on the 12-month naturalistic follow-up of 96 depressed children and adolescent who completed the above-mentioned 8-week, double-blind placebo-controlled, acute phase treatment trial of fluoxetine (Emslie et al.,1998). This paper examines acute response, recovery from the index episode, and subsequent recurrences in this population. The paper also examines clinical and demographic factors which could predict recovery and recurrence. Follow-up treatment was not controlled; however, a subsample of patients (n = 35) who underwent at least 4 months of subsequent continuation phase treatment with fluoxetine were evaluated for effects of medication treatment on outcome over a naturalistic 1-year follow-up.

METHODS

Subjects included in this study were all subjects who had been randomized in a double-blind placebo-controlled trial of fluoxetine. The method for the initial evaluation has been previously described (Emslie et al., 1997a). In summary, the subjects were child and adolescent outpatients (ages 7-18 years) who met DSM-III-R criteria for nonpsychotic MDD single or recurrent. They were in good general medical health and of normal intelligence. Subjects with Bipolar I or II Disorder, psychotic depression, alcohol and substance abuse (within the past year), anorexia or bulimia (lifetime), or previous adequate treatment with fluoxetine were excluded. Additionally, any subjects with at least one first -relative with Bipolar I disorder were excluded.

Evaluation for inclusion in the double-blind study took place over three consecutive weekly visits. Prior to the initial interview, the study was explained and written informed consent was obtained from the parent(s) and assent from the patient. At the initial visit, each patient and parent(s) were interviewed separately using the Diagnostic Interview for Children and Adolescents (DICA; Herjanic and Reich, 1982; Reich et al., 1982), a semistructured DSM-III-R based diagnostic interview to establish that the patient met DSM-III-R criteria for MDD and to identify other concurrent and lifetime psychiatric disorders. Additionally, MDD criteria symptoms and depressive symptom severity were assessed using the depressive items of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Chambers et al., 1985) and the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1984), respectively. Overall, social functioning was assessed using the Children's Global Assessment Scale (CGAS; Shaffer et al., 1985) and global family functioning was measured using the Family Global Assessment Scale (FGAS; Mrazek, 1985).

Following the initial interview, the patients were seen for two additional interviews. The patients and parent(s) were interviewed separately by an experienced clinician on each visit, with each interview separated by 1 week. These clinicians independently reviewed the DICA diagnosis and scored the K-SADS depressive items and completed the CDRS-R. The course of illness, including the number, length, and timing of prior and current episodes were established during these interviews.

Final consensus diagnoses were determined following visit three in a weekly diagnostic conference, utilizing information from all three interviews. Following the completion of the evaluation period, appropriate subjects were then entered into a 1-week single-blind, placebo run-in prior to being randomized to fluoxetine 20 mg/day or placebo. Following randomization, the patients were seen weekly for 8 weeks. To be randomized, patients had to continue to meet criteria for MDD, have a CDRS-R score of > 40, and meet above inclusion/exclusion criteria. Response to treatment following randomization was determined by the Clinical Global Impression (CGI) improvement score, as assessed by clinician, with a 1 "very much improved" and 2 "much improved" being used to determine response. Response was further assessed by weekly CDRS-R scores.

FOLLOW-UP

The method for follow-up has been described previously in an inpatient sample (Emslie et al., 1997b). On exiting the acute treatment trial, patients were given the option of continuing blind on study medication or being treated openly. Most nonresponders were treated openly with fluoxetine.

Patients were followed for 12 months following the end of acute treatment. Treatment was not controlled and information collected was primarily a naturalistic follow-up of patients completing the acute trial.

Systematic assessment of clinical course was conducted at 6 and 12 months following end of acute treatment. Patients and parents were interviewed using the Kiddie-Longitudinal Interval Follow-Up Evaluation (K-LIFE), a modification of the LIFE (Keller et al., 1987). During the interview, course of depressive symptoms were assessed during the previous 6 months. Additionally, comorbid diagnosis and treatment were assessed. The severity of MDD during the follow-up period was coded using the criteria in the K-LIFE (6 = severe, 5 = definite criteria, 4 = marked symptoms, 3 = partial re-

mission, 2 = residual symptoms, 1 = usual self). Changes in status, i.e., change in MDD rating, improvement or development of other disorders or treatment, were coded by dates. When this change was approximately identified, then the midpoint of that time was used as the change point, e.g., patient met criteria for MDD again in mid-September was coded September 15th. Episode length, time to recovery, etc., were all coded in days.

For describing the course of depressive symptoms during the follow-up, we used the terms proposed by Frank et al. (1991). The level of symptom rating was the MDD criteria from the K-Life. A subsequent episode of depression was defined as an MDD K-Life rating of 5 or greater for 14 days. Remission was defined as a relatively asymptomatic period (MDD K-LIFE rating of 1 or 2) for at least 14 days. Recovery was defined as an asymptomatic period of at least 60 days. Relapse was an episode of depression after remission but before recovery. Recurrence was defined as an episode of depression after recovery and is generally considered to be a new episode of depression as opposed to a relapse of the initial episode. As proposed by Frank et al. (1991), these terms were assessed independent of treatment.

STATISTICAL ANALYSIS

Differences between groups of subjects, recovered versus nonrecovered, recovered on medication versus no medication, and recurrence versus nonrecurrence, were tested with t-test or χ^2 tests as appropriate. Time to recurrence was estimated using the Kaplan-Meier (Kaplan and Meier, 1958) survival curve. Cox Proportional-Hazard Regression was used to identify predictors of recovery and recurrence.

RESULTS

RESPONSE

Ninety-six subjects were randomized in the acute phase of the study, 48 to fluoxetine and 48 to placebo. Using a CGI of 1 or 2 (much or very much improved) to determine response, then 27/48 (56%) responded to fluoxetine and 16/48 (33%) responded to placebo. The clinician rated depression severity as measured by the CDRS-R at end of acute phase for fluoxetine was 38.4 ± 14.8 and 47.1 ± 17.0 for placebo. However, few subjects had only minimal symptoms (CDRS-R ≤ 28) at end of acute treatment (fluoxetine 31% and placebo 23%).

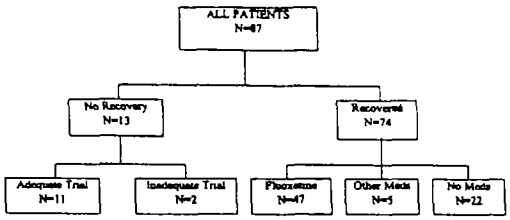

Figure 1. Patient flow.

RECOVERY

Eighty-seven subjects completed the 1-year naturalistic follow-up with K-LIFE interviews at 6 and 12 months following the end of acute treatment. Treatment was not controlled. Subjects who responded to the acute phase were continued on study medication or treated openly with fluoxetine. Generally, nonresponders were treated openly with fluoxetine. Five subjects were treated with other antidepressants or lithium (see Fig. 1).

Recovery was defined as minimal symptoms (K-LIFE MDD ≤ 2) for a period of 60 days. Of the 87 subjects followed, 13 (14.9%) did not meet criterion for recovery during the 12 month follow-up period, of which two had a remission of symptoms, i.e., minimal symptoms for at least 2 weeks, but they did not stay well for at least 60 days. Table 1 compares the demographic and clinical characteristics of the 13

TABLE 1. Recovered versus not recovered

	No recovery n=13		Recovered n=74		
Variables	Mean	(S.D.)	Mean	(S.D.)	*P*-value
Age	13.9	(1.9)	12.1	(2.8)	<.02
% Female N (%)	7	(53.8%)	34	(45.9%)	.79
SES (socioeconomic status)	3.2	(1.3)	2.8	(1.2)	.31
Age of onset (years)	12.0	(2.9)	10.6	(2.6)	<.091
Length of illness (weeks)	23.1	(24.2)	17.4	(19.3)	.35
CDRS-R	63.6	(14.0)	56.9	(9.9)	<.03
CGAS	44.3	(5.3)	45.7	(6.0)	.44
FGAS	54.4	(14.9)	63.5	(13.9)	<.03
First episode of MDD	4	(30.8%)	37	(50.0%)	.57
MDD only	2	(15.4%)	22	(29.8%)	.51
Comorbid dysthymia	7	(53.8%)	23	(31.1%)	.39
Comorbid anxiety	5	(38.5%)	29	(39.2%)	1.0
Comorbid behavior	8	(61.5%)	29	(39.2%)	.43

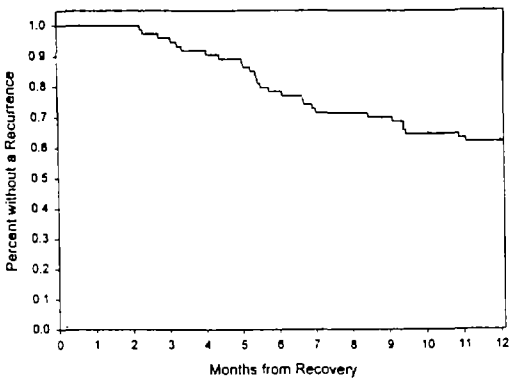

Figure 2. Survival curve from time of recovery to recurrence for all patients.

subjects who did not recover with the 74 who did recover during the follow-up period. Those who did not recover were older (13.9 ± 1.9 versus 12.1 ± 2.8) at baseline evaluation, and had lower global social functioning (CGAS) scores, lower family functioning scores (FGAS), and higher severity of depression scores (CDRS-R). There was a trend for the unrecovered group to include fewer first episode depressed patients (31% versus 50%) and to have fewer subjects with MDD as their only diagnosis (15% versus 30%).

Of the 74 subjects who recovered from the index episode, 22 recovered while taking no medication. Seventeen of these 22 subjects were initially randomized to placebo and never received medication. Five subjects received only brief medication trials, then discontinued. Recovery occurred several months later while on no medication. Five additional subjects received medication other than fluoxetine and eventually recovered.

Forty-seven subjects recovered while taking fluoxetine (see Fig. 1). There were no significant differences in the demographic and clinical characteristics of subjects who recovered on fluoxetine or off medication. The time to recovery from initiating fluoxetine (n = 47) was 69.4 ± 58.1 days. Sixty-two percent had recovered within 2 months and 85% within 4 months.

RECURRENCE

Once recovered, 17/47 (36%) of those who had recovered on fluoxetine and 9/22 (41%) of those who recovered on no medication and 3/5 (69%) who recovered on other medication had a recurrence (i.e., a new episode of MDD within the follow-up period). The average time from recovery to recurrence for these three groups was similar, 176.6 ± 56.7, 191.6 ± 99.8, and 265.0 ± 150.3 days, respectively. Figure 2 displays the survival curve for all 74 subjects from time of recovery to recurrence. The probability of having a recurrence was .22 at six months and .39 at 12 months following recovery; 16/29 (55%) subjects who had a recurrence during the follow-up did so within 6 months.

In examining the population who recovered on fluoxetine, few demographic or clinical features distinguished those with and without recurrence (Table 2). Those who had a recurrence were more likely to have comorbid diagnosis including dysthymic disorder and anxiety disorders and have taken longer to recover from the index episode, but these differences are not statistically significant. Of the17 who had a recurrence, 7 (41.2%) were still on fluoxetine at the time of recurrence.

In summary, for those treated with fluoxetine, 81% recovered within 12 months. The average time to recovery was over 2 months (69.4 days) and those who had a recurrence did so on average 6 months (176.6 days) following recovery. There is a substantial amount of individual variability.

TABLE 2. Subjects who recovered on fluoxetine: No recurrence versus recurrence

	No recurrence n=30		Recurrence n=17		
Variables	Mean	(S.D.)	Mean	(S.D.)	*P*-value
Age	12.1	(2.9)	12.4	(3.0)	.77
% Female N (%)	15	(50%)	6	(35.3%)	.59
SES (socioeconomic status)	2.6	(1.2)	2.6	(1.2)	.82
Age of onset (years)	10.9	(2.7)	10.1	(3.3)	.35
Length of illness (weeks)	14.4	(16.5)	26.6	(25.9)	<.05
Time to recovery (days)	65.5	(53.8)	76.4	(66.1)	.54
CDRS-R	57.3	(10.3)	56.8	(10.7)	.85
CGAS	45.9	(6.4)	46.5	(4.4)	.73
FGAS	65.8	(13.8)	66.4	(12.8)	.88
First episode of MDD	16	(53.3%)	7	(41.2%)	.79
MDD only	11	(36.7%)	3	(17.6%)	.35
Comorbid dysthymia	7	(23.3%)	7	(41.2%)	.37
Comorbid anxiety	12	(40.0%)	10	(58.8%)	.59
Comorbid behavior	10	(33.3%)	7	(41.2%)	.77

EFFECTS OF MEDICATION

As the follow-up period was not controlled, it is difficult to assess the impact of medication on recurrence or nonrecurrence. However, in an attempt to shed light on this question, a subsample of patients was selected who would have been considered to have entered a continuation phase of treatment. This group consisted of subjects who responded to treatment with fluoxetine and who had a minimum of 3 months of treatment. Thirty-five patients received fluoxetine for at least 3 months, and were then followed for 9 more months to determine their clinical outcome. Only ten patients remained on fluoxetine throughout the entire year.

Similar to the total group, 15/35 (43%) patients had a recurrence of MDD, eight of whom had a recurrence after discontinuing medication. Comparing the mean CDRS-R scores at the start of medication of those who had a recurrence versus those who did not recur, no significant difference was found between the two groups. Likewise, CDSR-R scores at the start of continuation (after 90 days) were similar between the 2 groups and were relatively asymptomatic for both groups (recurrers and nonrecurrers) 24.8 ± 5.4 vs. 24.0 ± 5.7.

A Cox proportional hazards regression was done to compare the risk of recurrence while on drug to the risk off drug. This analysis does not explicitly take into consideration the length of time the subject was on or off drug. The risk of recurrence when off drug is 2.3 times as great as when on drug (risk ratio 2.31, 95% CI 0.75–7.18).

The same analysis was repeated with age and beginning CDRS as covariates, but these had no effect on the risk of being off drug and were not significant predictors so they were not used. However, a larger sample may reveal predictors not found in the present smaller sample.

Next, a Cox regression was done where survival was measured from the time the subject was off drug until a recurrence occurred or the follow-up period ended. This analysis excluded subjects who were not discontinued from the drug or who had a recurrence while on drug (since the survival analysis is based on time until FIRST recurrence). This left 21 subjects. Time on drug was used as the predictor variable. The risk of recurrence when off drug decreases by 9% for each month the subject is on drug (risk ratio 0.93, 95% CI 0.66–1.31). Once again, this analysis was repeated with age and beginning CDRS score as covariates, but these had no effect on the risk ratio.

CONCLUSIONS

The results of the acute treatment were similar to adult studies with 56% of those randomized to fluoxetine responding, but only 33% having relative remission of symptoms. Similar to adults, the majority of patients were improved but not in remission at the end of an acute trial. Improvement, however, did occur during the continuation treatment.

Response of MDD in children and adolescents to fluoxetine was superior to placebo. Most (85%) patients recover from the episode within a year, but on average around 40% have a new episode within 12 months, which is a higher recurrence rate than that reported in adults (Keller et al., 1982).

Recovery appears to be associated with younger age, lower severity of depressive symptoms, higher family functioning, and fewer comorbid diagnoses, especially dysthymia.

Recurrence of depression occurs both off and on medication as in adults where 20% recurrence on fluoxetine has been reported (Montgomery et al., 1996). Of particular interest is that exposure to medication does not appear to induce further episodes with an equal number of recurrences occurring in those never exposed to medication. Clinically, there is little that differentiates those who will or will not have a recurrence. Some of the reasons for this apparent lack of predictor variables is the truncated design of the follow-up period. A much longer follow-up period is needed, as some patients in the nonrecurrence group can go on to have a recurrence at a later date. Also, the relatively small sample size hampers the ability to distinguish between group differences. As mentioned above, previously identified predictors of recurrence include psychotic depression (which is excluded from the sample), three of more previous episodes (which is not common in such a young sample), and double-depression (which was lower in the nonrecurrence group but not significant). One area not addressed in this paper is family history of recurrent depression, which was not obtained in this sample.

In conclusion, more research is needed in controlled studies of continuation and maintenance treatment including both psychotherapy and psychopharmacology. Effectiveness of both forms of treatment is beginning to be demonstrated in acute treatment and further work is needed on the relative effectiveness of psychopharmacology and psychotherapy, either separately or combined, in continuation and maintenance treatment.

Acknowledgments. This work was supported in part by grant MH39188 from the National Institute of Mental Health (NIMH), Bethesda, MD (Dr. Emslie), K07-MH01057-01A2 from NIMH (Dr. Kowatch), and contributions from Celeb C. and Julia W. Dula Education and Charitable Foundations, Mr. and Mrs. Woody Hunt, Cimmaron Foundation, Mr. and Mrs. Morton Meyerson, and the Azoulay Family (Dr. Weinberg).

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16.1.8.
Important Publications Referenced in the Report

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS

(THIRD EDITION - REVISED)

DSM-III-R

Published by the
American Psychiatric Association
Washington, DC
1987

Manufactured in the U.S.A.

Available outside North America from the Press Syndicate of the University of Cambridge, the Pitt Building, Trumpington Street, Cambridge, CB2 1RP.
ISBN 0-521-34509-X (casebound); 0-521-36755-6 (soft cover).

The correct citation for this book is:
American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC, American Psychiatric Association, 1987.

Library of Congress Cataloging-in-Publication Data

Diagnostic and statistical manual of mental disorders.

Prepared by the Work Group to Revise DSM-III of the American Psychiatric Association.
Includes index.
1. Mental illness—Classification. 2. Mental illness—Diagnosis. I. American Psychiatric Association. II. American Psychiatric Association. Work Group to Revise DSM-III.
[DNLM: 1. Mental Disorders—classification. 2. Psychiatry—nomenclature. WM 15 D536]
RC455.2.C4D54 1987 616.89'075 87-1458
ISBN 0-89042-018-1
ISBN 0-89042-019-X (soft)

First printing, 75,000, May 1987

Contents

The Family History Method Using Diagnostic Criteria

Reliability and Validity

Nancy C. Andreasen, PhD, MD; Jean Endicott, PhD; Robert L. Spitzer, MD; George Winokur, MD

• **Data concerning familial history of psychiatric disorders are often used to assist in diagnosis, to examine the role of genetic or nongenetic familial factors in etiology, or to develop new methods of classification. Information concerning familial prevalence may be collected by two different methods: the family history method (obtaining information from the patient or a relative concerning all family members), and the family study *method (interviewing directly as many relatives as possible* concerning their own present or past symptomatology). This study compares these two methods. In general, the family study method is preferred since information is likely to be more accurate. The family history method leads to significant underreporting, but this can be minimized through the use of diagnostic criteria. This study reports on an instrument that has been developed for collecting information concerning family history and that provides criteria for 12 diagnoses—the Family History-Research Diagnostic Criteria. Using diagnostic criteria leads to *greater sensitivity, but underreporting remains a major problem* of the family history method.**

(*Arch Gen Psychiatry* 34:1229-1235, 1977)

Research on familial aspects of psychiatric disorders has relied in the past on two techniques, the family history method and the family study method. This investigation compares the results obtained using these two methods and examines the ways in which the reliability and validity of the family history method can be improved when criteria for making family history diagnoses are specified.

Each of these two techniques for familial investigation has inherent advantages and disadvantages. The family history method is the simplest technique used to collect information for psychiatric research concerning genetic or nongenetic familial transmission of disorders. The family history method involves interviewing patients or relatives about any type of psychiatric illness in any of the patient's first-degree relatives (parents, siblings, and offspring). Although the family history method has provided interesting and informative data about familial prevalence of illness, in most instances it has been supplanted by the family study method since the family history method tends to underestimate the amount of actual illness and also to give some false-positives. The family study method, which involves directly interviewing all available first-degree relatives about any illness they themselves have had, yields data that are more precise and accurate, and consequently it is the preferred technique in any up-to-date study of familial prevalence.[1-3]

Nevertheless, the family history method will continue to be used for a variety of reasons. Family history data are usually collected before a family study is begun in order to determine how many relatives are available for direct interviewing and to assist in their location. When some relatives have died, the family history information will be

Accepted for publication March 31, 1977.

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the only data available on their psychiatric status, and these data may be used to fill in the familial pedigree. Family history data can be collected much more cheaply, quickly, and efficiently than family study data, and therefore the family history method may be used to screen large numbers of families in order to select particular families that may be highly informative for genetic or nongenetic familial research by the family study method: families with children who have been adopted in or out, families with half-siblings, families with monozygotic or dizygotic twins, families with particular genetic markers such as color blindness, or very large families for pedigree or extended pedigree studies. In some instances, family history data will be the only information readily available, such as in studies of populations characterized by high geographic mobility (military personnel, professional athletes, performing artists, etc).

Description of Family History-Research Diagnostic Criteria

Since the family history method is still used in many situations for a variety of reasons, this investigation was undertaken to determine its reliability and validity when the information is collected and recorded on a new instrument, the Family History-Research Diagnostic Criteria (FH-RDC).[4] This instrument describes specific operational criteria for determining a diagnosis on the basis of information obtained by the family history method, with the goal of improving the reliability of the family history method by making explicit the operations that are involved in the diagnostic process. Specific criteria are provided for the following diagnoses: chronic schizophrenia, remitting schizo-affective disorder, chronic schizo-affective disorder, depressive disorder, manic disorder, senile organic brain syndrome, unspecified functional psychosis, alcoholism, drug abuse, antisocial personality, other psychiatric disorder, and no known mental disorder. The instrument also permits the recording of information concerning hospitalization, treatment, attempted and completed suicides, social incapacity, and age when first ill.

In general, since the family history method usually provides less specific descriptive data, less stringent criteria are required to make a diagnosis using the FH-RDC than would be required were the individual interviewed directly, using an instrument such as the Schedule for Affective Disorders and Schizophrenia (SADS) or the Present State Examination.[5-7] For example, the FH-RDC specifies criteria for chronic schizophrenia, depressive disorder, and alcoholism as follows:

Chronic schizophrenia

A through C are required.

A. No prominent symptoms of a mood disturbance (as described under A of schizo-affective disorder)
B. At least one of the following:
   1. Delusions
   2. Hallucinations
   3. Incoherence
   4. Grossly bizarre behavior
C. Evidence of an illness that lasted at least one year from which he never recovered, ie, continued to show significant signs of the illness (eg, impaired functioning, blunted affect, social withdrawal)

Depressive disorder

A through E are required.

A. Evidence of a dysphoric mood change to either:
   1. A depressive mood (eg, sad, down in the dumps, don't care, worthless, suicidal ideation, tearful), or
   2. Some other dysphoric mood (eg, anxious, irritable, worried), and at least two of the following *associated* symptoms: loss of interest, appetite or weight change, sleep change, loss of energy, psychomotor agitation or retardation, guilt or self-reproach, impaired concentration
B. At least one of the following is associated with symptoms in A:
   1. Electroconvulsive therapy or known antidepressant medication
   2. Hospitalization
   3. Suicidal behavior
   4. Treated for either A1 or A2
   5. Gross impairment in work, housework, or school, or social withdrawal
   6. Had four *associated* symptoms listed in A
C. No evidence suggestive of a chronic nonaffective deteriorating course (but may have some residual symptoms)
D. No evidence that the period lasted less than two weeks
E. Does not meet the criteria for schizo-affective disorder for the same period of illness

Alcoholism

A and B are required.

A. Problem with drinking not limited to isolated incidents
B. At least one alcohol-related problem in the following areas:
   1. Legal problem (eg, public intoxication, disorderly conduct, traffic violations)
   2. Health problem (eg, cirrhosis, delerium tremens, blackouts)
   3. Marital or family problems
   4. Work problem or impairment as housekeeper
   5. Treatment for alcoholism (eg, disulfirum [Antabuse]) or attended Alcoholics Anonymous
   6. Social problems, fights, loss of friends

Reliability of Family History-Research Diagnostic Criteria

The FH-RDC were developed and piloted in several different ways through the cooperation of the four centers participating in the National Institute of Mental Health Collaborative Studies of the Psychobiology of Depression Pilot Study: Boston (Harvard Medical School), Iowa City (University of Iowa College of Medicine), New York (New York State Psychiatric Institute), and St Louis (Washington University School of Medicine).

Reliability Using Case Vignettes.—The first study undertaken after the writing of the FH-RDC was an examination of the reliability that could be achieved for a variety of different diagnoses. Three of us (N.C.A., J.E., and R.L.S.) complied a set of 75 case vignettes, using family history data obtained from actual patients. These 75 cases were sent to each of the participating centers, where psychiatrists and other professional raters reviewed them, applied the FH-RDC, and made a specific diagnosis. This study was completed by four raters in Boston, three in Iowa City, six in New York, and three in St Louis. The diagnoses made by these raters were then compared with an "expert diagnosis" determined jointly by two of the authors (J.E. and R.L.S.).

Table 1.—Agreement With Consensus Ratings for 75 Case Vignettes for Selected Diagnoses*

	Chronic Schizophrenic	Chronic Schizoaffective, Manic	Chronic Schizoaffective, Depressive	Depressive Disorder	Manic Disorder	Unspecified Functional Psychosis	Alcohol	Drug Abuse	Antisocial Personality	Other Psychiatric Disorder
Boston (4 raters)	.74	.53	.46	.74	.88	67	.92	.96	.85	.52
Iowa City (3 raters)	.70	.46	.52	.83	.89	.52	.91	.73	.93	.58
New York (6 raters)	.76	.69	.52	.86	.81	.63	.98	.92	.87	.63
St Louis (3 raters)	.78	.55	.56	.88	.83	.57	.91	.86	.52	.51

*Agreement with the consensus diagnosis of "experts," based on the κ coefficient of agreement.

Table 1 presents the results of this initial study. It indicates the agreement of raters in each of the participating centers with the consensus rating determined by "experts," using the κ statistic to evaluate the amount of agreement.[4] Agreement is considered to be adequate when κ is greater than .5 and to be good when it is greater than .6. This initial study examined two aspects of reliability: the ability of each of the centers to agree with a prespecified diagnostic standard, and the relative reliability of each of the individual diagnostic categories.

As Table 1 indicates, reliability tends to be very good for most of the diagnostic categories. Agreement is poorest for the diagnosis of schizo-affective disorder. The criteria for this disorder require the temporal overlap of dysphoric or manic mood with delusions, hallucinations, or grossly bizarre behavior not clearly related to the disturbance in mood. These criteria thus require the rater to make a judgment that can often be quite difficult, and this probably accounts for the rather poor agreement. Agreement is also relatively lower for other psychiatric disorder, which is "for subjects with good evidence of significant psychopathology which is not clearly classifiable in any of the previous categories." Some of the criteria for this category are relatively subjective and require difficult judgments of the raters: persistent odd, bizarre, or eccentric behavior; extreme and persistent social isolation; persistent impulsive or unrealistic behavior. Unspecified functional psychosis, a residual category to be used for those patients with symptoms of psychosis or severe impairment (delusions, hallucinations, incoherence, grossly bizarre behavior, hospitalization for several years) who do not meet the criteria for schizophrenia, depression, mania, or organic brain disorder, also has poorer reliability than the other categories. Except for schizo-affective disorder, in each of the instances in which reliability is relatively low, the category is residual; ie, it is used for individuals who have psychiatric symptoms, but for whom insufficient information is available to make a more specific diagnosis.

In general, the agreement of each of the individual centers with the criterion diagnoses is very good. The four participating centers have the potentiality of reflecting considerable differences in orientation, since they represent different geographic areas and different blends of the various models currently used in psychiatry (medical,

Table 2.—Frequency Distribution and Agreement on the Family History–Research Diagnostic Criteria

	Data Provided by Patient Only		
	N	Relative Frequency, %*	Kt
Item			
Suicidal attempt	16	1.6	.91
Successful suicide	4	0.4	.67
Period of social incapacitation for psychiatric reason	38	3.7	.72
Hospitalized for psychiatric reason	64	6.3	.94
Somatic treatment for psychiatric reason	71	7.0	.85
Psychological treatment for psychiatric reason	84	8.2	.82
Diagnostic category			
Chronic schizophrenia	2	0.2	.80
Remitting schizo-affective, manic	0	...	...
Remitting schizo-affective, depressed	2	0.2	.40
Chronic schizo-affective, manic	0	...	...
Chronic schizo-affective, depressed	0	...	...
Depressive disorder	87	8.5	.93
Manic disorder	10	1.0	.95
Senile organic brain syndrome	1	0.1	1.00
Unspecified functional psychosis	5	0.5	.50
Alcoholism	76	7.5	.96
Drug abuse	23	2.3	.93
Antisocial personality	8	0.8	.78
Other psychiatric disorder	106	10.4	.81
No known mental disorder	746	73.1	.94
II unspecified functional psychosis or other psychiatric disorder			
Remitted	45	4.4	.80
Dysphoric mood	50	4.9	.74

*The number and percentage figures are those of the primary interviewer for evaluation of 1,020 relatives.

†These κ statistics are based on FH-RDC evaluations made with the patients only. The 150 patients in the study described 1,020 first-degree relatives. Two raters jointly interviewed the patient and made independent ratings.

Table 3.—K Coefficients of Agreement for the FH-RDC by Individual Centers*

	Boston			Iowa City			New York			St Louis		
	N	Relative Frequency, %	K	N	Relative Frequency, %	K	N	Relative Frequency, %	K	N	Relative Frequency, %	k
Item												
Suicidal attempt	4	1.2	.89	1	0.5	.66	3	1.7	1.00	8	2.5	.94
Successful suicide	1	0.3	.00	1	0.5	1.00	1	0.6	1.00	1	0.3	.00
Period of social incapacitation for psychiatric reason	9	2.8	.52	5	2.4	.80	11	6.2	.65	13	4.1	.84
Hospitalized for psychiatric reason	21	6.5	.88	12	5.9	1.00	9	5.0	1.00	22	7.0	.95
Somatic treatment for psychiatric reason	18	5.6	.79	15	7.3	1.00	13	7.3	.85	25	7.9	.83
Psychological treatment for psychiatric reason	31	9.6	.88	10	4.9	.69	16	8.9	.93	27	8.5	.70
Diagnostic category												
Chronic schizophrenia	2	0.6	1.00	0	0.0	.00	0	0.0	.00	0	0.0	.00
Remitting schizo-affective, manic	0	0.0	.00	0	0.0	.00	0	0.0	.00	0	0.0	.00
Remitting schizo-affective, depressed	0	0.0	.00	0	0.0	.00	1	0.6	.00	1	0.3	1.00
Chronic schizo-affective, manic	0	0.0	.00	0	0.0	.00	0	0.0	.00	0	0.0	.00
Chronic schizo-affective, depressed	0	0.0	.00	0	0.0	.00	0	0.0	.00	0	0.0	.00
Depressed disorder	30	9.3	.94	14	6.8	.92	14	7.8	.88	29	9.2	.94
Manic disorder	3	0.9	.86	3	1.5	1.00	4	2.2	1.00	0	0.0	.00
Senile organic brain syndrome	0	0.0	.00	1	0.5	1.00	0	0.0	.00	0	0.0	.00
Unspecified functional psychosis	3	0.9	.50	0	0.0	.00	2	1.1	.66	0	0.0	.00
Alcoholism	30	9.3	.95	9	4.4	.87	17	9.5	1.00	20	6.3	1.00
Drug abuse	12	3.7	.91	1	0.5	.00	4	2.2	1.00	6	1.9	1.00
Antisocial personality	3	0.9	.80	0	0.0	.00	0	0.0	.00	5	1.6	1.00
Other psychiatric disorder	34	10.5	.78	22	10.7	.86	24	13.4	.74	26	8.2	.87
No known mental disorder	221	68.4	.91	161	78.5	.97	127	71.0	.93	240	75.6	.94
If unspecified functional psychosis or other psychiatric disorder												
Remitted	12	3.7	.88	4	2.0	.72	19	10.6	.80	10	3.2	.75
Dysphoric mood	13	4.0	.72	4	2.0	.72	19	10.6	.80	14	4.4	.68

*The data are based on joint interviews of the index subjects.

Table 4.—Family History Method (FH-RDC) as Validated by Family Study Method

Diagnosis	No. of Probands Ill by Family Study Method (RDC)	No. of Relatives Interviewed by Family History Method (FH-RDC) Agreeing With RDC*	Probability That Family History Method Will Agree With Family Study Method, %
Bipolar	22	28/46	61
Unipolar	26	31/38	82
All affective disorder	48	73/84	87

*Expressed as a ratio of number of relatives agreeing with proband diagnosis to number of relatives interviewed.

Table 5.—Lifetime Prevalence Rate of Illness Among Relatives, Using Various Study Methods

	Family History Method (FH-RDC)				Family Study Method (SADS-L)	
	Using Proband Only as Informant		Using Both Probands and Relatives as Informants			
	N*	%	N*	%	N*	%
Relatives ill with any diagnosis	92/297	31	114/297	38	28/88	32
Relatives ill with affective disorder (includes schizo-affective)	32/297	11	51/297	17	22/88	25

*Expressed as a ratio of number of relatives with specific diagnosis to number of relatives available (at risk).

psychoanalytic, social, and behavioral). The good agreement in spite of these potential differences may reflect either the usefulness of objective criteria or the improved communication between the centers based on scientific collaboration.

Reliability Using Joint Interviews.—After this initial case study was completed, some minor modifications were made in the FH-RDC, and a second study of reliability and validity was conducted on a much larger scale. The sample for this study consisted of a total of 150 index cases collected by the four participating centers. Fifty probands per center were interviewed by Boston and St Louis, while Iowa City and New York each interviewed 25. Subjects were all hospitalized and had met screening criteria for a depressive or manic syndrome.

Diagnoses of these probands were made using the SADS[5] and the Research Diagnostic Criteria (RDC),[6] instruments with high reliability that have been described elsewhere.[7,8] A majority of the patients suffered from some type of affective disorder, while a few were given diagnoses of schizophrenia, hysteria (Briquet's disorder), alcoholism, or drug abuse.

These 150 probands described the psychiatric history of all their relatives (1,020), including very young children and deceased relatives. Two raters were always present when the FH-RDC data were obtained, and they rated the data independently. The data recorded included background information (age at onset, treatment, etc) as well as diagnosis.

Table 2 portrays the frequency with which items or diagnoses specified by the FH-RDC occurred and the interrater reliability achieved by two raters interviewing jointly but making independent ratings. Table 3 breaks these data down by participating centers. Both tables indicate excellent interrater reliability for nearly all items and diagnoses.

Comparison of Family History and Family Study Methods

Data collected only at New York and Iowa City were used to compare results obtained by the family history method and the family study method. In these two centers, all available first-degree relatives over the age of 18 were interviewed concerning their own psychiatric history, using the SADS-L (a lifetime version of the SADS) and RDC, and concerning family history, using the FH-RDC. A total of 88 first-degree relatives were interviewed by the two centers.

Agreement Between Relative's Description of Proband and Direct Evaluation of the Proband.—Since relatives were asked to describe the proband in the course of giving family history for the FH-RDC interview, these data provide a simple check on its validity. Table 4 summarizes the results. Among the 50 probands, 48 had affective disorder, 22 of them bipolar (ie, positive for manic disorder either during the current episode or in the past) and 26 unipolar. The number of relatives interviewed with the FH-RDC varies depending on the diagnostic subtype. Forty-six relatives of bipolar probands and 38 relatives of unipolar probands were interviewed. For each specific diagnostic subtype, the validity of the FH-RDC can be expressed as a ratio of the number of relatives agreeing with the proband's specific RDC diagnosis to the number of relatives interviewed for probands with that particular diagnosis. This ratio reflects the probability that a relative can accurately describe a proband's symptoms so that a specific FH-RDC diagnosis can be made. As Table 4 indicates, the probability is quite good for unipolar disorder, bipolar disorder, or all affective disorder. It is not as good for bipolar disorder as for unipolar disorder, however. The probability for all affective disorder is greater than for both subtypes combined, because probands called unipolar when bipolar or vice versa were scored as "misses" as to subtype but as "hits" for overall diagnosis of affective disorder. Although the validity of the instrument appears to be very good from these data, they are somewhat misleading, because the family member is describing a relative who is actually ill at the time of the interview, a situation that rarely occurs when family history data are obtained.

Table 6.—Specific FH-RDC Results as Validated by SADS-L (N = 88)

	Probands' FH-RDC				Probands' & Relatives' FH-RDC			
	Any Illness		Affective Disorder		Any Illness		Affective Disorder	
	N	%	N	%	N	%	N	%
Sensitivity*	19/28	68	9/22	41	22/28	79	13/22	59
Specificity†	53/60	88	59/66	89	52/60	87	58/66	88
False-positive rate‡	7/60	12	7/66	11	8/60	13	8/66	12
False-negative rate§	9/28	32	13/22	59	6/28	21	9/22	41
Predictive value‖	9/26	73	9/16	58	22/30	73	13/21	62

*Diseased persons detected by the test (based on a proportion of relatives, of those ill by SADS-L, who were called ill by FH-RDC).

†Well persons called well by the test (based on a proportion of relatives, of those well by SADS-L, who were called well by FH-RDC).

‡Proportion of relatives, of those well by SADS-L, who were called ill by FH-RDC.

§Proportion of relatives, of those ill by SADS-L, who were called well by FH-RDC.

‖Positive tests are true-positives (based on a proportion of relatives correctly called ill by FH-RDC to all those called ill by FH-RDC).

Table 7.—Sensitivity and Specificity of FH-RDC in Comparison With Other Methods

	FH-RDC (N = 88)		Rimmer & Chambers[9] (N = 395)		Winokur et al[10] (N = 167)	
	Any Illness	Affective Disorder	Any Illness	Affective Disorder	Any Illness	Affective Disorder
Sensitivity, %	79	59	38	31	...	43
Specificity, %	87	88	99	99	...	97

Agreement Between Description by Relatives and Direct Interview of a Family Member.—Table 5 summarizes the diagnostic precision of the FH-RDC when familial data are collected from the proband only, from the proband and an additional first-degree relative, and from the SADS-L administered to the relatives themselves. In this analysis the SADS-L represents an external validator of the FH-RDC, since the SADS-L provides data about illness in the relative through direct and detailed interview. A total of 88 first-degree relatives were interviewed using the SADS-L. These 88 were out of a possible total of 297 relatives over age 18 for whom family history diagnoses were available. When disagreement occurred between several relatives, the most positive or severe diagnosis was used in data analysis. Table 5 indicates that agreement in the percentage of ill relatives tends to increase as the number of informants increases, so that obtaining FH-RDC data from both a proband and additional relatives gives numbers more like those obtained with the SADS-L. (It should be noted, however, that the percentages of relatives diagnosed as ill with the SADS-L probably are an underestimation, since all relatives were not interviewed, and well relatives may be more likely to be readily available for interviewing than ill relatives). The FH-RDC is also more successful in detecting any illness than it is in detecting specific illnesses: even when information is gathered from both a proband and relatives, the data produced by the FH-RDC give a substantial underestimate of the amount of affective disorder among relatives.

Sensitivity and Specificity of the Family History Method When Specified Criteria Are Used.—In order to examine these data more objectively and to compare the value of the FH-RDC to the methods of collecting family history data in other studies, it is useful to draw on the concepts of sensitivity and specificity. The sensitivity of a diagnostic test is the percentage of true-positives that the test will actually detect. On the other hand, the specificity of a diagnostic test is the percentage of true-negatives that the test will actually detect.[11] Sensitivity is indicated by the number of relatives called ill by the FH-RDC who were ill when diagnosed by the SADS-L; specificity is indicated by the number of relatives called well by the FH-RDC who were well when diagnosed by the SADS-L; the false-positive rate is indicated by the number of relatives called ill by the FH-RDC who were well when diagnosed by the SADS-L; and the false-negative rate is indicated by the number called well by the FH-RDC who were ill when diagnosed by the SADS-L. The predictive value is the percentage of positive tests that are true-positives, and is based on a ratio of true-positives on the FH-RDC to all positives on the FH-RDC.

Table 6 portrays the raw data collected in the pilot study and all relevant rates in order to evaluate the sensitivity and specificity of the FH-RDC. In this table, only FH-RDC data describing the 88 relatives actually interviewed with the SADS-L are evaluated, and the SADS-L is assumed to be the best possible validator available. Diagnoses made by the FH-RDC in describing the 88 relatives interviewed with the SADS-L are broken down into sensitivity, specificity, false-positive rate, false-negative rate, and predictive value. These data are presented both in terms of increasing particularity as to diagnosis and in terms of increasing information by increasing the number of informants. As the table indicates, increasing the number of informants decreases the false-negative rate and increases the sensitivity. Likewise, increasing the particularity as to diagnosis increases the false-negative rate and decreases the sensitivity.

Table 7 uses the measurement of sensitivity and specificity to compare the FH-RDC to two other studies that collected family history data without specific diagnostic criteria, that of Winokur et al[1] and that of Rimmer and Chambers.[2] Since both these studies present data based on interviewing both the proband and a relative about family history, only FH-RDC data based on proband and relative data (last two columns of Table 6) are compared. Table 7 indicates that the FH-RDC may represent a significant advance over previous methods of collecting family history data. For any illness, the FH-RDC has a sensitivity of 79%, as compared to only 38% in Rimmer and Chambers' study. More importantly, the FH-RDC is also significantly more sensitive in determining a specific diagnosis of affective disorder than methods used in either of the other studies. Based on the test of the significance of difference between two proportions, the 59% sensitivity of the FH-RDC to affective disorder is markedly better than Rimmer and Chambers' results ($P < .003$) and also considerably better than the 43% of Winokur et al ($P < .025$). This improved sensitivity is achieved with some loss of specificity, but in family history studies a decreased specificity is not a major consideration, since the family history data usually represent an underestimate and poor sensitivity is the most important source of error.

COMMENT

The family history method will probably continue to be used in studies of the relationship of familial factors to psychiatric illness, either as a preliminary to family studies or as a supplement. In a few cases, family history alone will be used. Mendlewicz et al[3] have recently evaluated the accuracy of the family history method in affective disorders, paying particular attention to identifying the most accurate informant. Their work indicates that understimation of illness is the major problem of the family history method and that increasing the number of informants increases the accuracy of the family history method. In their study, a person describing the psychiatric condition of his parents or spouse was likely to be the most accurate informant.

The FH-RDC were developed as an effort to further refine the family history method. Based on their previous work in family history studies, family studies, and instrument development,[4,5,9,12,13] the investigators wrote a set of operational criteria for as broad a range of diagnoses as was felt to be practical. This study reports the results of pilot testing in a variety of ways, and it suggests that the FH-RDC probably represent a substantial improvement over previous methods of doing family history studies, which have either used no criteria or described criteria only vaguely. It is the first careful assessment of the reliability and validity of the family history method when criteria are used. Our investigation suggests a number of ways to

improve studies of familial factors in psychiatric illness:

1. In general, such studies should probably use predefined criteria for diagnosing illness in relatives when only family history data are available. A major advantage of predefined criteria is that they are likely to improve reliability significantly. The FH-RDC have excellent interrater reliability, and their reliability measured against a diagnostic standard (a much more difficult test of reliability) is also quite good.

2. Criteria used in family history studies should have maximal sensitivity, since the major problem in family history studies is underestimation of illness. The FH-RDC have significantly better sensitivity than the methods used for collecting family history data in other studies. This significant increase in sensitivity is achieved with some loss of specificity. For the purposes of familial studies, however, sensitivity is much more important than specificity, and consequently the FH-RDC are significantly more valid than other methods of collecting family history data.

3. As in the study of Mendlewicz et al,[1] our investigation suggests that the accuracy of the family history method can be increased by increasing the number of informants. Whenever possible, information should be collected from at least one informant in addition to the proband.

4. Even though the FH-RDC probably represent a significant advance over previous methods for collecting family history data, FH-RDC data should only be used tentatively and with some reservations. This investigation has only dealt with the instrument's sensitivity and specificity with respect to two categories: affective disorder and any illness. The samples of relatives with other diagnoses were too small to make analysis of specificity and sensitivity worthwhile. While the reliability of the FH-RDC has been tested for the full range of diagnoses for which criteria are specified, the validity has only been tested for two categories, affective disorder and any psychiatric illness.

5. This investigation supports others that have compared the family history and family study method[1-4] by further substantiating the finding that the family history method seriously underestimates the amount of illness among first-degree relatives. Although the FH-RDC may decrease the underestimation, underestimation remains a significant problem. Consequently, family history studies should be supplemented by family studies whenever possible.

This investigation was supported in part by grant MH25415 from the Public Health Service.

This study was completed through the cooperation of other investigators participating in the National Institute of Mental Health-Clinical Research Branch Collaborative Program on the Psychobiology of Depression, Clinical Studies, Pilot Phase: Martin M. Katz, PhD, and Gerald Klerman, MD, *co-chairman*; Eli Robins, MD, Amos Welner, MD, and Jack Croghan, MD, at Washington University, St Louis; Robert Hirschfeld, MD, *Coordinator*, Clinical Research Branch, and James Barrett, MD, at Harvard University, Boston.

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Vol. 7

Modern Problems of Pharmacopsychiatry

Psychological Measurements in Psychopharmacology

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Psychological Measurements in Psychopharmacology

Volume Editor:
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Subject Index

INTERNAL CONSISTENCIES OF THE ORIGINAL AND REVISED BECK DEPRESSION INVENTORY

AARON T. BECK[1] AND ROBERT A. STEER

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Studied internal consistencies of the 1961 and 1978 versions of the Beck Depression Inventory in two different samples of psychiatric patients. The alpha coefficient for the 598 inpatients and outpatients who were administered the 1961 version was .88, and the alpha coefficient for the 248 outpatients who were self-administered the 1978 version was .86. The patterns of corrected item-total correlations were also similar, and it was concluded that the internal consistencies of both versions were comparable.

Although the Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) has been used to assess the intensity of depression in over 500 published clinical studies (Steer, Beck, & Garrison, in press) and has been evaluated psychometrically within a wide variety of psychiatric and normal populations (Beck & Beamesderfer, 1974, pp. 151-169; Mayer, 1977, pp. 358-425), it is sometimes forgotten that there are two versions of the BDI. The 1961 instrument was revised in 1978 (Beck, Rush, Shaw, & Emery, 1979) to present clearer statements more amenable to self-administration and to permit simpler scoring. The revised form eliminated the alternate ways of asking the same questions that were employed in the 1961 edition and avoided the use of double negative statements. Although the 1978 version has received popular acceptance since its introduction 5 years ago, no comparative study about the internal consistencies of the two versions has appeared in the psychological literature.

The purpose of the present study was to evaluate the internal consistencies of the 1961 and 1978 versions of the BDI to ascertain whether both versions' internal consistencies were comparable.

METHOD

Subjects

The patients administered the 1961 version were drawn from the 606 persons whom Beck (1972) had sampled from the 975 consecutive admissions to the inpatient and outpatient services of two Philadelphia hospitals during the 1960s. The present study of 598 patients was restricted only to those patients out of the 606 who had answered all of the BDI's 21 questions. The restricted sample was 60.9% female and 64.7% Caucasian. The modal age category (32.4%) was 25-34 years, and 47.0% had completed high school. The sample was composed of 66.0% outpatients and 34.0% inpatients. Diagnostically, there were a variety of subgroups, the two largest were schizophrenic reactions (28.2%) and psychoneurotic depressive reactions (25.3%).

The sample self-administered the 1978 version of the BDI represented 248 consecutive admissions to the Center for Cognitive Therapy in Philadelphia between June 1978 and July 1979. The outpatients were 50.3% female and 93.6% Caucasian. The mean educational attainment was 15.14 (SD = 2.78) years. The modal diagnosis was depressive neurosis (55.2%), and 76.7% reported past treatment for an affective disorder.

Instrument

The 1961 (Beck et al., 1961) and 1978 (Beck et al., 1979) versions of the BDI both contain 21-items, which are rated from 0 to 3 in terms of intensity. The ratings are

[1]Reprint requests should be sent to the senior author at the Center for Cognitive Therapy, 133 South 36th Street, Room 602, Philadelphia, Pennsylvania 19104.

summed to calculate total depression scores, which can range from 0 to 63. The symptoms and attitudes are (1) Mood; (2) Pessimism; (3) Sense of Failure; (4) Lack of Satisfaction; (5) Guilt Feelings; (6) Sense of Punishment; (7) Self-dislike; (8) Self-accusations; (9) Suicidal Wishes; (10) Crying; (11) Irritability; (12) Social Withdrawal; (13) Indecisiveness; (14) Distortion of Body Image; (15) Work Inhibition; (16) Sleep Disturbance; (17) Fatigability; (18) Loss of Appetite; (19) Weight Loss; (20) Somatic Preoccupation; and (21) Loss of Libido. As mentioned previously, the 1961 version was designed for administration by trained personnel and asked the respondents to describe "the way you feel today, that is, right now!" In contrast, the 1978 version was developed for self-administration and asked the respondents to describe "how you have been feeling for the past week including today." Importantly, the 1961 version was administered to both the inpatients and oupatients as soon as practical after admission by a trained technician, whereas the 1978 version was self-administered at the time of admission to the outpatient clinic.

TABLE 1

Means, Standard Deviations, Corrected Item-total Correlations and Overall Alpha Coefficients for 1961 and 1978 Versions of the Beck Depression Inventory

	BDI version					
	1961			1978		
BDI item	*M*	*SD*	*r* tot.	*M*	*SD*	*r* tot.
1. Sadness	.97	1.03	.62	1.42	1.00	.62
2. Pessimism	.97	1.02	.62	1.31	.93	.55
3. Sense of Failure	1.25	1.09	.57	1.09	.96	.61
4. Dissatisfaction	1.00	.90	.63	1.63	.88	.52
5. Guilt	.89	1.05	.55	.95	.84	.53
6. Expectations of Punishment	.85	1.04	.43	.66	1.07	.50
7. Self-dislike	.94	.83	.52	1.51	.80	.37
8. Self-accusations	1.02	.80	.44	1.36	.79	.58
9. Suicidal Ideas	.58	.83	.54	.70	.68	.53
10. Crying	.91	1.11	.43	1.21	1.08	.40
11. Irritability	1.08	.88	.23	1.13	.75	.36
12. Social Withdrawal	.70	.91	.54	1.14	.87	.60
13. Indecisiveness	.79	.89	.57	1.42	1.02	.52
14. Body Image Change	.66	.96	.45	.92	1.01	.39
15. Work Difficulty	1.07	.89	.47	1.52	.85	.64
16. Insomnia	1.29	1.15	.41	1.14	.98	.28
17. Fatigability	1.01	.93	.48	1.27	.90	.50
18. Loss of Appetite	.75	1.01	.48	.68	.92	.38
19. Weight Loss	.73	1.07	.23	.33	.70	.14
20. Somatic Preoccupation	1.07	1.01	.31	.72	.82	.18
21. Loss of Libido	.84	1.04	.43	1.05	1.07	.40
Alpha coefficient		.88			.86	

Note.—*N* for 1961 version = 598, and *N* for 1978 = 248.

Data Analysis

The Statistical Package for the Social Science's subprogram, RELIABILITY, (Hull & Nie, 1981) was used to calculate the alpha coefficients and corrected item-total correlations for the 1961 and 1978 versions.

Results

Table 1 presents the means, standard deviations, corrected item-total correlations, and overall alpha coefficients for the 1961 and 1978 versions of the BDI. As Table 1 indicates, the majority of the corrected item-total correlations for both versions were high ($> .50$), and all were significant beyond the .05 level. Only Weight Loss and Irritability in the 1961 version and Insomnia, Weight Loss, and Somatic Preoccupation in the 1978 version had low corrected item-total correlations $< .30$. The alpha coefficients for the 1961 and 1978 versions were .88 and .86, respectively, which suggested that both versions were internally consistent in measuring an underlying dimension of depression.

The mean 1961 and 1978 versions' total scores were 19.28 ($SD = 10.87$) and 23.16 ($SD = 9.55$), respectively. According to Beck (1972), the former sample was moderately depressed, whereas the latter sample was severely depressed. The mean difference (3.88) was significant ($t(844) = 5.16$, $p < .001$).

Discussion

The 1961 and 1978 versions of the BDI were found to possess high levels of internal consistency, despite differences in the background characteristics of the samples, modes of administration, decades in which the samples were tested, and time frames that the patients were asked to describe. Obviously, a more definite design to test whether the two versions demonstrated significantly different psychometric properties would call for a cross-over design in which the same respondents were asked to complete both versions. A matched sample design in which respondents drawn from the same time cohorts also would be preferable to the current design. However, the present study does suggest that the 1978 revision of the BDI has a level of internal consistency with an outpatient psychoneurotic sample comparable to that presented by the mixed diagnostic sample of inpatients and outpatients upon which the 1961 BDI originally was validated.

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An Open Naturalistic Trial of Fluoxetine in Adolescents and Young Adults with Treatment-Resistant Major Depression

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ABSTRACT

Fifteen adolescents and young adults (ages 16–24) with a DSM-III-R diagnosis of major depression, who failed to respond to prior treatment with tricyclic antidepressants, were treated in an open trial using fluoxetine. Of the 11 patients who completed a 6–7 week trial, 64% showed a therapeutic response (≥50% change) on the Hamilton Depression Rating Scale (HDRS), and 73% showed a positive response when rated by the Clinical Global Impression Scale (CGI).

Side effects generally were mild, and the most common were tremor, dry mouth, nausea, sweating, and decreased appetite. Sweating, drowsiness, dry mouth, tremor, and alopecia appeared more commonly than in adult studies. One patient became manic, and none showed an increase in suicidal ideation. A starting dose of 20 mg daily often was tolerated poorly, and patients generally did better with 5–10 mg daily for the first week. Some patients appeared to exhibit antidepressant responses on 5–10 mg daily.

These preliminary data suggest that fluoxetine, in doses ranging from 5 to 40 mg daily, when used in combination with psychosocial treatments, may be an effective antidepressant in adolescents or young adults who have not previously responded to adequate tricyclic therapy. Double-blind placebo-controlled studies are needed to evaluate the potential efficacy of fluoxetine in treating major depression in adolescents and young adults.

INTRODUCTION

MAJOR DEPRESSION IS A clearly recognizable condition in adolescents with an overall prevalence rate of between 4 to 8% (Cantwell and Carlson 1983, Friedman et al. 1983, Kashani et al. 1987). Long-term follow-up studies of clinical populations have found high recurrence rates ranging from 60 to 80% (Garber et al. 1988, Harrington et al. 1990). Adolescent depression is associated with a variety of difficulties including poor school performance, eating disorders, disturbed interpersonal relationships; problematic family

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functioning, and suicide (Cantwell and Carlson 1983, Carlson and Strober 1979, Kashani and Sherman 1989, Kutcher and Marton 1989). The high prevalence rates and significant short- and long-term morbidity of this disorder demand appropriate and effective treatment for this age group.

Tricyclic antidepressant medications are clearly established as an effective treatment for major depression in adults (Baldessarini 1989). Studies of noradrenergic-type antidepressants in depressed adolescents have not shown similar treatment efficacy to adult studies in either open or double-blind placebo trials (Boulos et al. 1991, Geller 1989, Kramer and Feiguine 1981, Ryan et al. 1986, Strober 1989). For example, Kramer and Feiguine reported a 67% maximum improvement following a 6-week placebo-controlled study of amitriptyline in a small sample of adolescent inpatients. Ryan et al. found a response rate of 44% in an open 6-week trial of imipramine in 34 outpatients between the ages of 10–17. Geller et al. described a response rate of less than 10% in an 8-week placebo-controlled double-blind trial of nortriptyline in 31 adolescents with a mean age of 14.2 years. In an open trial of imipramine on 34 inpatients aged 13–18, Strober et al. reported a less than 40% improvement rate. Augmentation with lithium was said to be minimally effective. Boulos et al. found a 50% response rate using desipramine in a placebo-controlled double-blind 6-week study in 30 adolescents aged 15–20 years.

Treatment-resistant major depression is found in upward of 20% of adults diagnosed with depressive disorders (Kennedy and Joffe 1989). There is a paucity of studies reported regarding adolescent treatment-resistant major depression. Ryan et al. (1988) reported on 23 adolescents with major depression who were partially responsive to initial treatment with tricyclic antidepressants. Of the total, 74% were found to have a fair to good response following treatment with monoamine oxidase inhibitors (MAOI).

Fluoxetine is a bicyclic antidepressant that is chemically unrelated and pharmacologically distinct from tricyclic antidepressant medications. It is a highly selective serotonin re-uptake inhibitor, with little or no effect on other neurotransmitters (Bardeleben et al. 1989). Studies in adults have shown that it has a unique side effect profile in comparison to more traditional antidepressants. Fewer total side effects have been reported in comparative studies (Cooper 1988). A recommended starting and maintenance dose of 20 mg in adults suggests increased ease in clinical management and a greater possibility of patient compliance (Cooper 1988). These features suggest that its consumer acceptance in adolescents may be more favorable than that of traditional tricyclic antidepressants. Although not etiologically specific, recent neuroendocrine studies of depressed probands in the adolescent age group suggest that abnormal CNS serotonin function may be present (Kutcher et al. 1991). This suggests that serotonin-specific antidepressants may be of particular therapeutic benefit in this population (Kutcher et al. 1991, Ryan et al. 1988b). Given these characteristics, fluoxetine may be a useful medication in the treatment of adolescent major depression.

Fluoxetine has not been adequately evaluated in this age group. To our knowledge, no open studies have been reported. The one published double-blind placebo-controlled study in depressed adolescents has shown ambiguous results, and methodological difficulties make interpretation uncertain (Simeon et al. in press). No studies that we are aware of regarding fluoxetine's antidepressant effect have been carried out in treatment-resistant adolescent depressives. The purpose of this naturalistic study was to examine the potential role of fluoxetine in treatment-resistant depression in adolescents and young adults.

METHOD

Subjects

Fifteen subjects between the ages of 16 and 24 (7 males and 8 females, 12 outpatients and 3 inpatients) enrolled in the adolescent outpatient psychopharmacology clinics at a university teaching hospital were deemed to have treatment-resistant depression, as defined by at least two consecutive months of unsuccessful antidepressant treatment at effective dosages. Twelve met *DSM-III-R* criteria for major depression and three met *DSM-III-R* criteria for bipolar disorder-depressed type, as determined by clinical interview and the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS). Comorbid diagnoses included anxiety disorders (N = 5), conduct disorder (N = 2), and attention-deficit disorder (N = 3) (see Table 1).

TABLE 1. CHARACTERISTICS OF THE 15 PATIENTS WITH DEPRESSION

Patient	Age	Gender	Current Axis I diagnoses	No. of Previous Depressive Episodes	Current Episode Length (months)	Family History in First-Degree Relatives
1	16	M	UP	2	24	None
2	19	M	UP	2	6	UP
3	19	M	UP	None	24	SA
4	20	F	UP, PA	None	24	UP, EtOH
5	17	F	UP, GAD, CD	None	30	EtOH
6	21	F	UP, GAD, PA	None	60	UP, EtOH
7	20	M	BP	4	4	BP
8	18	F	UP, ADD	2	36	UP, EtOH
9	21	F	BP	1	4	UP, EtOH
10	18	M	BP	3	4	BP, EtOH
11	17	M	UP	None	7	None
12	14	F	UP, GAD	None	22	None
13	20	F	UP, CD, ADD	None	24	Adopted
14	17	F	UP, ADD, PA	None	5	UP
15	24	M	UP	2	24	UP, EtOH

Abbreviations: UP = unipolar depression, BP = bipolar depression, ADD = attention-deficit disorder, PA = panic attacks, CD = conduct disorder, EtOH = alcohol abuse, GAD = generalized anxiety disorder.

Exclusion criteria included significant medical or neurological disorders; substance abuse within the last year; current psychosis; a suicide attempt within the previous month; and an Axis I diagnosed eating disorder.

The mean duration of the current episode was 19 months (range 4–60 months). All subjects previously had been unsuccessfully treated for at least 2 consecutive months with a tricyclic antidepressant at effective serum levels. Of the 15 subjects, 13 had also undergone various psychotherapies. In addition, 8 patients also had failed a previous tricyclic augmentation trial with either lithium, anticonvulsants, methylphenidate, or triiodothyronine (see Table 2).

At the time of entering the open fluoxetine trial, all subjects were assessed using the K-SADS to ensure that they continued to meet *DSM III-R* diagnostic criteria for depression, and were rated on the Clinical Global Impression Scale (CGI). They also scored ≥17 on the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960). Prior to starting fluoxetine, all subjects underwent a complete medical workup including laboratory investigations, an EKG, and our fluoxetine side effects scale (FSES) (see Appendix 1). The FSES is a clinician-rated assessment used to follow the emergence of medication side effects. It was administered prior to starting the medication, and weekly throughout the treatment period.

Treatment

Fluoxetine initially was administered at a dose of 20 mg daily in the morning or on alternate days. However, observations of side effects in the initial stages of the trial led to a lowering of the starting dose to 5 or 10 mg daily. Dosage was adjusted further as tolerated, to a maximum of 40 mg daily. It was administered either in the morning or at night, depending on whether the patient experienced "sedating" or "activating" phenomena on the medication. Given that the lowest marketed dose of fluoxetine is 20 mg, the manufacturer (Eli Lilly) provided dissolving instructions to enable patients to make up lower doses. Doses of 5 or 10 mg were prepared by dissolving the contents of a 20 mg capsule in 8 oz. of a specified liquid (apple juice, Gatorade, Ocean Spray CranGrape); the patient was then advised to drink 2 oz. to obtain 5 mg of the medication, or 4 oz. to obtain 10 mg (*Note:* fluoxetine now is available in the U.S. in liquid form). Dosage adjustments were made according to clinical assessment of side effects and efficacy, determined by clinical interview and completion

TABLE 2. CURRENT AND PREVIOUS TREATMENT OF THE 15 DEPRESSED PATIENTS

Patient	Dose of Fluoxetine (mg/day)	Previous Treatment		Concurrent Treatment	
		Medication	Nonmedication	Medication	Nonmedication
1	20	Imipramine, protriptyline ± methylphenidate	IT + FT	Lithium + clonazepam	IT
2	20	Desipramine ± methylphenidate	None	None	IT
3	20	Desipramine ± lithium ± methylphenidate	None	None	IT
4	20	Trimipramine, trazodone, maprotiline Tranylcypromine, phenelzine ± lithium	IT + FT	Lithium + clonazepam + triiodothyronine	IT
5	20	Desipramine ± clonazepam	IT	Clonazepam	IT
6	20[a]	Desipramine	IT		IT
7	10	Lithium ± perphenazine	IT	Valproic acid	IT
8	10[b]	Desipramine	IT	Noncompliance	IT
9	40[c]	Desipramine ± lithium ± valproic acid	IT	Lithium + valproic acid	IT
10	20[b]	Lithium ± perphenazine	IT	Lithium	IT
11	20	Desipramine	IT	None	IT + FT
12	5	Imipramine	IT + FT	None	IT + FT
13	20	Desipramine	IT + FT	Noncompliance	IT
14	5[b]	Imipramine ± lorazepam	IT	Discontinued, skin rash	IT
15	20	Desipramine ± triiodothyronine	IT	None	IT

[a]After stabilization with fluoxetine, patient developed a manic episode.
[b]Dosage given on alternate days.
[c]20 mg given twice a day.
Abbreviations: IT = individual therapy; FT = family therapy.

of the CGI, HDRS, and SES. All subjects were also involved in once weekly individual psychotherapy, and 2 of the 15 subjects were also involved in family therapy (see Table 2).

RESULTS

Eleven of the 15 patients (73%) completed at least 6 consecutive weeks of treatment. Of the dropouts, two were noncompliant, one suffered a rash and withdrew from the protocol, and one developed a manic episode. Treatment response was defined using the HDRS and the CGI. Using the HDRS, the percent change from initial to final HDRS scores was computed. A $\geq$ 50% change from baseline was considered a positive response. A <50% change was considered a negative response. Of the 11 patients who completed at least 6 weeks of fluoxetine treatment, a positive response (Δ in HDRS $\geq$ 50%) was found in 64% (see Table 3).

The CGI was completed at the end of treatment week 6 or 7. A score of $\leq$2 (4 = no change, 3 = minimally improved, 2 = much improved, 1 = very much improved) was achieved by 73% of the completers. No significant correlation was found between drug response (as measured by either the HDRS or CGI) and such factors as comorbidity, family history, age, or gender. No significant change was detected in pre- and post-laboratory investigations, EKG parameters, or blood pressure.

A downward trend (improvement) was noted in the final versus initial FSES scores, with a tendency for some subjects to experience a transient increase in total symptom scores part of the way through treatment. Final FSES scores were collected at week 6 or 7 for the completers, at week 4 for the two noncompleters, and at week 2 for the patient who developed a skin rash. Side effects scored at $\geq$3 were considered severe, while those scored at <3 were considered nonsevere. The most commonly occurring severe side effects were

TABLE 3. RESPONSE TO FLUOXETINE IN DEPRESSED PATIENTS ACCORDING TO HAMILTON DEPRESSION RATING SCALE (HDRS) SCORES AND CLINICAL GLOBAL IMPRESSION (CGI)

Patient	*Initial HDRS*	*HDRS at Week 6 or 7*	*CGI at Week 6 or 7*
1	20	13	+3
2	22	2	+1
3	19	3	+1
4	26	20	+4
5	17	10	+3
6	16	Developed a manic episode	
7	20	5	+1
8	25	Noncompliant	
9	19	7	+2
10	17	0	+1
11	19	11	+2
12	19	2	+1
13	29	Noncompliant	
14	29	Skin rash	
15	25	7	+2
	n = 15 avg. = 21.4	n = 11 avg. = 7.2	
	n = 11 avg. = 20.2		

restlessness (27%) and sweating (20%). The most frequently occurring nonsevere side effects were dry mouth and tremor (each seen in 33% of the patients), nausea, and decreased appetite (20%). On combining both severe and nonsevere side effects, the most common complaints, in decreasing order of frequency, were tremor and dry mouth (40%); decreased appetite, sweating, and nausea (33%); and restlessness and drowsiness (27%) (see Table 4). One subject developed a skin rash, and another subject developed a manic episode following an initial period of moderate mood improvement on fluoxetine.

DISCUSSION

Although notable limitations in extrapolation from this study exist as it was an open naturalistic pilot of a small number of patients in one setting, our results suggest that fluoxetine in doses ranging from 5 to 40 mg daily, when used in combination with psychosocial treatments, may be an effective antidepressant in adolescents or young adults who have not previously responded to adequate tricyclic therapy.

Comparisons with other adolescent depression studies are somewhat difficult given this study's slightly older population who were also, by definition, treatment resistant. Our finding of a positive response rate of 73% (CGI) in this study, however, is comparable to the rate reported by Ryan et al. using MAOIs in a somewhat younger adolescent group. Although the relative merits of fluoxetine and MAOI therapies have not been compared at this time, fluoxetine may theoretically be the safer agent to use in this population given its favorable cardiovascular side effects profile as well as its lack of dietary restrictions.

In this trial, a starting dose of 20 mg daily was often found to be too high in regard to side effects. Subjects generally showed greater tolerance to an initial dose of 20 mg on alternate days, or 5–10 mg daily for the first week, followed by 20 mg daily thereafter. Furthermore, some patients exhibited an antidepressant response on doses as low as 5 or 10 mg daily, suggesting that antidepressant efficacy may occur over a wider dose range than that reported in adult populations.

The more commonly occurring side effects were similar to those found in other adolescent fluoxetine treatment studies. Gastrointestinal complaints and restlessness were reported by Riddle et al. (1990) in a study of fluoxetine treatment of Tourette's syndrome and obsessive compulsive disorder in children and adolescents. Mild and transient side effects, including headaches, vomiting, insomnia, and tremor, were

TABLE 4. FLUOXETINE SIDE EFFECTS AMONG 15 ADOLESCENTS AND YOUNG ADULTS

	Nonsevere (score 1–2)	*Severe (score 3–4)*	*Total side effects*	*% of total*
Trouble sleeping	1	1	2	13.3
Heart racing		1	1	6.7
Heart pounding				0.0
Feeling dizzy				0.0
Feeling the room spin			2	13.3
Feeling tense inside	1	2	3	20.0
Restlessness		4	4	26.7
Numbness of hands or feet	1		1	6.7
Tingling in hands or feet	1			6.7
Trouble keeping balance				0.0
Dry mouth	5	1	6	40.0
Blurry vision	1		1	6.7
Seeing double				0.0
Constipation				0.0
Diarrhea	1	2	3	20.0
Delays in urinating		1	1	6.7
Itchiness				0.0
Light hurting eyes	2	1	3	20.0
Nausea	3	2	5	33.3
Vomiting				0.0
No appetite	3	2	5	33.3
Stomach pains				0.0
Drowsy	2	2	4	26.7
Leg spasms at night				0.0
Sweating	2	3	5	33.3
Tremor	5	1	6	40.0
Tinnitus	2		2	13.3
Headache		1	1	6.7
Nightmares		2	2	13.3
Weight change		1	1	6.7
Other				
Alopecia		2	2	13.3
Mania		1	1	6.7

reported by Simeon et al. (in press). Side effects experienced by patients in this study, such as sweating, drowsiness, dry mouth, tremor, and alopecia, were found to occur more commonly than in adult studies (Jenike et al. 1989, Masco and Sheetz 1985, Schneider et al. 1990, Schweizer et al. 1990). Some adverse side effects, in particular orthostatic hypotension, and allergic reactions which were of significant frequency (33%) in a double-blind study of desipramine in adolescents (Boulos et al. 1990), were not found to be as much of a problem in this open trial.

In this study, two patients complained of hair thinning. Concurrent medications included lithium plus valproic acid in one, and clonazepam in another. All other medications, however, had been administered for several months previous without any complaints of hair thinning. Family histories of hair loss were negative, and thyroid indices both pre- and posttreatment were normal. This side effect was transient, did not require medication withdrawal, and was not associated with any significant hair loss. A case of severe hair loss in an adult during fluoxetine treatment has been reported by Jenike (1991). He referred to a <1% rate in a multicentered trial of approximately 600 patients, suggesting that true hair loss as a fluoxetine side effect is negligible.

The occurrence of fluoxetine-induced mania has been reported in the adult literature (Chouinard and Steiner 1986, Settle and Settle 1984). One patient in our study developed full-blown mania at 8 weeks, after an initial positive response to medication. After discontinuation of fluoxetine, she was stabilized on valproic acid and has since remained relatively euthymic.

In a recent publication, Teicher et al. (1990) suggested that the emergence of intense suicidal preoccupation in 6 patients may have been induced by fluoxetine. The evidence for this is not conclusive, given that the majority of those patients had previously experienced suicidal ideation and often had been concurrently treated with a variety of psychotropic medications. Similarly, King et al. (1991) have reported four cases of young adolescents treated for obsessive compulsive disorder in whom suicidal ideation or self-injurious behavior seemed to be associated with fluoxetine treatment. However, the type and severity of illness in their sample, the length of time from onset of treatment to onset of the presumed side effects (1–6 months), and the length of time to offset these behaviors following medication withdrawal (1 month), suggest that factors other than simply fluoxetine use may have been involved. Several more recent detailed reports have failed to demonstrate an association between fluoxetine treatment and suicidality (Ayd 1990, Beasley et al. 1991, Fava and Rosenbaum 1991). None of our patients treated with fluoxetine reported any increase in suicidal ideation, nor were there any gestures of suicide attempts or self-inflicted injuries in either the month prior to or during the fluoxetine treatment period.

CONCLUSION

Although the conclusions are only speculative given the design of this study, the preliminary data suggest that fluoxetine in doses of 5–40 mg daily may be a useful medication in treatment-resistant adolescents and young adults with major depression. It is, however, a naturalistic study with a small sample size and no placebo control group. Double-blind placebo-controlled studies are required to further evaluate the efficacy of this medication as well as to examine in greater depth the issues of dosage, scheduling, duration of treatment, and adverse effects.

ACKNOWLEDGMENTS

The authors wish to thank Doug Quackenbush for educational assessments, Jill Roberts for secretarial assistance, Patric Abtan for computer assistance, and Eli Lilly for providing medication and product information.

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APPENDIX 1: FLUOXETINE SIDE EFFECTS SCALE

Name: _____ Date: _____

	never		somewhat		constantly
Trouble sleeping	0	1	2	3	4
Heart racing	0	1	2	3	4
Heart pounding	0	1	2	3	4
Feeling dizzy	0	1	2	3	4
Feeling the room spin	0	1	2	3	4
Feeling tense inside	0	1	2	3	4
Restlessness	0	1	2	3	4
Numbness of hands or feet	0	1	2	3	4
Tingling in hands or feet	0	1	2	3	4
Trouble keeping balance	0	1	2	3	4
Dry mouth	0	1	2	3	4
Blurry vision	0	1	2	3	4
Seeing double	0	1	2	3	4
Constipation	0	1	2	3	4
Diarrhea	0	1	2	3	4
Delays in urinating	0	1	2	3	4
Itchiness	0	1	2	3	4
Light hurting eyes	0	1	2	3	4
Nausea	0	1	2	3	4
Vomiting	0	1	2	3	4
No appetite	0	1	2	3	4
Stomach pains	0	1	2	3	4
Drowsy	0	1	2	3	4
Leg spasms at night	0	1	2	3	4
Sweating	0	1	2	3	4
Tremor	0	1	2	3	4
Tinnitus	0	1	2	3	4
Headache	0	1	2	3	4
Nightmares	0	1	2	3	4
Weight change	0	1	2	3	4
Other	0	1	2	3	4

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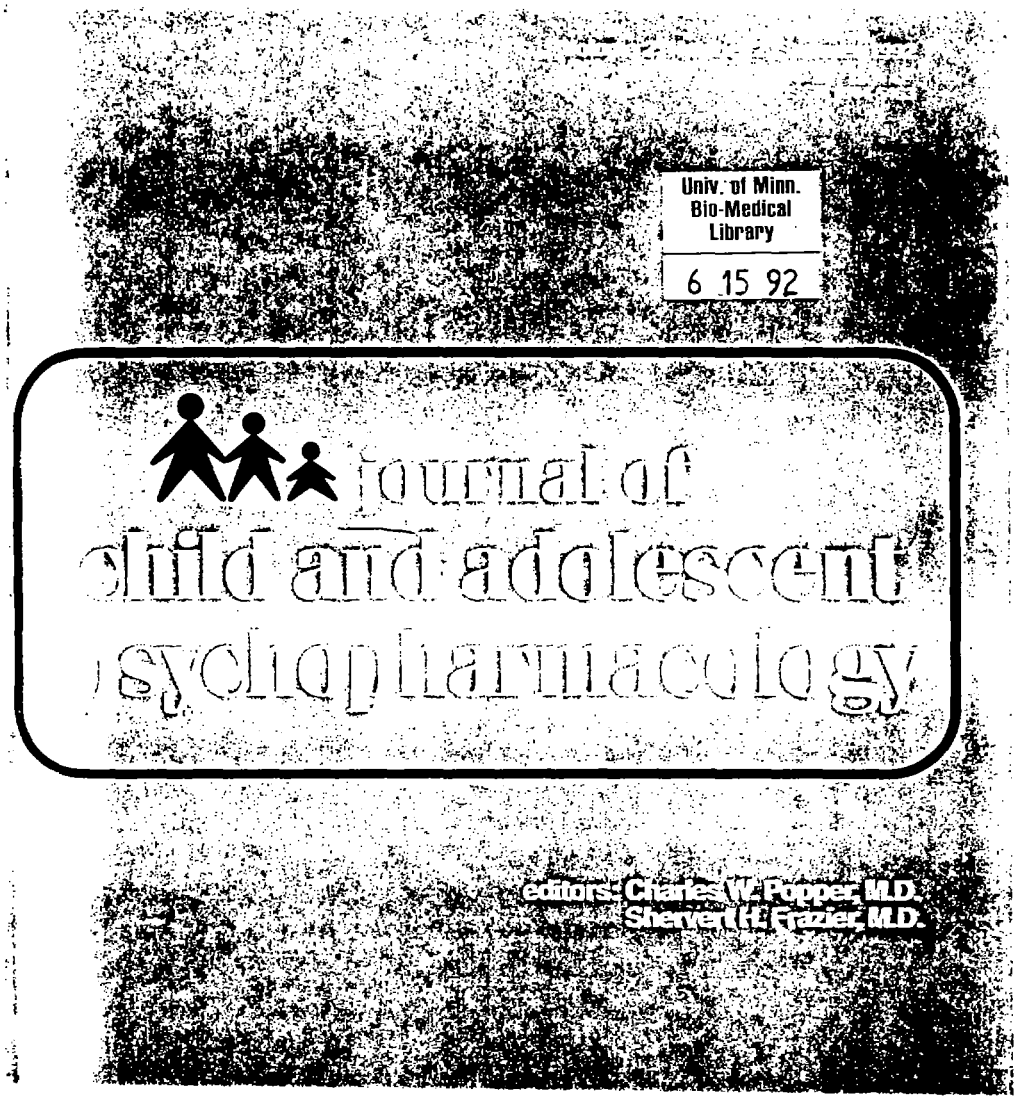
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Correlates of the Medical Lethality of Suicide Attempts in Children and Adolescents

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Abstract. The relationship between the medical lethality of suicidal behavior and demographic, psychiatric, social, and familial/environmental variables was examined in chart review of a consecutive series of youthful suicide attempters presenting in a Children's Hospital over a 5-year period. Correlates of the lethality of suicidal behavior included male sex, diagnoses of affective disorder and substance abuse, high suicidal intent, and the ingestion of a psychotropic agent. Patients who made medically lethal attempts appeared to have characteristics which converge with those who have completed suicide. The availability of a lethal agent may be the most significant determinant of the lethality of impulsive attempts, whereas suicidal intent and severity of psychopathology may make the most important contributions to the lethality of attempts by hopeless, dysphoric individuals. The implications of these findings for the prediction and prevention of suicide in children and adolescents are discussed. *J. Amer. Acad. Child Adol. Psychiat.*, 1987, 26, 1:87–89. **Key Words:** suicide attempts, intent, lethality, hopelessness.

Suicidal behavior is one of the most common psychiatric emergencies in children and adolescents (Mattsson et al., 1969; Shafii et al., 1979). The study of this problem has become more critical in recent years in the context of a dramatic rise in the rate of both attempted and completed suicide among youths (Shaffer and Fisher, 1981; Weissman, 1974; Wexler et al., 1978). In spite of the increased attention devoted to this vexing trend, the study of factors predictive of completed suicide is inherently limited in several ways. First, because suicide is so rare an event, even among a high-risk population, any prospective study must encompass a very large number of subjects to be followed over a long period of time (Otto, 1972; Pokorny, 1983). Second, although psychological autopsies of completed suicide are of considerable value, most proponents of such an approach acknowledge the possibility of considerable bias resulting from such procedures (Barraclough et al., 1974; Robins et al., 1959).

An alternative approach to augment these other methods is the intensive study of suicidal individuals who have made attempts which most closely resemble those of completers, but through medical resuscitation or chance circumstances have survived. Previous studies of individuals who have engaged in dangerous but nonlethal behavior have shown that they do have some characteristics in common with those persons who complete suicide (Garfinkel et al., 1982; Goldney, 1981; Henderson et al., 1977; Pallis and Sainsbury, 1976; Robbins and Alessi, 1985). In fact, survivors of medically dangerous suicide attempts are at higher risk to complete suicide than are survivors of less dangerous attempts (Motto, 1965; Otto, 1972; Pierce, 1981; Rosen, 1970; Tuckman and Youngman, 1963, 1968). In addition to the support of this previous work, the study of the lethality of suicidal behavior is warranted because this parameter is observable, easily objectified, can be elucidated independent of informant cooperation, and most important, represents the ultimate determinant of the success of the suicide attempt. Although these results are promising, generalization to younger populations is difficult, insofar as only a few of these studies focused on children and adolescents (Garfinkel et al., 1982; Otto, 1972; Robbins and Alessi, 1985).

This paper will examine the relationship of the medical lethality of a suicide attempt to other descriptors of the attempt as well as to the demographic, psychiatric, and familial/environmental variables in a consecutive series of suicide attempters seen at Children's Hospital of Pittsburgh. In addition, these correlates of the lethality of suicidal behavior will be: (1) assessed in subgroups deemed to be at high and low risk for suicide and (2) compared with known risk factors for completed suicide.

Method

The charts of 131 consecutive suicide attempts by 126 patients seen at Children's Hospital of Pittsburgh (CHP), 1978–1983 were reviewed by the author. All suicide attempters who presented at the emergency room at CHP were routinely admitted to a pediatric service for 48 hours, during which time psychiatric and social service consultations were obtained. The author was the psychiatric consultant for 21 of these patients.

Sample Characteristics. Sample characteristics abstracted from the chart are summarized in Table 1. Subjects were primarily white, female, and made suicide attempts of low lethality.

Measures. The Risk Rescue Rating (RR) was utilized to assess the medical lethality of the suicide attempt. The scale has two components—"risk," which measures the actual dangerousness of the attempt, and "rescue," which examines the circumstances of the attempt that would either facilitate or impede rescue. This measure of lethality was chosen in favor of others such as "level of consciousness" (Birthnell and Alarcon, 1971, 1977; Williams et al., 1977) or "intensity of treatment required" (Goldney and Pilowsky, 1980) because only the RR considers the *context* in which the attempt has taken place. Also, the RR has been utilized in previous studies

Received July 8, 1985; accepted Nov. 4, 1985.

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Some of the results in this paper were presented at a Poster Session at the 30th Scientific Meeting of the American Academy of Child Psychiatry, October, 1983, San Francisco, California.

The assistance of Drs. Evelyn Bromet, David Kolko, Maria Kovacs, and Helen Orvaschel in the conception and revision of this manuscript is gratefully acknowledged. Rich Ulrich, M.S., provided statistical consultation. Ms. Ellen Lipshitz and Ms. Susan Pietrusinski helped obtain the medical records.

This work was supported in part by NIMH Training grant 2 T3MH 1569-06 and a Clinical Investigator Award to the author (1 K08 MH00581-01).

0890-8567/87/2601-0087 $02.00/0

TABLE 1. *Characteristics of the Study Sample*

Variable	Category	Frequency
Age	7–12	23
	13–15	76
	16–18	31
Race	White	89
	Other	42
Sex	Male	37
	Female	94
Occupation of head of household[a]	Professional	10
	Manager	17
	Semiprofessional	21
	Other white collar	19
	Skilled labor	25
	Semiskilled labor	11
	Unskilled labor	8
	Unemployed	20
Marital status of parents	Married	53
	Married, one stepparrent	20
	Single parent	43
	Foster parents or group home	12
Method of attempt	Firearms	1
	Hanging	2
	Laceration	4
	Overdose	124
Distribution of risk-rescue rating	25–29	30
	30–34	14
	35–39	20
	40–44	18
	45–49	23
	50–54	13
	55–59	10
	60–64	3

[a] Hollingshead and Redlich (1958).

of adolescent (Garfinkel et al., 1982) and young adult (Goldney, 1981) suicide attempters. The RR was designed to be utilized for chart reviews, and has high internal consistency, interrater reliability and both discriminant and construct validity (Weisman and Worden, 1972).

Suicidal intent was assessed by use of the Beck Suicidal Intent Scale (SIS) (Beck et al., 1974). Since this scale was not designed to be utilized as an instrument for chart review, interrater reliability was tested on a subset of charts and found to be adequate ($r = 0.73$, $df = 9$, $p < 0.01$).

Measures of hopelessness and suicidal intent after the attempt were coded as dichotomous variables. Hopelessness was noted to be present if, on mental status examination, the patient described pessimism about the future. Suicidal intent after an attempt was noted to be present if the patient showed a persistent wish to die. Social adjustment was assessed in three areas—school, peers, and family, and rated on a three point scale in each area, based upon anchor points utilized to assess social functioning (Axis V) in DSM-III. Interrater reliability for these measures were adequate (r values range from 0.64 to 1.00, p values < 0.05–0.01).

Psychiatric diagnoses were recorded in the chart as DSM-II or DSM-III diagnoses; DSM-II diagnoses were recorded as their equivalent DSM-III categories for purposes of comparison. A subset of these patients was referred for inpatient psychiatric hospitalization, and a comparison of the diagnoses of the consulting psychiatrist at CHP with the *discharge diagnoses* of the inpatient hospital showed an acceptable rate of concordance ($r = 0.76$, $df = 21$, $p < 0.01$).

Adequate data were present for all variables, with the exception of family history of psychiatric disorder and suicidal behavior, where in many cases information was not recorded. Statistical tests employed include Pearson's correlation coefficient, Student's t-test, the chi-square (χ^2) statistic, analyses of variance and covariance, and multiple linear regression. All statistical tests are two-tailed.

Results

Significant correlates of the medical lethality of suicidal behavior in this sample included male sex ($t = 2.87$, $df = 129$, $p = 0.005$), diagnosis of affective disorder, particularly in combination with substance abuse ($F = 3.41$, $df = 7,123$, $p = 0.03$) and family history of affective disorder ($F = 3.98$, $df = 3,83$, $p = 0.01$) (Table 2).

In addition, the medical lethality was correlated with suicidal intent both prior to ($r = 0.51$, $p < 0.0001$) and subsequent to the suicide attempt ($t = 2.57$, $df = 123$, $p = 0.01$), as well as with degree of planning ($F = 5.89$, $df = 2,127$, $p = 0.004$), and use of a psychotropic agent (60% of which were antidepressants) as the agent of the attempt ($F = 10.41$, $df = 2, 117$, $p = 0.0001$). The association between the use of a psychotropic agent and the medical lethality of suicidal behavior has been reported previously (Goldney, 1981). However, in contradistinction to Goldney's report on a sample of young adult female attempters, only 6% of the present series of children and adolescents overdosed on their own medication. The relationship between class of agent and the medical lethality of the attempt remained robust, even after covarying out the effects of other possibly mediating variables (e.g., parental medical or psychiatric illness, chronic medical or psychiatric illness in the child, stress at home, suicidal intent; $F = 9.65$, $df = 2, 117$; $p = 0.0001$).

The medical lethality of suicide attempts was not associated with other demographic (age, race, social class), social (school function, peer and family relations), or family/environmental variables (abuse, inter-parental or parent-child discord, parental illness, or number and type of stressful life events).

Regression of demographic variables and those variables shown to be significantly associated with RR on univariate analyses revealed that 37% of the variance could be explained by sex, class of agent, and most importantly, suicidal intent.

The sample was then dichotomized on the presence or absence of hopelessness. Hopelessness was chosen because of its prognostic value in the prediction of future suicidal attempts and completions (Beck et al., 1975b, 1985; Pierce, 1981). In this sample, hopelessness was unrelated to age, race, sex, medical lethality or class of agent ingested. However, hopelessness was related to suicidal intent ($r = 0.43$, $df = 121$, $p < 0.0001$), to diagnosis of affective disorder ($\chi^2 = 35.92$, $df = 6$, $p < 0.0001$), and degree of planning ($r = 0.74$, $df = 121$, $p < 0.0001$). Therefore, dichotomization of the sample on

TABLE 2. *Significant correlates of medical lethality*

Variable	Category	Frequency	Mean RR ± SE	*p* Value
Sex	Male	37	43.86 ± 11.16	0.005
	Female	94	38.42 ± 9.19	
Marital status of parents				0.03
	Married	56	42.06 ± 10.80	
	Stepfamily	20	34.83 ± 9.66	
	Single parent	43	38.97 ± 9.11	
	Out-of-home	12	42.27 ± 7.16	
Psychiatric diagnoses				0.03
	Affective disorder	26	37.51 ± 10.53	
	Affective/conduct disorder	9	42.17 ± 6.76	
	Affective/substance abuse	13	47.54 ± 8.79	
	Conduct disorder	8	37.94 ± 9.21	
	Conduct/substance abuse	15	41.02 ± 9.54	
	Adjustment disorder	32	35.88 ± 10.65	
	Other	28	39.20 ± 11.37	
Continued suicidal intent				0.01
	No	98	38.66 ± 10.06	
	Yes	27	44.20 ± 9.25	
Family history of psychiatric illness				0.01
	None	15	39.11 ± 8.20	
	Affective disorder	36	43.20 ± 9.30	
	Antisocial personality	4	31.16 ± 5.19	
	Alcohol/drug abuse	32	36.67 ± 10.04	
Expectation of lethal outcome				0.0001
	No	76	37.30 ± 9.72	
	Uncertain	37	41.69 ± 8.86	
	Certain	17	48.29 ± 9.27	
Degree of planning				0.004
	None	87	37.97 ± 10.13	
	Some (<24 hr)	35	43.55 ± 7.96	
	A great deal (>24 hr)	8	46.26 ± 12.12	
Class of agent (ingestions only)				0.0001
	Over-the-counter	59	36.01 ± 7.83	
	Nonpsychotropic prescriptions	28	41.03 ± 10.32	
	Psychotropic	33	45.08 ± 10.37	

TABLE 3. *Regression Analyses of Medical Lethality*

Subject Pool	Variable	Beta ± S.E.	Partial Correlation	*t*	Significance (*p*)
Total	Suicidal intent	0.50 ± 0.08	0.43	5.99	<0.0001
($N = 131$)*	Class of agent	−0.28 ± 0.08	−0.26	−3.65	0.0004
	Sex	−0.14 ± 0.07	−0.14	1.98	0.05
Non-hopeless	Class of agent	−0.41 ± 0.11	−0.37	−3.73	0.0004
($N = 78$)**	Suicidal intent	0.32 ± 0.10	0.31	3.17	0.002
Hopeless	Suicidal intent	0.56 ± 0.10	0.44	5.43	<0.0001
($N = 45$)***	Race	−0.29 ± 0.08	−0.27	−3.39	0.002
	Affective disorder	0.26 ± 0.10	0.20	2.54	0.02
	Sex	−0.23 ± 0.09	−0.20	−2.49	0.02
	Substance abuse	0.21 ± 0.09	0.18	2.25	0.03

* $R^2 = 0.37$; ** $R^2 = 0.27$; *** $R^2 = 0.76$.

this variable yielded a hopeless, affectively disordered group who made planned attempts of high intent, and a non-hopeless group whose attempts were impulsive and of variable intent.

The regression equations fit to the two subsamples are decidedly distinct (Table 3). In the group that did not report hopelessness, 27% of the variance in the RR was accounted for ($F = 7.79$, $df = 2, 75$, $p < 0.0001$), with 18% of the variance explained by the class of agent and the remaining 9% associated with suicidal intent. In the group that endorsed hopelessness, 76% of the variance in the RR was explained ($F = 16.80$, $df = 7, 37$, $p < 0.0001$) by the following variables: sex, race, suicidal intent, and diagnoses of affective disorder and substance abuse.

Discussion

This study is subject to two main limitations. First, there are difficulties inherent in data gathered from chart review—

particularly in the assessment of more subtle variables such as social adaptation and family interaction. Some of our negative findings with respect to the relationship between these variables and the medical lethality of the attempts may have been due to this limitation. Second, the investigator assessed both medical lethality and other variables, which might have resulted in an overestimate of the strength of some of these relationships. While the reliability of these results is buttressed by the demonstration of interrater reliability for a subset of measures in the chart reviews, the findings of this study should be viewed as more appropriate for hypothesis generation than for hypothesis testing.

This study is consistent with other work correlating the lethality of suicide attempts in children and adolescents with such factors as male sex, suicidal intent, depression, and family history of affective disorder (Garfinkel et al., 1982). Such variables are also associated with the greatest risk of completed suicide (Otto, 1972; Shaffer, 1974; Welner et al., 1979). These findings support the view that suicide attempters that are especially lethal represent a subgroup whose characteristics converge with those of suicide completers.

Multivariate analyses revealed the association between intent and RR as the most consistent and significant relationship between lethality and any response variable. Because the content of the "rescue" subscale of the RR overlaps with the SIS, both the univariate and multivariate analyses were repeated utilizing just the "risk" subscale as the dependent variable, without substantial changes in the findings. Therefore, the role of suicidal intent as a determinant of the medical lethality of the attempt appears robust, and is not simply an artifact of some common items between the two scales. While the relationship between medical lethality and intent may have been inflated due to the investigator filling out both scales, Beck et al. (1975a), utilizing a scale similar to the "risk" subscale, found a correlation between lethality and intent ($r = 0.19$, $p < 0.001$), similar to the correlation in the present study between "risk" and intent ($r = 0.30$, $df = 129$, $p < 0.0001$).

The subdivision of this sample by hopelessness seemed to separate subjects into a non-hopeless group of adjustment and conduct disorders who made unplanned attempts of variable intent, and a group of hopeless, affectively disturbed patients who made planned attempts of high suicidal intent. Similar groupings have been demonstrated empirically in samples of adult suicide attempters (Goldney, 1981, 1982; Henderson et al., 1977; Paykel and Rassaby, 1978).

The RR for the hopeless group appeared to be very much a function of known risk factors for completed suicide (e.g., substance abuse, affective disorder, high intent, male sex, white race) (Otto, 1972; Shaffer, 1974; Welner et al., 1979). In contrast, the *type of agent* ingested by the non-hopeless group was actually a more important determinant of RR than suicidal intent. This is consistent with the report that impulsive suicide attempters are more likely to overdose on pills that are easily accessible to them (Williams et al., 1977).

While the role of the availability of lethal agents in attempted and completed suicide is controversial (Maxwell, 1984; McClure, 1984), there is support for the viewpoint that availability in and of itself poses a risk factor for completed suicide. For example, restriction of the quantity of sedative prescriptions in Australia (Goldney and Katsikitis, 1983), diminution of the toxicity of domestic gas in Great Britain (Brown, 1979; Kreitman, 1976), and strictness of handgun control in the United States (Boyd, 1983; Lester and Murrell, 1980, 1982) have been related to lower suicide rates both specific to a given method, as well as overall.

These findings have implications for further investigation into the prediction and prevention of suicide in adolescents. Prediction of suicide may be quite difficult for the non-hopeless group, given that a low amount of the variance of RR is explained by psychosocial variables, and that what variance is explained is primarily a function of agent. Prevention of suicide in this group may rest primarily upon public health measures aimed at the restriction of availability of lethal agents (Boyd, 1983; Goldney and Katsikitis, 1983; Jones, 1977; Lester and Murrell, 1980, 1982; Robin and Freeman-Browne, 1968).

In contrast to the situation among the non-hopeless, impulsive group, prediction of suicide may be attainable for the hopeless attempters, for whom the RR was intimately related to the severity and range of psychopathology. Secondary prevention of suicide in this group should be directed towards the amelioration of underlying psychopathology.

Further research is warranted to confirm and extend these results.

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Comparing Age at Onset of Major Depression and Other Psychiatric Disorders by Birth Cohorts in Five US Community Populations

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• **Using data collected in the National Institute of Mental Health (Rockville, Md) Epidemiologic Catchment Area Program, we examined the proposed hypothesis that there has been a shift in major depression to younger ages at onset, or increased prevalence in younger age periods, for recent birth cohorts. Life-table survival methods were used to examine the hazard rates for major depression as well as for other specific mental disorders. The findings are consistent with a gradual shift to increased rates for major depression between the ages of 15 and 19 years for Epidemiologic Catchment Area respondents born more recently. The findings also suggest a similar shift for drug abuse/dependence; similar but less pronounced changes were found for alcohol abuse/dependence and obsessive-compulsive disorder. However, in this study, bipolar disorder, panic disorder, and phobias did not exhibit a consistent increase in onset at younger ages. Further research is required to determine if the shifts in major depression, drug abuse/dependence, and possibly alcohol abuse/dependence are linked. It is important to note that these shifts to adolescent onset are occurring when nearly half the 31 million Americans without health insurance are aged 24 years or younger.**

(*Arch Gen Psychiatry*. 1991;48:789-795)

A recent life-table analysis of the age at onset of mental disorders among respondents from the National Institute of Mental Health (NIMH, Rockville, Md) Epidemiologic Catchment Area (ECA) Program[1-6] suggested the importance of onset in adolescence and early adulthood for several specific mental disorders, including major depression.[7] This finding is consistent with the suggestion by Klerman et al[8-11] and others[12-17] that members of recent generations are displaying higher rates and/or younger ages at onset for major depression compared with members of older generations.

Klerman and Weissman[11] recently reviewed evidence suggesting an increase in the rate of major depression among people born since World War II. In 1976, Klerman[8] hypothesized that western societies were entering an "Age of Melancholy" and reported that clinical depression was increasing in adolescence and young adulthood. Later, results from a longitudinal study conducted between 1947 and 1972 in Lundby, Sweden, demonstrated that the probability of suffering a mild or moderate case of depression increased during that 25-year period for both sexes.[13] More recent studies examining relatives of patients have also reported evidence in support of increased rates of major depression,[9] earlier onset of major depression in successive birth cohorts,[14] and a statistically significant difference between the hazard rates for major depression developing for patients born before 1940 and patients born after 1940.[15] Similarly, a study examining hospital records in Zurich, Switzerland, reported that the number of admissions for major depression increased substantially from 1920 to 1982.[16] Most recently, Wickramaratne et al[12] examined birth cohort trends among a subsample of NIMH ECA respondents. For the 10 640 white ECA respondents, they reported increased rates of major depressive episode for both men and women born after 1935, with evidence of a period effect on respondents of all ages after 1960.

Three studies have also examined data relative to bipolar disorders. Angst's[16] study of Zurich admission records also showed increases for bipolar disorder since 1920, and two reports examining relatives in family studies have suggested increases for bipolar I disorder[17] or a category combining bipolar and schizoaffective disorders.[15]

Although findings from these recent investigations suggest a temporal change in recent generations, with major depression and possibly bipolar disorder having earlier ages at onset and/or higher rates than had been true in older generations, the studies have to varying degrees been subject to two limitations. First, these studies generally have not examined other nonaffective disorders to investigate whether the shift to earlier ages at onset is a general phenomenon displayed in all disorders or perhaps a methodologic artifact. Second, these studies typically have not used large, representative general population samples.

To address these problems, this analysis examines selected Diagnostic Interview Schedule (DIS)–*DSM-III* psychiatric disorders, in addition to major depression, in the

Accepted for publication September 20, 1990.

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total NIMH ECA sample of community and institutional residents in terms of two questions. (1) For major depression, has there been a shift to younger ages at onset in more recent birth cohorts? (2) Has any such shift for major depression been matched by similar shifts for other disorders, including drug or alcohol abuse/dependence, the anxiety disorders, or bipolar disorder? In this analysis, self-reported onset experience for the first 30 years of life will be compared for all NIMH ECA respondents grouped into four birth cohorts over the past century.

SUBJECTS AND METHODS

NIMH ECA Program

The data used to analyze the hypothesized shift in the age at onset and/or the increase in rates for major depression were collected as part of the NIMH ECA Program. The NIMH ECA Program was a combined household and institutional survey of mental disorders conducted in five sites throughout the United States, and it has been described in detail elsewhere.[17,18] This analysis is based on data from 20 745 household and institutional respondents who were aged 18 years and older at time of entry into the study. Data were excluded for an additional 116 respondents for whom year of birth was missing.

Diagnoses of specific mental disorders were made using the DIS.[19] Designed for use by nonclinicians in epidemiologic studies, this instrument uses self-reported information about symptoms to make diagnoses of specific mental disorders based on *DSM-III* criteria.[20] If a positive diagnosis can be made based on the symptoms reported, an inquiry is made to determine the age at first occurrence of the symptoms. Although it is possible that this first occurrence may not have been severe enough to pass the threshold for a *DSM-III* diagnosis, that initial episode is generally used as the one for dating onset of the disorder in the NIMH ECA data set and appears to be most relevant for dating onset in general.[7,11,12]

The NIMH ECA Program involved complex multistage sampling procedures[21]; therefore, the respondents have been weighted to reflect their probability of selection and then have been weighted to the 1980 US Census on the basis of age, sex, and race/ethnicity as described previously.[18,21]

Life-Table Survival Methods

Life-table survival methods, similar to those used in a recent examination of the age at onset of mental disorders in the NIMH ECA,[7] were used to compare the age at onset of selected mental disorders by birth cohorts. Survival methods were used to examine average yearly hazard rates for specific 5-year age intervals. A hazard rate gives the probability that a disorder will develop during a time interval in a respondent who enters that interval and who is free of a disorder at the beginning of that interval.[7,22,23] In this analysis, the time interval was defined as a range of 5 years during which age at onset could occur, for example, 15 to 19 years or 20 to 24 years.

Using the Statistical Package for the Social Sciences (SPSS) Survival program,[24] hazard rates to age 30 years were examined across four birth cohorts. The birth cohorts examined were those born before 1917 (unweighted n = 6566), between 1917 and 1936 (n = 4432), between 1937 and 1952 (n = 4981), and between 1953 and 1966 (n = 4766). Using an observation period from birth to 30 years of age allowed the comparison of each birth cohort for equivalent periods of risk; 30 years was the oldest age possible for a respondent born in the youngest birth cohort (1953 to 1966) at the time of interview. The youngest birth cohort is the only one whose members may have been less than 30 years of age, but life tables have the advantage of adjusting for the fact that subjects have different ages, or, in analogy to treatment outcome studies, that they have been followed up for different periods.[25]

For each disorder, the hazard rates of the four birth cohorts were compared using the Lee-Desu[26] statistic, which follows a χ^2 distribution with $g-1$ df, where g is the number of groups under comparison. This approach tests whether the distributions of onset in the first 30 years of life for the four birth cohorts were drawn from the same population or were significantly different. It compares the probabilities in the cohorts in all age intervals simultaneously[27] and is similar to other analyses of the cohort effect.[15,28] However, there is no method (eg, based on proportional hazards models) to test specifically for shifts in the peak age at onset while applying the complex weights of the ECA data.[29] Rather than using unweighted data, which would be inappropriate for the total ECA sample, we have relied on a graphic approach to identify apparent shifts in peak age at onset.[26] However, these apparent shifts cannot be tested for statistical significance by this approach.[26]

The SPSS software program appropriately weighted the data based on the sampling procedures to produce estimates of hazard rates. However, the program cannot accurately determine the variance associated with complex sampling designs like that used in the NIMH ECA Program. Therefore, two adjustments were necessary before tests of significance could be performed to determine if the onset experience differed by birth cohorts.[30] First, to assure that the sampling weights did not inflate the statistical power of comparisons, the weighted sample was adjusted to the same size as the total actual sample; to accomplish this, the sampling weight used for the five sites was multiplied by the number of respondents in the NIMH ECA sample and then divided by the 1980 US Census population. Second, the χ^2 test statistics were divided by the estimated sample design effect before calculation of P values. This conservative adjustment was done based on repeated estimates of the design effect for prevalences in these conditions that ranged from 1.5 to 2.0[7,30]; these design effect estimates were produced by the program SESUDAAN[31] developed for analyzing such complex surveys. These adjustments are equivalent to reducing the sample size by the design effect.[32]

RESULTS

Hazard rates were plotted and compared for statistically significant differences. The four cohorts examined will be referred to as cohort 1 (respondents born between 1953 and 1966), cohort 2 (respondents born between 1937 and 1952), cohort 3 (respondents born between 1917 and 1936), and cohort 4 (respondents born before 1917). These cohorts were similar to those used by Weissman et al[28] in the initial analysis of NIMH ECA data from New Haven (Conn) respondents. Since the five NIMH ECA sites entered the field at different times in the early 1980s, the end point for cohort 1 is shown as 1966, which is the latest year of birth of any NIMH ECA respondent and applies to the Los Angeles (Calif) site.

Mood Disorders

Unipolar Major Depressive Episode.—For the first 30 years of life in each cohort, Fig 1 plots the hazard rates for development of unipolar major depressive episode (with no lifetime history of manic episodes). For those NIMH ECA respondents born between 1953 and 1966, the hazard rates for unipolar major depression developing peak during two age intervals: 15 to 19 and 25 to 29 years of age. In the age interval 15 to 19 years, there also appears to be an increase in the magnitude of the hazard rate for respondents in cohort 1 compared with those respondents in cohort 2, and similarly for cohort 2 compared with cohort 3. This trend is made apparent by examining the ratio of the hazard rate for ages 15 to 19 years to the hazard rate for ages 25 to 29 years: cohort 1, 0.0055/0.0064 = 0.86; cohort 2, 0.0032/0.0062 = 0.52; and cohort 3, 0.0005/0.0019 = 0.26. The ratio for cohort 4 goes against this trend, but it is based on much smaller hazard rates (0.0003/0.0002 = 1.50).

The hazard rates for major depression developing for respondents born in cohort 1 and for those respondents born in cohort 2 are significantly different ($\chi^2 = 14.2$, $df = 1$, $P = .0002$). The hazard rates for major depression developing for respondents in cohort 2 compared with cohort 3 are also significantly different ($\chi^2 = 85.3$, $df = 1$, $P < .0001$).

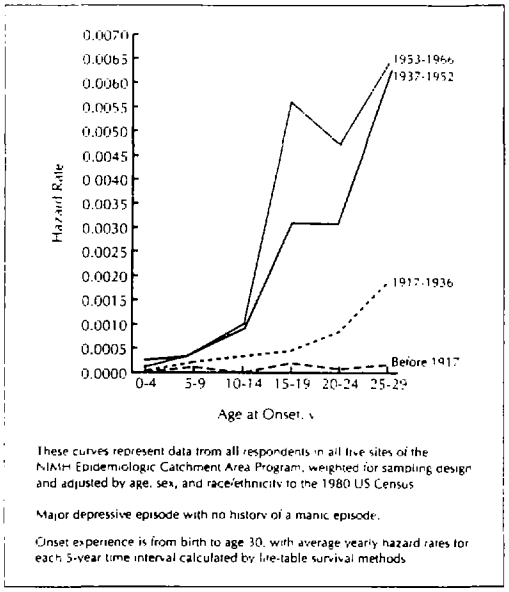


Fig 1.—*Hazard rate by year of birth for unipolar major depression (with no history of a manic episode), by Diagnostic Interview Schedule–DSM-III criteria, for cohorts born before 1917 (dashed line), from 1917 to 1936 (broken line), from 1937 to 1952 (solid line), and from 1953 to 1966 (lightly shaded line). NIMH indicates National Institute of Mental Health.*

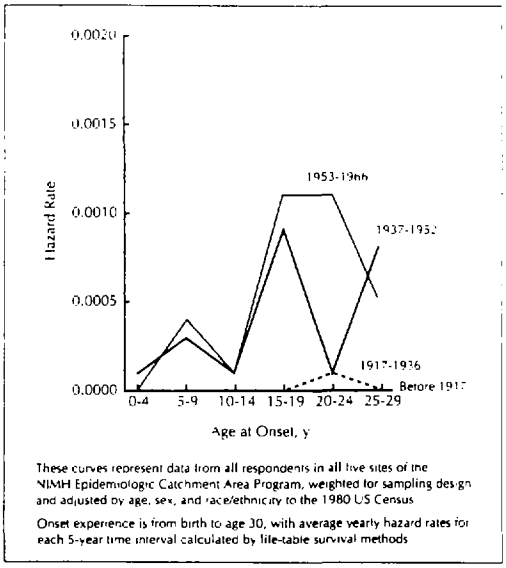


Fig 2.—*Hazard rate by year of birth for mania by same criteria and for same cohorts as in Fig 1. NIMH indicates National Institute of Mental Health.*

Bipolar Disorder.—For those respondents with a diagnosis of mania, there is no apparent shift to an earlier age at onset for the manic episode for those born most recently (Fig 2). The hazard rates for respondents born in cohort 1 compared with the hazard rates for those born in cohort 2 are not significantly different ($\chi^2 = 1.4$, $df = 1$, $P = .240$). However, for those respondents born in cohort 2 compared with those born in cohort 3, the hazard rates are significantly different ($\chi^2 = 24.0$, $df = 1$, $P < .0001$).

In Fig 3, additional information on bipolar disorder is presented. For those ECA respondents with a lifetime diagnosis of mania, the age at onset information presented is the youngest age at which either a major depressive or manic episode occurred, using the age for whichever episode came first. As with manic episode alone (Fig 2), there does not appear to have been a change in age at onset for respondents born in cohort 1 compared with those born in cohort 2 ($\chi^2 = 0.18$, $df = 1$, $P = .6705$). The hazard rates for respondents born in cohort 2 compared with those born in cohort 3 are significantly different ($\chi^2 = 27.2$, $df = 1$, $P < .0001$).

Anxiety Disorders

Panic Disorder.—For ECA respondents, there has been no apparent shift in the age at onset for panic disorder (Fig 4). The peak hazard occurs in the age interval 25 to 29 years for birth cohorts 1, 2, and 3. There is no significant difference between the hazard rates for respondents born after 1953 compared with the hazard rates for respondents born in cohort 2 ($\chi^2 = 0.5$, $df = 1$, $P = .5$). However, the rates for birth cohort 2 are significantly different from the rates for respondents born in cohort 3 ($\chi^2 = 20.2$, $df = 1$, $P < .0001$).

Obsessive-Compulsive Disorder.—For obsessive-compulsive disorder, there appears to have been a shift to a younger age at onset for the most recent birth cohort (cohort 1). Figure 5, a plot of the hazard rates by birth cohorts, shows that the peak hazard rate for cohort 1 occurs during the age interval 20 to 24 years, while the peak hazards for cohorts 2 and 3 both occur in the age interval 25 to 29 years. The hazard rates for respondents born in cohort 1 compared with the rates for respondents born in cohort 2 are significantly different ($\chi^2 = 9.5$, $df = 1$, $P = .002$). The hazard rates for respondents born in cohort 2 and respondents born in cohort 3 ($\chi^2 = 16.3$, $df = 1$, $P < .0001$) are also significantly different.

Phobias.—Figure 6 demonstrates that the hazard rate for development of phobias is highest for cohort 1 in the age interval 10 to 14 years, while the peak hazard for cohorts 2, 3, and 4 occurs in the interval 5 to 9 years. The difference between cohort 1 and cohort 2 just reaches statistical significance ($\chi^2 = 4.3$, $df = 1$, $P = .04$). A significant difference in developing phobias for those respondents born in cohort 2 and those respondents born in cohort 3 is found ($\chi^2 = 21.1$, $df = 1$, $P < .0001$).

Drug and Alcohol Use Disorders

Drug Abuse/Dependence.—In addition to the much higher rates in the youngest cohort, which may be observed by the need to break the vertical axis of the graph, there also appears to be a shift to a younger age at onset for respondents born in cohort 1 compared with cohort 2 for drug abuse/dependence (Fig 7). The peak hazard occurs between the ages of 15 and 19 years for cohort 1 and between the ages of 20 and 24 years for cohort 2; the difference between the hazard rates for respondents born in cohort 1 and for respondents born in cohort 2 is significant ($\chi^2 = 179.4$, $df = 1$, $P < .0001$). There is also a significant difference between the hazard rates for respondents born in cohort 2 and respondents born in cohort 3 ($\chi^2 = 159.1$, $df = 1$, $P < .0001$).

Alcohol Abuse/Dependence.—Like drug abuse/dependence, the hazard rates for alcohol abuse/dependence are highest for those NIMH ECA respondents born between 1953 and 1966 (Fig 8). The difference between the hazard rates for cohort 1 compared with cohort 2 ($\chi^2 = 58.0$, $df = 1$, $P < .0001$) is significant. A significant difference is also found between the hazard rates for respondents born in cohort 2 and rates for respondents born in cohort 3 ($\chi^2 = 62.3$, $df = 1$, $P < .0001$). As with major depression, a trend toward increasing importance of the 15- to 19-year age interval is also seen in Fig 8 across the four cohorts.

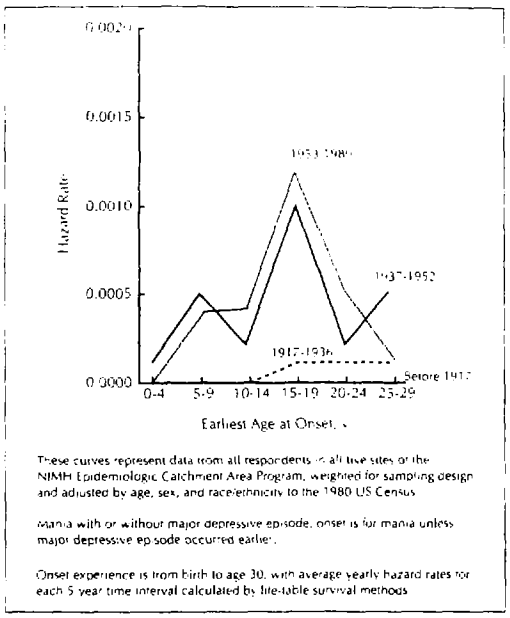


Fig 3.—*Hazard rate by year of birth for mania (with or without a major depressive episode; onset is for mania unless major depressive episode occurred earlier) by same criteria and for same cohorts as in Fig 1. NIMH indicates National Institute of Mental Health.*

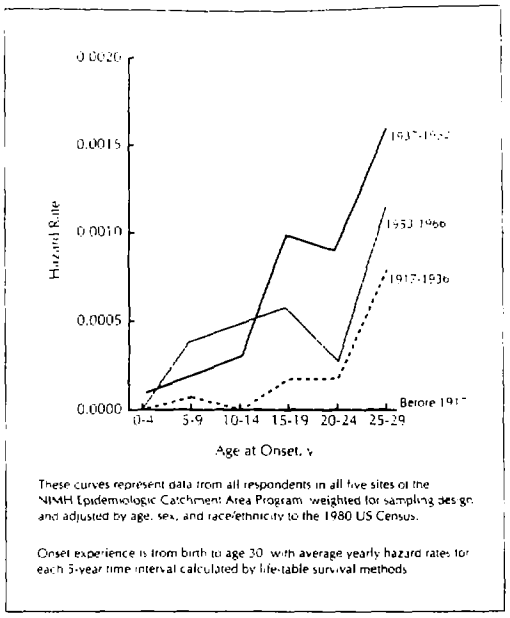


Fig 4.—*Hazard rate by year of birth for panic disorder by same criteria and for same cohorts as in Fig 1. NIMH indicates National Institute of Mental Health.*

Fig 5.—*Hazard rate by year of birth for obsessive-compulsive disorder by same criteria and for same cohorts as in Fig 1. NIMH indicates National Institute of Mental Health.*

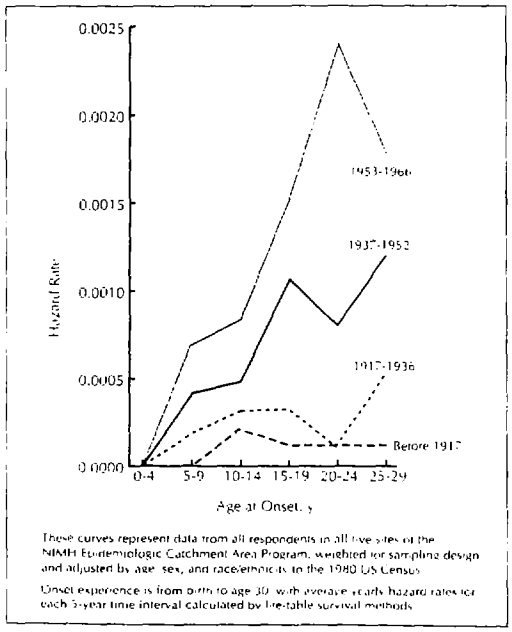
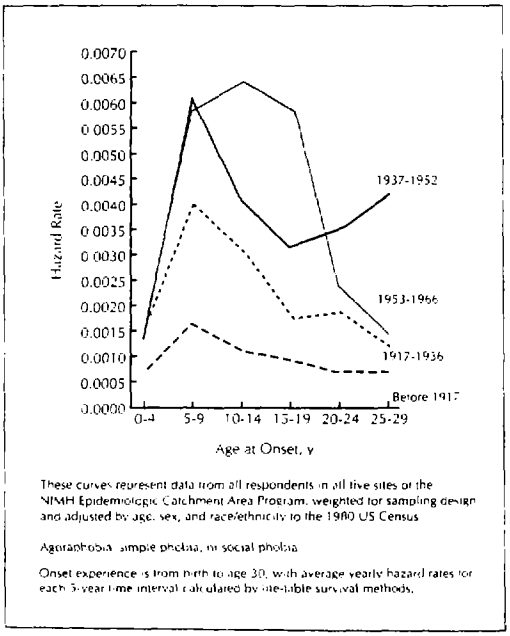


Fig 6.—*Hazard rate by year of birth for phobias (agoraphobia, simple phobia, or social phobia) by same criteria and for same cohorts as in Fig 1. NIMH indicates National Institute of Mental Health.*



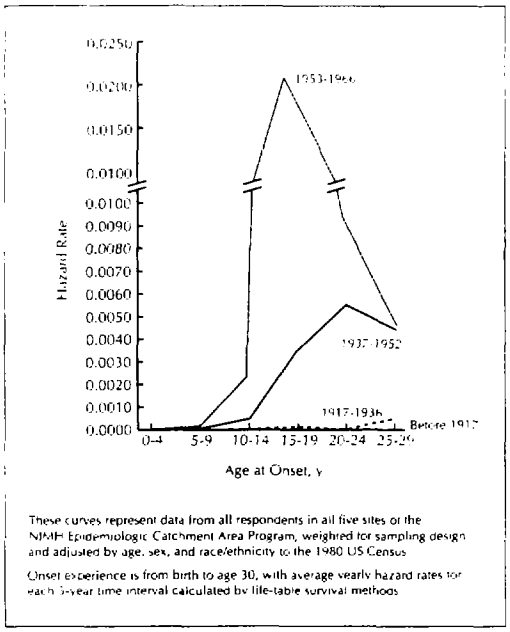


Fig 7.—*Hazard rate by year of birth for drug abuse/dependence by same criteria and for same cohorts as in Fig 1. NIMH indicates National Institute of Mental Health.*

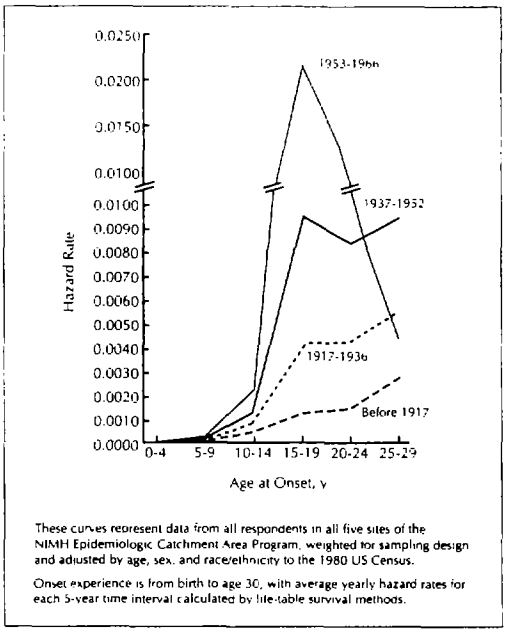


Fig 8.—*Hazard rate by year of birth for alcohol abuse/dependence by same criteria and for same cohorts as in Fig 1. NIMH indicates National Institute of Mental Health.*

COMMENT

For unipolar major depression, there appears to have been a gradual increase in the hazard rate for the interval 15 to 19 years of age across the three cohorts born since 1917. These findings are consistent with Klerman's hypothesis[8-11] and the findings of other studies[12-16] that members of recent birth cohorts have a higher risk of having a major depressive episode. One interesting but unexplained finding is the apparent importance of the 15- to 19-year age interval for the oldest cohort, born before 1917. Gershon et al[15] reported a similar, unexplainable increase in hazard rates for relatives born from 1910 to 1919 in an earlier family study, compared with other decades of birth before 1940. That study, and the current findings from the ECA, depend on retrospective recall from respondents for documenting lifetime history and age at onset, but the similarity may suggest the need to examine possible commonalities between that cohort and the more recent ones that appear to experience higher onset rates in adolescence.

For bipolar disorder, these results are not able to corroborate suggestions of a cohort effect shown in some earlier studies.[15-17] Whether this difference is caused by differences in sampling, as those studies used either relatives of probands or admission rates to a psychiatric hospital, or by differences in diagnostic assessment is not clear. It is also possible that a small effect that could be detected in a sample of high-risk family members could not be demonstrated in a general population study for a relatively uncommon disorder such as bipolar disorder.

For drug abuse/dependence, there has been a shift to a younger age at onset for the most recent cohort as well as an increase in the magnitude of the hazard rate for those respondents born between 1953 and 1966. For alcohol abuse/dependence, there has not been a shift in the peak age at onset, since the age period 15 to 19 years was also of predominant importance for cohort 2, but there has been a progressive increase in the magnitude and predominance of the hazard rate in the 15- to 19-year age interval.

Earlier Studies

These findings are interesting for several reasons. They corroborate earlier analyses of a subsample of ECA respondents and findings from other, more targeted, samples for major depression. It is noteworthy that the earlier results can be shown in a large general population sample that includes both sexes, multiple racial and ethnic groups, and five different community sites. They also demonstrate that some disorders, particularly drug abuse/dependence, exhibit the same changes. The demonstration of widely different patterns of onset across the two most recent birth cohorts for the specific disorders examined herein suggests that the shifts observed for major depression and drug abuse/dependence are not the result of a simple methodologic artifact.

The evidence of increasing onset from 15 to 19 years of age for major depression, drug abuse/dependence, and possibly alcohol abuse/dependence raises important questions about the possible association of these conditions. Prior analyses of a subset of ECA respondents in the 18- to 30-year age range have shown that an earlier major depressive or anxiety disorder approximately doubles the risk of subsequent drug abuse/dependence for both men and women (but not alcohol abuse/dependence).[33] Find-

ings from the Yale University (New Haven) Family Study have also shown that major depression occurring before the age of 30 years is linked with panic and drug use disorders.[34] Klerman and Weissman[11] have discussed environmental factors that may contribute to the apparent shift to earlier onset for depression and higher rates in younger cohorts, such as changing family structure and increasing urbanization. In this analysis of ECA data, the youngest cohort also appears to have increased onset of drug abuse/dependence in adolescence. While it has been known that first use of drugs typically occurs in this age period, it is not clear whether the earlier occurrence of major depression somehow contributes to an earlier onset of clinical disorders of drug abuse/dependence in adolescents who may have only experimented with drug use in earlier cohorts. If so, the shift to an earlier age at onset for major depression could be one of the factors leading to increased drug abuse/dependence in the same period of late adolescence.

For obsessive-compulsive disorder, the peak hazard has shifted to a somewhat younger age at onset for the most recently born cohort (respondents born between 1953 and 1966). The onset has shifted from 25 to 29 years of age to 20 to 24 years of age. This demonstration of an apparent shift in onset of an anxiety disorder, if it is found in other studies, may raise the possibility of studying whether onset of the disorder is also possibly linked to the shifts in depression and drug abuse/dependence, or at least whether it results from similar factors.

By restricting analysis to the first 30 years of life for each cohort, this approach does not permit identification of period effects like those shown by Lavori et al[14] for the 1970s and Wickramaratne et al[12] for the 1960s and 1970s. A period effect would operate uniformly on respondents without regard to their age at a particular time in history. The analysis is restricted herein to life before the age of 30 years to allow meaningful tests of significance of any differences observed between cohorts. For that reason, there is no adequate basis for examining the effects of particular calendar years to determine if all respondents show increased rates (period effect) or only those born more recently (cohort effect).

For all disorders examined, a significant difference was found in onset between cohorts 3 and 2. This finding is consistent with earlier reports of the cohort effect for major depression for persons born after 1940. However, the uniform finding for all disorders may represent either a profound effect or a methodologic limitation resulting from retrospective reporting. Further efforts to understand the basis of this apparently uniform effect would be of great importance, especially if methodologic limitations can be ruled out.

Limitations

Findings from epidemiologic studies must be interpreted cautiously, especially when they are early and information is available from only a few other similar studies. In addition to this general caution, there are two possible limitations in this specific analysis that deserve further consideration.

First, test-retest reliability of age-at-onset questions from the DIS suggests that agreement is adequate for all disorders examined herein, with the possible exception of phobias, where agreement with independent clinical examiners was weaker.[35] However, the test-retest agreement has not been good enough to justify use of narrow, 3-year age intervals, so this analysis has used 5-year intervals; onset patterns cannot be determined as precisely as desired in this retrospective analysis. For that reason, the apparent shift for obsessive-compulsive disorder (from 25 to 29 years to 20 to 24 years) and for drug abuse/dependence (from 20 to 24 years to 15 to 19 years) may be less robust than the larger shifts for major depression (from 25 to 29 years to 15 to 19 years).

Second, poor recall or poor reporting by older respondents of either symptom or onset data, or earlier mortality of those respondents with psychiatric disorders in the older cohorts, are also of concern in this retrospective analysis of cross-sectional data.[3,36] Recent evidence from one study that examined the reliability of recall for self-reported age at onset for specific mental disorders demonstrated a tendency for older respondents to increase their reported age at onset for major depression by a few years across interviews[37]; another more recent study found the opposite, that older subjects tend to lower rather than raise their estimated age at onset.[38] If older subjects do increase their reported age at onset, our finding of a uniform significant difference in the risk of developing disorders for respondents in cohort 2 (born between 1937 and 1952) and for respondents in cohort 3 (born from 1917 to 1936) for all disorders may be explained by this tendency. This finding may also support the cautious recommendation by Lavori et al[14] not to rely on age-at-onset reports for subjects older than 50 years. In the NIMH ECA study, there are no data that allow evaluation of recall problems in older subjects or the differential mortality problems in aging cohorts. However, the consistent demonstration of differences between cohorts 2 and 3 may indicate methodologic problems rather than a cohort effect applying to every disorder examined herein. While the shift around World War II was found in earlier studies for major depression, its considerably strong showing for every disorder may raise skepticism about the validity of such retrospective reporting for the oldest respondents (eg, >50 years).

CONCLUSION

With the apparent shift to earlier ages at onset, and with the general demonstration that childhood and adolescence are important periods for development of mental disorders, both research and policy issues arise. Ideally, research on the age at onset of psychiatric disorders should be conducted prospectively to improve accuracy of the onset data and to distinguish cohort and period effects more directly. However, prospective studies to examine the proposed shift for recent birth cohorts have not been reported. As a result, increased study of the onset of disorders in adolescence and early adulthood appears to be of great importance, especially to examine patterns of co-occurrence of depressive and drug use disorders. As noted by Klerman and Weissman,[11] research that is cross-cultural would be especially important in examining how different genetic and environmental factors interact to produce these changes in age at onset.[39]

In terms of policy implications, it should be noted that of the estimated 31 million Americans with no health insurance coverage in 1987, almost half (46%) were 24 years old or younger.[40] As a result, the general problem of ensuring adequate access to mental health services in this country is even more serious for the age group most likely to experience onset of these disorders.

The ECA is a series of five epidemiologic research studies performed by independent research teams in collaboration with staff of the NIMH

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NIMH Project Officer.—Carl A. Taube, PhD (1978-1985), and is now William Huber.

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Helpful comments on earlier drafts of the manuscript by Susan Ahmed, PhD, are gratefully acknowledged.

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Journal of Affective Disorders, 19 (1990) 63–75
Elsevier

JAD 00704

EEG sleep in adolescents with major depression: the role of suicidality and inpatient status

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(Received 9 July 1989)
(Accepted 31 October 1989)

Summary

All night sleep EEG recordings were performed for three consecutive nights in 27 adolescents with a diagnosis of major depressive disorder (MDD) and 30 normal adolescent controls. Group comparisons between the entire MDD group and the normal controls revealed no significant diagnostic group differences for any of the major sleep variables.

Analyses within subgroups of MDD adolescents, however, revealed heterogeneity of EEG sleep findings in association with suicidality and inpatient status. The findings of this study suggest that the discrepancies among the EEG sleep studies in adolescent MDD may be accounted for by the relative proportions of inpatients, suicidality, or bipolarity within the MDD sample being studied.

Key words: EEG sleep; Depression: Adolescents

Introduction

Despite relative agreement concerning the changes in EEG sleep variables in depressed adults (Kupfer, 1976; Gillin et al., 1979; Coble et al., 1980; Rush et al., 1982; Reynolds and Kupfer, 1987), there are discrepant data concerning similar sleep changes in children and adolescents with major depressive disorder (MDD) (Taub et al., 1978; Kupfer et al., 1979; Gillin et al., 1981; Puig-Antich et al., 1982; Young et al., 1982; Lahmeyer et al., 1983; Hawkins et al., 1985; Emslie et al., 1987, 1988; Goetz et al., 1987; Appelboom-Fondu et al., 1988). Two of these studies did not have their own controls (Kupfer et al., 1979; Emslie et al., 1987) and two others included some patients on medication (Taub et al., 1978; Hawkins et al., 1985) and will be excluded from further discussion. Of the remaining published results, three studies have reported reduced REM latency findings associated with MDD (Gillin et al., 1981; Lahmeyer et al., 1983; Emslie et al., 1988) while four studies failed to find REM latency dif-

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ferences in the MDD sample (Puig-Antich et al., 1982; Young et al., 1982; Goetz et al., 1987; Appelboom-Fondu et al., 1988). Of these seven studies only one (Lahmeyer et al., 1983), reported higher REM density, and a single study (Emslie et al., 1988) found increased stage REM in the MDD group. The MDD group has demonstrated longer sleep latencies in only three studies (Gillin et al., 1981; Goetz et al., 1987; Emslie et al., 1988) and had significantly increased awake time in only two published reports (Goetz et al., 1987; Appelboom-Fondu et al., 1988). There are no reported differences in stage 3/4 (delta sleep) in any of these studies.

The methodological differences among these studies include sample age, sample size, diagnostic criteria, nature of controls, inpatient status, determination of bedtimes (lights-out and wake-up times) and definitions of sleep variables. With respect to sample age, two studies consisted of prepubertal samples with a mean age of approximately 10 years (Puig-Antich et al., 1982; Young et al., 1982), one had both prepubertal and adolescent subjects with a mean age of 12.5 years (Emslie et al., 1988), three studies examined adolescents with an approximate mean age of 15 years (Lahmeyer et al., 1983; Goetz et al., 1987; Appelboom-Fondu et al., 1988), and in one study the sample was essentially adolescent/young adults aged 15–24 years (Gillin et al., 1981). Sample size was large (47–54 subjects with MDD) in three studies (Puig-Antich et al., 1982; Goetz et al., 1987; Emslie et al., 1988), and small (8–13 subjects with MDD) in four studies (Gillin et al., 1981; Young et al., 1982; Lahmeyer et al., 1983; Appelboom-Fondu et al., 1988). Criteria for diagnosis included RDC (Gillin et al., 1981; Puig-Antich et al., 1982; Goetz et al., 1987; Appelboom-Fondu et al., 1988), DSM-III criteria (Lahmeyer et al., 1983; Emslie et al., 1988) and Weinberg criteria (Young et al., 1982). In three studies the entire MDD sample consisted of inpatients (Gillin et al., 1981; Young et al., 1982; Emslie et al., 1988), in three studies the MDD sample was predominantly outpatients (Puig-Antich et al., 1982; Lahmeyer et al., 1983; Goetz et al., 1987) and in one case inpatient status is not reported (Appelboom-Fondu et al., 1988). In some protocols, subjects' bedtimes were variable according to their usual bedtimes at home and subjects were permitted to sleep ad lib in the morning (Puig-Antich et al., 1982; Goetz et al., 1987; Appelboom-Fondu et al., 1988), while in at least one study, time in bed was uniform across all subjects and rigidly controlled (Lahmeyer et al., 1983). There is also considerable variation in definitions of sleep variables – particularly sleep onset and REM latency – among different centers. At least one study examined two different definitions of REM latency and found only minor differences with an alternative REM latency definition (Emslie et al., 1988).

Review of the methodologic differences among these studies does not reveal a conclusive explanation for these discrepant findings. One possible difference with respect to positive REM findings appears to be an association of reduced REM latency with inpatient MDD samples. In the large study by Emslie et al. (1988) with positive REM latency findings all MDD subjects were inpatients. In the study by Gillin et al. (1981) with positive REM latency findings in the adolescent sample, all MDD subjects were inpatients. In the large adolescent study by Goetz et al. (1987) with negative REM latency findings, 42/48 of MDD subjects were outpatients. Only one study in child and adolescent MDD has found reduced REM latency in a predominantly outpatient MDD sample (Lahmeyer et al., 1983). This positive study had a small sample (13 MDD and 13 controls) and reported much longer REM latency values than any other adolescent studies (mean REM latency of 182 min in the normals). In addition, the sleep protocol utilized uniform bedtimes and wake-up times in all subjects, a difference from the other outpatient protocols where bedtimes varied according to the subjects' usual bedtime.

One important difference in the inpatient sample may be the uniformity of sleep and social schedules on the ward; bedtime, wake-up time, meals, and activities are more highly structured on the unit than for most adolescents at home. An alternative possibility is that MDD adolescents who are suicidal (and frequently inpatients) are more likely to show the EEG sleep changes associated with depression. Our group has recently reported on psychobiologic correlates of MDD in children and adolescent which are significantly related to the presence of suicidality (Puig-Antich

1987; Ryan et al., 1988). In that context, we examined the EEG sleep of 27 adolescents with MDD compared to a matched group of 30 rigorously screened, normal adolescent controls while carefully assessing the role of suicidality, inpatient status, severity of illness, comorbidity of other illnesses, and clock time variables. We now report those comparisons.

Methods

Referral and clinical assessment

Adolescents were accepted for screening in the Child and Adolescent Depression Clinic at WPIC if they were reported to appear sad, and/or said they were sad, and/or presented suicidal ideation or behavior. If the result of screening was suggestive of depression, the adolescent was entered into a 2-week diagnostic protocol that included psychiatric, psychosocial, and pediatric assessments, including pediatric history, physical exam and an ECG. Subjects were evaluated using the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS-P) (Chambers et al., 1985), the K-SADS-E (for lifetime diagnosis) (Orvaschel et al., 1982), and a pediatric examination including Tanner staging (Marshall and Tanner, 1969, 1970). Seven to 14 days after the initial evaluation adolescents who met criteria for RDC major depression at the first evaluation had a second K-SADS-P evaluation rating only symptoms from the previous week. All symptom ratings were made by first interviewing the parent(s) alone, then interviewing the adolescent alone. As the interview with the adolescent proceeded summary ratings were determined for every K-SADS-P and K-SADS-E item.

Criteria for inclusion. (1) RDC criteria for non-bipolar MDD at least probable at both K-SADS-P evaluations; (2) Tanner stage III of sexual development; and (3) medically healthy as determined by the pediatrician. Informed consent was obtained from both the adolescent and the parent or guardian.

Criteria for exclusion. (1) Any medication that could produce depressive-like syndromes (e.g., amphetamines, phenothiazines, reserpine, birth control pills) or other medications that could interfere with brain or hypothalamic functioning or sleep. In cases with medications a 2-week wash-out period determined if the adolescents' affective symptoms were primary or secondary to drug intake; (2) significant medical illnesses; (3) obesity (weight/height ratio greater than 95th percentile on the National Center for Health Statistics curve) or significant growth failure (weight or height under the third percentile); (4) clinical seizures or other major neurological illnesses; (5) IQ lower than 70; (6) DSM-III criteria for anorexia nervosa, autism or schizophrenia; and (7) pregnancy or, if sexually active, not using a reliable non-hormonal contraceptive method (in the case of girls).

Suicidal group. In several analyses, adolescents with MDD are divided into suicidal (MDD-S) and non-suicidal (MDD-NS) subgroups. The MDD-S group includes those adolescents who at any point in their current episode rated 4 or more on the K-SADS-P item for suicidal ideation or attempts. The rating of 4 requires that the adolescent often thinks of suicide *and has thought of a specific plan.* This dichotomy is based on prior studies of suicidality of prepubertal MDD children (Puig-Antich, 1987) and adolescents with MDD (Ryan et al., 1988).

Normal control group

Normal adolescents were recruited by word of mouth and newspaper advertising. Normal control adolescents were evaluated with the K-SADS-E, had Tanner staging, a pediatric history and physical examination, and an ECG. Inclusion required no history of a DSM-III axis I disorder as determined by a single K-SADS-E assessment. This assessment included a semi-structured interview with the parent and another with the adolescent. The same criteria for exclusion listed above were also applied to the normal controls. Informed consent was obtained from the parent or legal guardian and the adolescent. All normal adolescents were paid for their participation in this study.

Recording of sleep studies

After acceptance into the study the adolescents were admitted to the Sleep/Neuroendocrine Laboratory. Their sleep was polysomnographically monitored for three consecutive nights. An indwelling intravenous catheter was inserted the

morning after the second night of sleep and remained in place through the third night of sleep for a 24-h endocrine study. All procedures were explained in advance to the subjects in detail, and they had visited the laboratory during the diagnostic protocol.

Electrode placement for a standard polysomnographic recording (Rechtschaffen and Kales, 1968) was carried out 1 h before the subject's stated bedtime. Standard polysomnographic methods were used, as described previously (Puig-Antich et al., 1982). Lights-out times varied from subject to subject, depending on their usual bedtime. In the morning subjects were allowed to sleep ad lib and were not disturbed until they spontaneously awakened. In a few cases in which the subject had not awakened by 8 : 30 a.m. after the second night, he/she was awakened for the intravenous catheter placement for the hormonal studies. A two-way intercom connected the subject's room and allowed for bi-directional communication throughout the night.

Sleep records were scored visually in 30-s epochs by trained technicians using standard methods (Rechtschaffen and Kales, 1968). REM latency was defined as the time from sleep onset (the first 30-s epoch of 20 consecutive min of stage 2, 3, 4, or REM sleep) to the first 30-s epoch of REM followed by 2 min of REM within 25 min. Eye movement activity during REM sleep was scored using a 0–8 semi-quantitative scale (Taska and Kupfer, 1987). Definitions of all other sleep variables are given in a previous publication (Puig-Antich et al., 1982).

Data analysis

Visual examination of the data indicated non-normal distributions in some sleep variables. Statistical tests for normality (Shapiro and Wilk, 1965) were performed on each sleep variable for each night. Where significantly non-normal distributions were found, proper transformations were performed to normalize the data prior to tests of significance.

We next examined the role of night effects because of expected adaptation effects on night one (Agnew et al., 1966; Mendels and Hawkins, 1967; Kupfer et al., 1974) and catheter effects on night three (Adam, 1982; Jarrett et al., 1984). Paired comparisons of sleep variables between nights revealed significant differences in a number of variables and therefore all subsequent analyses were performed using each night separately.

The effects of age, diagnostic group, diagnostic subgroups (suicidality and inpatient status), and interactions were examined with analyses of variance (ANOVAs). Age was found to exert a large effect on many sleep variables and was used as a covariate in all subsequent ANOVAs. Additional ANOVAs compared sleep variables between groups using severity indices of depression as covariates. We also performed analyses examining alternative definitions of REM latency for comparison with other studies. These resulted in only minor changes so only comparisons using the original REM latency definitions are reported here.

Results

Sample

Of the 59 adolescents (28 MDD and 31 normals) entered in the study, two individuals (one with MDD and one normal) had technical difficulties (a power failure) on night two of the study and were excluded from all analyses. As night two is the index night for sleep variables in this study (no adaptation or catheter) missing data on this night meant exclusion from the primary sleep analyses. Six normal adolescents had some missing data from nights one or three and were eliminated from the analyses on those nights and analyses looking at night interactions, but were included in all other analyses.

Within the MDD group, eight individuals had attempted suicide and five non-attempters had suicidal ideation with a definite plan — these 13 adolescents were designated as MDD suicidal (MDD-S). Within the MDD-S group there were 11 inpatients and two outpatients. In the non-suicidal MDD group (MDD-NS) there were two inpatients and 12 outpatients. Comorbidity of the following diagnoses was observed among the MDD adolescents: phobias ($n = 5$); conduct disorder ($n = 6$); separation anxiety ($n = 2$); psychotic subtype ($n = 5$); general anxiety ($n = 2$); and obsessions/compulsions ($n = 1$). By design criteria none of the normal adolescents had present or past history of any axis I diagnoses.

TABLE 1

DEMOGRAPHICS AND SUICIDAL SUBGROUP COMPARISON

	Normal	MDD-NS	MDD-S	*F* test	χ^2	*P* value
Number	30	14	13			
Age (Years) (mean ± SD)	15.0 ± 1.6	15.2 ± 1.5	15.5 ± 1.4	2.1		NS
Sex (M/F)	13/17	5/9	6/7		0.5	NS
Race (Caucasian/Black)	30/0	12/2	10/3		7.8	NS
Patient status (in/out)	-	2/12	11/2		13.4	0.0003
Psychotic (yes/no)	-	1/13	4/9		2.5	NS
RDC endogenous (yes/no)	-	9/5	13/0		5.7	0.01
Bipolar/non-bipolar	-	1/13	3/10		1.3	NS
Depression severity (mean for 11 items) (mean ± SD)	-	3.2 ± 0.5	3.6 ± 0.6	0.0		NS
Extracted Hamilton (suicide item removed) (mean ± SD)	-	21 ± 6	24 ± 7	1.8		NS
K-GAS (mean ± SD)	-	51.6 ± 4.6	45.8 ± 17.5	1.0		NS

The MDD group contained two subjects diagnosed as bipolar at the entry of the study and two others who became bipolar within the treatment period immediately following the study; all met criteria for a depressive episode at the time of the study. No other adolescents became bipolar during their current episode. Additional analyses were performed with these four bipolar individuals separated from the rest of the MDD group.

Demographic statistics for this sample are presented in Table 1. There were no significant group differences for age, sex, or race among the three groups (MDD-NS, MDD-S, and normals). Comparisons between the suicidal and non-suicidal subgroups revealed no significant differences for the following variables: depression severity as rated by the 11-item K-SADS depression scale (12-item score with rating for suicidality excluded), depression severity as rated by extracted Hamilton Rating Scales (Endicott et al., 1981) with the suicidal item excluded, K-GAS scores, psychotic subtype, bipolar subtype, or percentage of patients exhibiting individual RDC symptoms (depressed mood, guilt, anhedonia, fatigue, psychomotor retardation, psychomotor agitation, insomnia, hypersomnia, anorexia, and increased appetite). There were more endogenous subtypes in the suicidal group ($P < 0.01$) and the majority of the suicidal adolescents were inpatients ($P < 0.0003$).

Age effects

Age was found to be an important covariate for a number of sleep variables even within the narrow range of this study (age 12.4–17.8 years). Increasing age was associated with decreased stage 4 time ($P < 0.0001$), decreased REM period latency ($P < 0.05$), decreased total sleep time ($P < 0.01$), decreased REM efficiency ($P < 0.001$), and decreased non-REM efficiency ($P < 0.05$). Age was also positively correlated with awake time ($P < 0.05$), duration of stage 1 ($P < 0.001$), and REM fragmentation index for REM periods 1 and 2 ($P < 0.01$ and 0.01). The magnitude of these effects is illustrated for stage 4 sleep in Fig. 1.

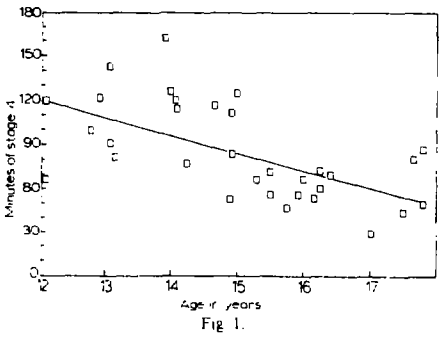

Fig. 1.

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TABLE 2

ANOVA WITH AGE AS COVARIATE FOR SLEEP VARIABLES COMPARING NORMALS WITH THE ENTIRE MDD GROUP

Time (min)	MDD (n = 27) Mean ± SD	Normal (n = 30) Mean ± SD	Group		Age	
			F	P	F	P
Sleep latency,						
mean 3 nights	25.0	21.3				
Night 1	27.9 ± 13.5	20.6 ± 9.9	3.0	NS (0.09)	2.8	NS (0.10)
Night 2	24.6 ± 17.2	18.4 ± 10.6	2.0	NS (0.16)	0.0	NS
Night 3	22.9 ± 19.2	23.6 ± 13.8	0.8	NS	0.7	NS
Total sleep time,						
mean 3 nights	447.0	453.1				
Night 1	447.0 ± 38.0	448.5 ± 46.7	0.0	NS	0.7	NS
Night 2	457.5 ± 26.5	459.1 ± 24.9	0.0	NS	4.4	0.04
Night 3	433.1 ± 37.6	451.5 ± 33.1	3.6	NS (0.06)	1.2	NS
Awake time,						
mean 3 nights	14.1	14.1				
Night 1	15.8 ± 13.5	15.5 ± 29.8	0.8	NS	2.9	NS (0.09)
Night 2	9.2 ± 7.7	8.8 ± 5.8	0.0	NS	5.0	0.03
Night 3	18.5 ± 20.5	18.8 ± 13.0	0.0	NS	0.0	NS
Stage 1,						
mean 3 nights	19.7	18.6				
Night 1	23.1 ± 13.7	18.1 ± 8.2	2.0	NS (0.16)	4.6	0.04
Night 2	17.3 ± 9.6	17.0 ± 11.0	0.0	NS	13.1	0.001
Night 3	19.3 ± 11.4	22.4 ± 12.5	1.0	NS	2.5	NS (0.12)
Stage 2,						
mean 3 nights	216.4	226.0				
Night 1	225.4 ± 27.5	225.3 ± 37.3	0.1	NS	3.0	NS (0.09)
Night 2	223.6 ± 33.3	225.0 ± 37.5	0.1	NS	1.7	NS
Night 3	207.3 ± 35.8	223.3 ± 34.8	3.2	NS (0.08)	0.3	NS
Stage 3,						
mean 3 nights	35.3	30.6				
Night 1	33.4 ± 19.8	32.3 ± 18.9	0.0	NS	0.0	NS
Night 2	36.4 ± 20.7	30.5 ± 13.3	1.5	NS	0.4	NS
Night 3	35.7 ± 18.9	30.6 ± 15.6	1.3	NS	0.1	NS
Stage 4,						
mean 3 nights	76.9	80.0				
Night 1	76.6 ± 27.1	85.6 ± 36.0	0.3	NS	18.0	0.0001
Night 2	74.5 ± 31.2	83.2 ± 32.4	1.0	NS	24.5	0.0000
Night 3	72.6 ± 31.8	75.3 ± 30.9	0.1	NS	9.3	0.004
Stage REM,						
mean 3 nights	98.6	97.8				
Night 1	87.9 ± 28.0	87.4 ± 25.4	0.0	NS	0.1	NS
Night 2	105.5 ± 24.0	101.5 ± 18.8	0.5	NS	0.1	NS
Night 3	98.0 ± 23.7	98.2 ± 18.7	0.0	NS	0.1	NS
Number of REM periods,						
mean 3 nights	4.5	4.4				
Night 1	4.4 ± 0.7	4.2 ± 1.0	1.4	NS	0.2	NS
Night 2	4.7 ± 0.9	4.4 ± 0.7	1.9	NS (0.17)	0.3	NS
Night 3	4.3 ± 0.7	4.4 ± 0.5	1.1	NS	0.1	NS

TABLE 2 (continued)

Time (min)	MDD ($n = 27$) Mean ± SD	Normal ($n = 30$) Mean ± SD	Group		Age	
			F	P	F	P
REM period latency,						
mean 3 nights	94.5	99.0				
Night 1	97.9 ± 40.5	104.0 ± 59.0	0.7	NS	4.4	0.04
Night 2	87.9 ± 45.0	99.7 ± 52.6	0.5	NS	6.0	0.02
Night 3	98.0 ± 52.2	94.1 ± 40.9	0.2	NS	5.3	0.02
REM density,						
mean 3 nights	1.23	1.23				
Night 1	1.24 ± 0.26	1.21 ± 0.40	0.3	NS	0.4	NS
Night 2	1.29 ± 0.29	1.17 ± 0.29	2.5	NS (0.12)	0.4	NS
Night 3	1.17 ± 0.29	1.29 ± 0.26	2.0	NS (0.16)	0.0	NS

NS, not significant at $P < 0.05$ level.

Stage 4 decreased by 12.0 min/year in this sample. The same scatter graph for REM period latency indicates a decrease of 12.6 min/year of age. There were no significant age by diagnosis interactions.

Night effects

A comparison between night one (the adaptation night) and night two (the index night) revealed more awake time ($P < 0.05$), more stage 1 sleep ($P < 0.05$), and less stage REM ($P < 0.01$) during the adaptation night. Comparison of night three (the catheter night) with night two indicated more awake time ($P < 0.01$) and more stage 1 ($P < 0.01$) on night three. There were no significant night by diagnosis interactions in the analyses comparing the entire MDD group to the normal controls. In the subgroup analyses, however, there were night effect interactions with the inpatient (and suicidal) subgroups showing smaller adaptation night effects (night 1 vs. night 2) compared to the outpatients and normal controls.

Because of the effects of night order, the presentation of further analyses will focus primarily on night two. Except where noted, analyses from nights one and three tend to confirm the findings from night two.

Major depression versus normals

Table 2 shows the results of ANOVA (using age as a covariate) performed on each sleep variable, for each night separately, comparing the entire MDD group with the normal control group. These comparisons revealed no significant diagnostic group differences for any of the major sleep variables including REM latency, REM density, REM time, delta sleep time, or sleep efficiency. In addition to the ANOVAs, we performed chi-square comparisons of the number of individuals in each group with REM period latencies shorter than cutoff values of 60 and 75 min; we examined each night separately as well as the shortest value of all three nights, and there were no significant group differences. Values for night two, using the 60-min cutoff, were 9/27 of the MDD group with a REM latency less than 60 min compared to 9/30 of the control group.

We also examined the data for group differences in chronobiologic variables: comparing the *clock time* of lights out, sleep onset, REM onset, and final awake time. The only diagnostic group difference was an earlier clock time of final awake on night one in the MDD group compared to the normal controls ($P < 0.05$).

Suicidality

Based on the results of neuroendocrine studies in our group indicating growth hormone secretory differences associated with the presence of suicidality in adolescents, additional analyses were performed with the MDD group divided into suicidal (MDD-S) and non-suicidal (MDD-NS) subgroups (by the presence of at least one suicidal attempt or a definite suicidal plan during the

TABLE 3

ANOVA WITH AGE AS COVARIATE FOR NORMAL vs. MDD-S AND -NS SUBGROUPS; NIGHT TWO (INDEX NIGHT)

Time (min)	Normal ($n = 30$) Mean ± SD	MDD-NS ($n = 14$) Mean ± SD	MDD-S ($n = 13$) Mean ± SD	Group F	P
Sleep latency [a]	18.4 ±10.6	18.1 ± 9.3	31.6 ±21.1	3.6	0.03
Awake [a]	8.8 ± 5.8	9.7 ± 5.3	8.8 ± 9.8	0.1	NS
Total Sleep	459.1 ±24.9	459.5 ±21.0	455.4 ±32.2	0.0	NS
Stage 1	16.9 ±11.2	16.7 ±10.4	18.4 ± 9.2	0.0	NS
Stage 2	225.0 ±37.5	225.5 ±36.4	221.6 ±31.0	0.1	NS
Stage 3 [a]	30.5 ±13.3	39.5 ±24.1	33.1 ±16.6	1.2	NS
Stage 4	85.2 ±33.0	81.0 ±30.6	67.6 ±31.4	1.0	NS
Stage REM [a]	101.5 ±19.9	96.9 ±26.0	114.8 ±18.2	2.8	NS (0.07)
REM period latency [a]	99.7 ±52.6	103.0 ±53.5	71.6 ±26.9	1.5	NS
REM density	1.17± 0.31	1.22± 0.30	1.38± 0.28	2.2	NS (0.09)

[a] Values are actual mean ± SD for comparison purposes, transformations were performed prior to tests of significance.

current episode). The same ANOVAs with age as a covariate were performed. Results of these analyses for summary sleep variables are shown in Table 3.

The suicidal subgroup had significantly longer sleep latencies than the MDD-NS and the normal control group ($P < 0.05$). Findings of reduced REM latency, increased stage REM, and increased REM density in the MDD-S group did not reach the $P < 0.05$ level in three-way comparisons.

Further analyses were performed subdividing the suicidal MDD group according to presence of a suicidal attempt, number of attempts, and perceived lethality of attempts by scores on the K-SADS. The numbers of subjects in each category were small but no clear relationship emerged between estimates of 'severity' of suicidality and sleep variable changes in this sample.

Results in the non-bipolar group

Although all MDD individuals met criteria for a depressive episode at the time of the study, two individuals were diagnosed as having a bipolar illness at the initial evaluation and two more adolescents (initially diagnosed as non-bipolar) became bipolar within the initial treatment period of the study. These four individuals were removed from the MDD group and all previous analyses were repeated. The overall findings were unchanged, however the magnitude of the REM differences increased with the bipolar subjects removed (Table 4). Mean REM period latency (on night two) in the MDD-S non-bipolar group was 65.2 ± 12.4 min compared to 106.4 ± 54.1 min in the MDD-NS non-bipolar group and 99.7 ± 52.6 min in the normal control group ($P = 0.07$). REM density comparisons with the bipolar subjects removed revealed REM density in the MDD-S group

TABLE 4

REM VARIABLES FOR NORMAL vs. MDD-S AND -NS SUBGROUPS WITH BIPOLARS REMOVED; NIGHT TWO

	Normal ($n = 30$) Mean ± SD	MDD-NS ($n = 13$) Mean ± SD	MDD-S ($n = 10$) Mean ± SD	F	P
Stage REM (min)	101.5 ±19.9	98.3 ±26.5	115.1 ±14.3	2.2	0.13
REM period latency (min)	99.7 ±52.6	106.4 ±54.1	65.2 ±12.4	2.6	0.08
REM density	1.17± 0.31	1.25± 0.30	1.42± 0.15	3.3	0.05

Values are actual mean ± SD for comparison purposes, transformations were performed prior to tests of significance.

of 1.42 ± 0.15 vs. 1.25 ± 0.30 in the MDD-NS and 1.17 ± 0.29 in the normals ($P < 0.05$).

Depression severity and comorbidity

We explored the possibility that depression severity contributed to the differences found in the suicidal adolescent group. As shown in Table 1, there were no differences (excluding suicide) between the MDD-S and the MDD-NS by the mean depression severity score or extracted Hamilton Depression Rating Scale (HDRS) scores (Endicott et al., 1981). The mean severity score was examined as a covariate in reanalyses of the major sleep variables and was not found to be a significant covariate for any of these variables.

Analyses examining the role of severity were also repeated with the four bipolar subjects removed, again failing to find significant differences. The mean extracted HDRS in the non-bipolar MDD-S group (with the suicidal item removed) was 24 ± 8, and in the non-bipolar MDD-NS was 21 ± 6.

We further examined depression severity by individual symptom. There were no significant differences between the MDD-S and the MDD-NS groups in the percentage of patients exhibiting any individual RDC symptom of depression (except suicidality). Analyses were also performed looking at the presence and severity of each symptom and at each individual sleep variable. The only significant findings were that the MDD adolescents with complaints of insomnia had significantly less stage 4 sleep (but no differences in total sleep, sleep efficiency, or sleep continuity measures) than non-insomniac individuals ($P < 0.05$). Conversely the MDD adolescents with complaints of hypersomnia had significantly more stage 4 sleep than the MDD adolescents with a negative history for hypersomnia ($P < 0.05$).

In addition to severity and individual symptoms of depression, we also explored the role of comorbidity of other psychiatric disorders. There were no differences in the rates of comorbidity of any other diagnosable illnesses in the subgroup of MDD-S adolescents compared to MDD-NS; further, none of the comorbid diagnoses was found to be a significant covariate for any sleep variable. We also compared the subgroup with psychotic features ($n = 5$) with non-psychotic subjects and controls; again there were no significant sleep variable differences.

Inpatient status

Within the suicidal group, 11 of the 13 subjects were inpatients at the time of sleep studies (but came into the Child and Adolescent Sleep Lab for the three nights of the studies); in the non-suicidal group, only two of the 14 subjects were inpatients at the time of the studies. Because of the overlap between the inpatient and suicidal groups, the results of comparisons split on inpatient status are essentially identical to the MDD-S/MDD-NS split (REM latency values in the inpatient MDD group were 73 ± 21 min vs. 72 ± 27 min in the MDD-S group). The small number of outpatient suicidal and inpatient non-suicidal patients makes it impossible to delineate the role of inpatient status vs. suicidality in this sample.

Endogenous subtype

All MDD-S subjects and nine of 14 MDD-NS subjects met RDC for endogenous subtype. Analyses of the MDD subgroup divided by endogenicity revealed trends similar to those findings in the suicidal and inpatient splits, however all of the subgroup differences were smaller for the endogenous split and failed to reach statistical significance.

Discussion

Our findings indicate that EEG sleep variables in the MDD adolescents taken as a whole were not significantly different from those in normal control adolescents. Age, suicidality, and inpatient status were all found to be important covariates for the major sleep variables. Subgroup analyses suggest that the non-bipolar MDD adolescents with suicidality and/or inpatient status have reduced REM latency, increased REM density, increased stage REM, and longer sleep latency compared to the normal controls. Given the number of comparisons performed in the analysis of this study and the borderline statistical significance of the findings, there is a possibility that these subgroup differences may have occurred by chance. On the other hand, these changes occurred in

expected sleep variables, in the expected direction, and they are consistent with results from previous studies. Failure to reach the $P < 0.05$ level in the three-way group comparisons for REM latency may in part be the result of the large variance in the sleep measures combined with a relatively small sample size in the subgroups. Paired comparisons of REM latency values between MDD-S and normals produce P values below 0.05 — consistent with the interpretation that if our study had contained only the suicidal or inpatient samples, we would have reported significantly reduced REM latency in our MDD group. Severity of depression, severity of suicidal behavior, and comorbidity of other illnesses, all failed to explain the findings in this group. The relative roles of suicidality and inpatient status cannot be determined in this sample because of the considerable overlap between the groups.

These findings appear to be consistent with previous sleep studies in depressed adolescents. The subgroup differences in our sample may explain some discrepancies among the previous studies with respect to REM latency results. In the large sample study by Emslie et al. (1988) with positive REM latency findings, the MDD sample contained *all inpatients* with REM latency values in their adolescent MDD group of 78.8 ± 27 min. REM latency values in *our inpatient* MDD adolescents were 73.0 ± 21 min (for comparison purposes we also determined REM latency values in our sample using *their* definition of REM latency resulting in values in our inpatients of 77.2 ± 23 min). Using the same REM latency definitions gives values in our adolescent controls of 104.8 ± 53 min, similar to the Emslie et al. adolescent controls of 112.1 ± 34 min. Comparison with the other large adolescent study (Goetz et al., 1987), again using the same REM latency definitions, reveals similar REM latency values in our MDD *outpatients* of 100.5 ± 55 min, as in their MDD adolescent sample (42 out of 48 were *outpatients*) with REM latency values of 97.6 ± 54 min. In the Goetz et al. study, as in our current paper, severity of illness was carefully assessed and was not found to have significant correlations with any of the REM or sleep continuity variables. In the Appleboom-Fondu et al. (1988) report, inpatient status was not specified, nor was the definition of REM latency: they reported REM latency values of 78 ± 36 min in their adolescent MDD group and 95.5 ± 39 min in their adolescent control group. The study by Gillin et al. (1981) did not give exact values for REM latency within the adolescent sample; the studies by Puig-Antich et al. (1982) and Young et al. (1982) contained only samples of prepubertal children.

Only one published study has reported REM latency in a predominantly outpatient sample of MDD adolescents (Lahmeyer et al., 1983). These authors also explored the role of severity of depression (based on Hamilton scores) and found no correlation between REM latency and depression severity in their sample ($r = 0.057$). One methodologic difference in their study was the control of sleep times in the adolescents. In our protocol, as in the previously described studies, the outpatients (and normals) had bedtime and wake-up time in the lab according to their usual home schedule. In the Lahmeyer et al. protocol all individuals were put to bed and awakened at the same time: 10.00 p.m. to 8.00 a.m. This methodologic difference may also explain the extremely long REM latencies found in this study (mean of 182 ± 68 min in the controls, 122 ± 54 min in the MDD group). Adolescents accustomed to a later bedtime shifting to an earlier sleep time in the protocol may have contributed to the very long REM latencies found in this study. The long sleep latency and low sleep efficiency reported in this study are also consistent with the interpretation that some adolescents were studied on a phase-advanced schedule in the protocol. An alternative possibility is that the rigid and uniform bedtimes may have contributed to the positive findings by controlling circadian entrainment variables. Carefully controlling variability in social schedules and sleep times may be necessary to detect subtle disturbances in the regulation of sleep in adolescent MDD subjects.

Two controlled studies with *prepubertal* MDD samples reported negative REM findings during the depressive episode (Puig-Antich et al., 1982; Young et al., 1982). The latter recorded inpatient subjects (suicidal status is not reported). These findings may indicate that in very young MDD subjects sleep changes are not evident even in the inpatient samples. There were, however, prepu-

bertal children in the positive Emslie et al. (1988) study and separate analyses within the prepubertal sample in this study also revealed the same positive REM findings. Another possible reason for the negative results in the inpatient study by Young et al. (1982) was the use of Weinberg criteria for diagnosis, as all of the other reports used DSM-III criteria (Lahmeyer et al., 1983; Emslie et al., 1988) or RDC (Gillin et al., 1981; Puig-Antich et al., 1982; Goetz et al., 1987).

Our findings and review of previous studies suggest that inpatient status and/or suicidality and age interact in MDD adolescents to produce REM latency changes similar to those described in adult depression. These findings must be replicated with larger samples of subgroups according to suicidality and inpatient status. Further research must also be directed at disentangling the role of suicidality vs. inpatient status.

We initially focussed on the suicidality component of these subgroup sleep differences based on our previous findings of psychobiologic changes within the subgroup of suicidal adolescents (Puig-Antich et al., 1987; Ryan et al., 1988). Growth hormone (GH) response to desipramine was significantly decreased in MDD adolescents with suicidal ideation or attempts (Ryan et al., 1988). In that study, severity of depression or the presence of depressive symptoms did not predict GH secretion within the depressed group. The data from that study support the hypothesis that suicidality per se is the important variable in GH secretion, and that differences in GH secretion to desipramine are probably related to differences in CNS β-adrenergic and/or serotonergic function associated with suicidality (Ryan et al., 1988).

An alternative interpretation is that these subgroup differences are directly related to some aspect of the hospitalization process, such as the uniform control of social schedules and sleep times. This possibility is supported by the positive REM findings in the outpatient study by Lahmeyer et al. (1983) which used control of bedtime and wake-up time in outpatients and controls. Inpatient status may also influence adaptation effects to the laboratory studies. Our *outpatients demonstrated larger adaptation effects in the laboratory.* On night one, the outpatients had more awake time (22 ± 5 vs. 8 ± 5 min, $P < 0.005$), less total sleep (434 ± 38 vs. 463 ± 33 min, $P < 0.05$) and less REM sleep (71 ± 22 vs. 107 ± 20 min, $P < 0.005$) than the inpatients. On night two the outpatients showed improved sleep while the inpatients showed only slight changes, resulting in no group differences in these variables on night two. It is not surprising that the outpatients show more sleep disruption on night one than the inpatients. The outpatients (and the normal controls) are adapting to the changes from home to the sleep lab. The inpatients are adapting to the change from the ward to the sleep lab, often reported as a change to a quieter, less stressful, more private and comfortable environment. In preliminary interviews with adolescents, they reported a few days of subjectively poor sleep in their initial adaptation to the ward and described sleeping better in the quiet lab, despite the presence of the EEG wires. In these cases, we may actually be comparing recovery sleep in inpatients to adaptation sleep in the outpatients and the normals. In addition, adaptation effects may persist longer than the 'one adaptation night' used in most sleep studies. In a study of 100 normal healthy children aged 6–16, measuring three consecutive nights of sleep, REM time, REM activity and sleep efficiency continued to increase across nights two and three (Coble et al., 1984). Another study of normal children, designed to examine the effects of IQ on sleep, reported a linear increase in REM sleep, REM percentage and number of REM periods across five consecutive nights of sleep recordings (Busby and Pivik, 1983). In addition, many adolescents have to shift from previously late night and erratic sleep schedules to the uniform early hours on the ward. This active process of entraining to the ward routine could have further influences on the regulation of sleep as later measured in the lab and compared to outpatients and normals who are coming to the lab, and sleeping in the lab, *on their own schedule.*

Further studies must focus specifically on these issues. Suicidality, inpatient status, sleep disturbances during adaptation, and circadian entrainment variables must be carefully controlled in order to further understand the changes in sleep regulation in child and adolescent MDD.

Acknowledgements

This work was initially supported by Grant MH40289 (to Dr. J. Puig-Antich) and the Mental Health Clinical Research Center Grant MH30915 to WPIC, from the National Institute of Mental Health. We gratefully acknowledge the statistical consultation of Satish Iyengar, Ph.D. and the assistance of Deborah Small in the preparation of the manuscript.

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DEPRESSION AND ANXIETY 7:32–39 (1998)

FLUOXETINE IN CHILD AND ADOLESCENT DEPRESSION: ACUTE AND MAINTENANCE TREATMENT

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The objective was to present naturalistic 1-year follow-up information of 96 child and adolescent outpatients with major depressive disorder who had been randomized in an 8-week double-blind, placebo-controlled trial of fluoxetine.

Subjects were children and adolescents, ages 8-18 years, who were entered in a randomized clinical trial of fluoxetine. Following the acute treatment trial, treatment was not controlled. At 6 months and 1 year, the subjects and parents were interviewed using the Kiddie Longitudinal Interval Follow-up Evaluation (K-LIFE) for course of depression.

Eighty-seven of the 96 subjects were followed for 1 year. Of these, 74 (85%) recovered from the depressive episode during that time (47 on fluoxetine, 22 on no medication, and 5 on other antidepressants or lithium). Twenty-nine of the subjects (39%) who recovered had a recurrence of depression during the 1-year follow-up, with 55% of these occurring within 6 months.

Results of this study are similar to adult studies, with respect to response and recovery of depressive episodes. Most patients (85%) recover from the episode within 1 year, but approximately 40% have a recurrence within 12 months, which is a higher recurrence rate than in adults. Recovery was associated with younger age, lower severity of depressive symptoms, higher family functioning, and fewer comorbid diagnoses. Recurrence, which occurs both on and off medication, was difficult to predict, as there was little clinical data associated with recurrence in this population. Depression and Anxiety 7:32–39, 1998. © *1998 Wiley-Liss, Inc.*

Key words: *depression; children; adolescents; fluoxetine; recovery; recurrence*

INTRODUCTION

Depressive disorders are a leading cause of morbidity and mortality in the pediatric age group (Fleming and Offord, 1990; Brent, 1987; Pfeffer et al., 1991). The prevalence of depressive disorders in children and adolescents ranges from 0.4% to 8.3% (Burke et al., 1991; Fleming and Offord, 1990; Kashani et al., 1987a,b; Lewinshon et al., 1986, 1993, 1994), and is greater in adolescents than in children. A recent paper reports on the results of structured diagnostic interviews of 1,285 children and adolescents in the Methods for the Epidemiology of Child and Adolescent Mental Disorders (MECA) study. Shaffer et al. (1996) highlight some of the reasons for differences in reported prevalence rates of depression and other disorders. In the MECA study, the prevalence rates for Major Depressive Disorder (MDD) and any depressive disorder ascertained by structured interview ranged from 1.1% to 7.1% and 1.2% to 8.8%, respectively. These differences reflected a variety of information sources (parent, child, or both) and differing levels of impairment required to make the diagnosis. In the MECA study, requiring the child to meet diagnostic criteria based on structured interviews of both

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Contract grant sponsor: NIMH; Contract grant numbers: MH39188, K07-MH01057-01A2; Contract grant sponsor: Celeb C. and Julia W. Dula Education and Charitable Foundations: Contract Grant Sponsor: Mr. and Mrs. Woody Hunt; Contract Grant Sponsor: Cimmaron Foundation; Contract Grant Sponsor: Mr. and Mrs. Morton Myerson; Contract Grant Sponsor: Azoulay Family

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Received for publication 16 December 1997; Accepted 17 December 1997

parent and child and have diagnosis specific impairment, and a Children's Global Assessment Scale (CGAS) score ≤ 70 led to a prevalence of MDD and any depressive disorder of 4.9% and 6.2%, respectively. This prevalence compares with adults (Kessler et al., 1994) where 12-month prevalence of MDD is reported to be 10.3% ± 0.8% (12.9% ± 0.8% females and 7.7% ± 0.8% males).This finding also highlights the gender differences. MDD in children appears to occur at approximately the same rate in girls and boys with the approximately 2:1 ratio becoming evident in adolescents (Emslie et al., 1990).

For adults, the efficacy of antidepressant medications for MDD is well established (Baldessarini, 1989; Depression Guideline Panel, 1993). No one antidepressant is clearly more effective than another, except that MAOIs are more effective than TCAs for depression with atypical features (Thase et al., 1995; Depression Guideline Panel. 1993). A meta-analysis of all available placebo-controlled trials (n = 12) of TCAs in patients between 6-18 years concluded that the difference between active treatment and placebo is too small to be clinically significant (Hazell et al., 1995). This lack of efficacy, as well as the prevalence of side effects of more noradrenergic antidepressants, has led to an increased interest in the selective serotonin reuptake inhibitors (SSRIs) in children and adolescents.

Fluoxetine is the best studied of SSRIs in depressed children and adolescents, though studies with sertraline and paroxetine are ongoing. Reports of SSRIs for depression in this age group include two double-blind placebo-controlled studies (Simeon et al., 1990, Emslie et al., 1998), two studies of "treatment-resistant" depression with fluoxetine (Boulos et al., 1992; Ghazuiddin et al., 1995), two retrospective chart reviews (Jain et al., 1992; Tierney et al., 1995), one with fluoxetine and one with sertraline, and one open study of depressed inpatients with sertraline (McConville et al., 1996). In these uncontrolled studies, response rates varied from 64% to 74%.

In a placebo-controlled double-blind study of fluoxetine (20-60 mg/day), Simeon et al. (1990) found no difference between fluoxetine and placebo in overall response rate. A full description of the methodology has not been published, however, making it difficult to interpret the results. Of the 40 (20/20) subjects randomized, 15/20 in each group completed the study; 10/15 of the subjects in each group, active drug and placebo, showed mild to moderate improvement, i.e., 50% (20/40) of those randomized responded. Fluoxetine was superior to placebo in all clinical measures except sleep by 5 weeks, but the differences were not statistically significant. Perhaps with a larger sample, and a longer period to wash out responders to nonspecific interventions, the study would have been positive.

Recently, Emslie et al. (1997a) reported the results of a double-blind placebo-controlled study of fluoxetine. Subjects were 96 outpatients (age 8 to 18 years) with MDD, who were randomized to fluoxetine 20 mg or placebo following a four-visit, 3-week evaluation. Of the 96 subjects randomized, 27/48 (56%) were rated as much or very much improved on fluoxetine as compared to 16/48 (33%) on placebo ($P = 0.02$). Weekly measures of depression severity (CDRS-R) were statistically different between the groups by week 5.

Response to acute treatment alone does not necessarily mean patients are asymptomatic. Full or partial recovery from the episode is also an important outcome. Recovery from an index episode of major depression is remarkably consistent across samples, independent of treatment, with over 90% of depressed child and adolescent outpatients (Kovacs et al., 1984a; McCauley et al., 1993), child and adolescent inpatients (Strober et al., 1993; Emslie et al., 1997), and 1 to 2 years. In two of these samples (Keller et al., 1991; Kovacs et al., 1984a), recovery occurred with minimal treatment in the majority of subjects.

Once recovered, however, depressed children and adolescents have a high rate of recurrence of their depression. Earlier studies assessed outcome primarily cross-sectionally. When reevaluated 6 to 7 years later, depression remained a problem in 40% to 50% of clinical patients (Asarnow et al., 1988; Eastgate and Gilmore 1984; Goodyer et al., 1991; Poznanski et al., 1976) and around 25% of nonreferred community samples (Fleming et al., 1993; McGee and Williams, 1988). Recurrences (new episodes of depression) are reported in 54-72% of depressed children and adolescents followed for 3-8 years, with similar rates in inpatients (Garber et al., 1988; Emslie et al., 1997) and outpatients (Kovacs et al., 1984b; McCauley et al., 1993; Rao et al., 1995).

In adults, Keller et al. (1992), in a 5-year prospective follow-up of 431 subjects, found 88% had recovered by 5 years. Fifty percent of the subjects recovered within the first 6 months, and after 6 months, the rate of recovery declined markedly. Similarly, Coryell et al. (1994) noted recovery occurring in 60% by 6 months and 80% by 1 year. Keller et al. (1982) reported on recurrences in 75 adults with MDD who had recovered from their index episode. Within one year, 16 (21%) met RDC criterion for a subsequent major depressive episode.

Factors predicting recurrence in adults include three or more previous episodes (Keller et al., 1982; Maj et al., 1992), severity of index episode (Gonzales et al., 1985), psychotic features (Schatzberg and Rothschild, 1992; Copeland, 1983), psychosocial factors, early age of onset of illness, and double depression (defined as a major depressive disorder superimposed on dysthymic disorder; Gonzales et al., 1985; Keller et al., 1983). In children, older age, race, psychotic disorder, and severity of symptoms predicted recurrence (Emslie et al., 1997).

As a result of the episodic nature of depression, studies of continuation and maintenance treatment for depressive disorders in adults have been conducted over the last several years. In adults, prophylactic drug treatment reduces the risk of relapse and recurrence of depressive episodes compared to no treatment (Frank

et al., 1990). Further, continued treatment appears to reduce the severity of subsequent episodes (Maj et al., 1992). Whether this is the same for children and adolescents is not known. The general consensus has been to continue treatment for at least 4 to 6 months (Cook et al., 1986; Montgomery, 1994a,b, 1996; Montgomery et al., 1991) following acute treatment response. Most (Depression Guidelines Panel, 1993; Stokes, 1993) suggest that patients should continue full-dose continuation therapy for 6 to 9 months following complete remission to prevent relapse. Other studies suggest as long as 1 to 5 years of continued treatment (Nemeroff, 1994; Kupfer, 1993; Kupfer et al., 1992). Unfortunately, as most acute treatment studies with depressed children and adolescents have been negative, no long-term continuation treatment studies have been reported on this age group.

This paper reports on the 12-month naturalistic follow-up of 96 depressed children and adolescent who completed the above-mentioned 8-week, double-blind placebo-controlled, acute phase treatment trial of fluoxetine (Emslie et al.,1998). This paper examines acute response, recovery from the index episode, and subsequent recurrences in this population. The paper also examines clinical and demographic factors which could predict recovery and recurrence. Follow-up treatment was not controlled; however, a subsample of patients (n = 35) who underwent at least 4 months of subsequent continuation phase treatment with fluoxetine were evaluated for effects of medication treatment on outcome over a naturalistic 1-year follow-up.

METHODS

Subjects included in this study were all subjects who had been randomized in a double-blind placebo-controlled trial of fluoxetine. The method for the initial evaluation has been previously described (Emslie et al., 1997a). In summary, the subjects were child and adolescent outpatients (ages 7-18 years) who met DSM-III-R criteria for nonpsychotic MDD single or recurrent. They were in good general medical health and of normal intelligence. Subjects with Bipolar I or II Disorder, psychotic depression, alcohol and substance abuse (within the past year), anorexia or bulimia (lifetime), or previous adequate treatment with fluoxetine were excluded. Additionally, any subjects with at least one first -relative with Bipolar I disorder were excluded.

Evaluation for inclusion in the double-blind study took place over three consecutive weekly visits. Prior to the initial interview, the study was explained and written informed consent was obtained from the parent(s) and assent from the patient. At the initial visit, each patient and parent(s) were interviewed separately using the Diagnostic Interview for Children and Adolescents (DICA; Herjanic and Reich, 1982; Reich et al., 1982), a semistructured DSM-III-R based diagnostic interview to establish that the patient met DSM-III-R criteria for MDD and to identify other concurrent and lifetime psychiatric disorders. Additionally, MDD criteria symptoms and depressive symptom severity were assessed using the depressive items of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS: Chambers et al., 1985) and the Children's Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1984), respectively. Overall, social functioning was assessed using the Children's Global Assessment Scale (CGAS; Shaffer et al., 1985) and global family functioning was measured using the Family Global Assessment Scale (FGAS; Mrazek, 1985).

Following the initial interview, the patients were seen for two additional interviews. The patients and parent(s) were interviewed separately by an experienced clinician on each visit, with each interview separated by 1 week. These clinicians independently reviewed the DICA diagnosis and scored the K-SADS depressive items and completed the CDRS-R. The course of illness, including the number, length, and timing of prior and current episodes were established during these interviews.

Final consensus diagnoses were determined following visit three in a weekly diagnostic conference, utilizing information from all three interviews. Following the completion of the evaluation period, appropriate subjects were then entered into a 1-week single-blind, placebo run-in prior to being randomized to fluoxetine 20 mg/day or placebo. Following randomization, the patients were seen weekly for 8 weeks. To be randomized, patients had to continue to meet criteria for MDD, have a CDRS-R score of > 40, and meet above inclusion/exclusion criteria. Response to treatment following randomization was determined by the Clinical Global Impression (CGI) improvement score, as assessed by clinician, with a 1 "very much improved" and 2 "much improved" being used to determine response. Response was further assessed by weekly CDRS-R scores.

FOLLOW-UP

The method for follow-up has been described previously in an inpatient sample (Emslie et al., 1997b). On exiting the acute treatment trial, patients were given the option of continuing blind on study medication or being treated openly. Most nonresponders were treated openly with fluoxetine.

Patients were followed for 12 months following the end of acute treatment. Treatment was not controlled and information collected was primarily a naturalistic follow-up of patients completing the acute trial.

Systematic assessment of clinical course was conducted at 6 and 12 months following end of acute treatment. Patients and parents were interviewed using the Kiddie-Longitudinal Interval Follow-Up Evaluation (K-LIFE), a modification of the LIFE (Keller et al., 1987). During the interview, course of depressive symptoms were assessed during the previous 6 months. Additionally, comorbid diagnosis and treatment were assessed. The severity of MDD during the follow-up period was coded using the criteria in the K-LIFE (6 = severe, 5 = definite criteria, 4 = marked symptoms, 3 = partial re-

mission, 2 = residual symptoms, 1 = usual self). Changes in status, i.e., change in MDD rating, improvement or development of other disorders or treatment, were coded by dates. When this change was approximately identified, then the midpoint of that time was used as the change point, e.g., patient met criteria for MDD again in mid-September was coded September 15th. Episode length, time to recovery, etc., were all coded in days.

For describing the course of depressive symptoms during the follow-up, we used the terms proposed by Frank et al. (1991). The level of symptom rating was the MDD criteria from the K-Life. A subsequent episode of depression was defined as an MDD K-Life rating of 5 or greater for 14 days. Remission was defined as a relatively asymptomatic period (MDD K-LIFE rating of 1 or 2) for at least 14 days. Recovery was defined as an asymptomatic period of at least 60 days. Relapse was an episode of depression after remission but before recovery. Recurrence was defined as an episode of depression after recovery and is generally considered to be a new episode of depression as opposed to a relapse of the initial episode. As proposed by Frank et al. (1991), these terms were assessed independent of treatment.

STATISTICAL ANALYSIS

Differences between groups of subjects, recovered versus nonrecovered, recovered on medication versus no medication, and recurrence versus nonrecurrence, were tested with t-test or χ^2 tests as appropriate. Time to recurrence was estimated using the Kaplan-Meier (Kaplan and Meier, 1958) survival curve. Cox Proportional-Hazard Regression was used to identify predictors of recovery and recurrence.

RESULTS

RESPONSE

Ninety-six subjects were randomized in the acute phase of the study, 48 to fluoxetine and 48 to placebo. Using a CGI of 1 or 2 (much or very much improved) to determine response, then 27/48 (56%) responded to fluoxetine and 16/48 (33%) responded to placebo. The clinician rated depression severity as measured by the CDRS-R at end of acute phase for fluoxetine was 38.4 ± 14.8 and 47.1 ± 17.0 for placebo. However, few subjects had only minimal symptoms (CDRS-R ≤ 28) at end of acute treatment (fluoxetine 31% and placebo 23%).

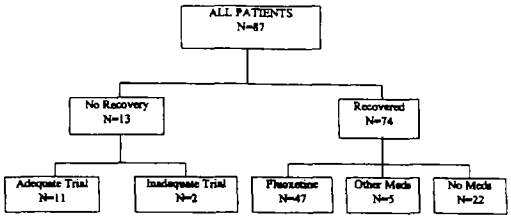

Figure 1. Patient flow.

RECOVERY

Eighty-seven subjects completed the 1-year naturalistic follow-up with K-LIFE interviews at 6 and 12 months following the end of acute treatment. Treatment was not controlled. Subjects who responded to the acute phase were continued on study medication or treated openly with fluoxetine. Generally, nonresponders were treated openly with fluoxetine. Five subjects were treated with other antidepressants or lithium (see Fig. 1).

Recovery was defined as minimal symptoms (K-LIFE MDD ≤ 2) for a period of 60 days. Of the 87 subjects followed, 13 (14.9%) did not meet criterion for recovery during the 12 month follow-up period, of which two had a remission of symptoms, i.e., minimal symptoms for at least 2 weeks, but they did not stay well for at least 60 days. Table 1 compares the demographic and clinical characteristics of the 13

TABLE 1. Recovered versus not recovered

	No recovery n=13		Recovered n=74		
Variables	Mean	(S.D.)	Mean	(S.D.)	*P*-value
Age	13.9	(1.9)	12.1	(2.8)	<.02
% Female N (%)	7	(53.8%)	34	(45.9%)	.79
SES (socioeconomic status)	3.2	(1.3)	2.8	(1.2)	.31
Age of onset (years)	12.0	(2.9)	10.6	(2.6)	<.091
Length of illness (weeks)	23.1	(24.2)	17.4	(19.3)	.35
CDRS-R	63.6	(14.0)	56.9	(9.9)	<.03
CGAS	44.3	(5.3)	45.7	(6.0)	.44
FGAS	54.4	(14.9)	63.5	(13.9)	<.03
First episode of MDD	4	(30.8%)	37	(50.0%)	.57
MDD only	2	(15.4%)	22	(29.8%)	.51
Comorbid dysthymia	7	(53.8%)	23	(31.1%)	.39
Comorbid anxiety	5	(38.5%)	29	(39.2%)	1.0
Comorbid behavior	8	(61.5%)	29	(39.2%)	.43

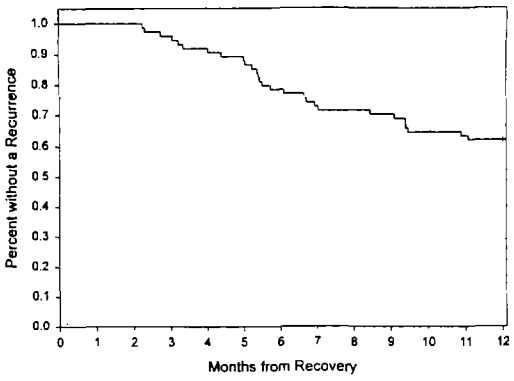

Figure 2. Survival curve from time of recovery to recurrence for all patients.

subjects who did not recover with the 74 who did recover during the follow-up period. Those who did not recover were older (13.9 ± 1.9 versus 12.1 ± 2.8) at baseline evaluation, and had lower global social functioning (CGAS) scores, lower family functioning scores (FGAS), and higher severity of depression scores (CDRS-R). There was a trend for the unrecovered group to include fewer first episode depressed patients (31% versus 50%) and to have fewer subjects with MDD as their only diagnosis (15% versus 30%).

Of the 74 subjects who recovered from the index episode, 22 recovered while taking no medication. Seventeen of these 22 subjects were initially randomized to placebo and never received medication. Five subjects received only brief medication trials, then discontinued. Recovery occurred several months later while on no medication. Five additional subjects received medication other than fluoxetine and eventually recovered.

Forty-seven subjects recovered while taking fluoxetine (see Fig. 1). There were no significant differences in the demographic and clinical characteristics of subjects who recovered on fluoxetine or off medication. The time to recovery from initiating fluoxetine (n = 47) was 69.4 ± 58.1 days. Sixty-two percent had recovered within 2 months and 85% within 4 months.

RECURRENCE

Once recovered, 17/47 (36%) of those who had recovered on fluoxetine and 9/22 (41%) of those who recovered on no medication and 3/5 (69%) who recovered on other medication had a recurrence (i.e., a new episode of MDD within the follow-up period). The average time from recovery to recurrence for these three groups was similar, 176.6 ± 56.7, 191.6 ± 99.8, and 265.0 ± 150.3 days, respectively. Figure 2 displays the survival curve for all 74 subjects from time of recovery to recurrence. The probability of having a recurrence was .22 at six months and .39 at 12 months following recovery; 16/29 (55%) subjects who had a recurrence during the follow-up did so within 6 months.

In examining the population who recovered on fluoxetine, few demographic or clinical features distinguished those with and without recurrence (Table 2). Those who had a recurrence were more likely to have comorbid diagnosis including dysthymic disorder and anxiety disorders and have taken longer to recover from the index episode, but these differences are not statistically significant. Of the17 who had a recurrence, 7 (41.2%) were still on fluoxetine at the time of recurrence.

In summary, for those treated with fluoxetine, 81% recovered within 12 months. The average time to recovery was over 2 months (69.4 days) and those who had a recurrence did so on average 6 months (176.6 days) following recovery. There is a substantial amount of individual variability.

TABLE 2. Subjects who recovered on fluoxetine: No recurrence versus recurrence

	No recurrence n=30		Recurrence n=17		
Variables	Mean	(S.D.)	Mean	(S.D.)	*P*-value
Age	12.1	(2.9)	12.4	(3.0)	.77
% Female N (%)	15	(50%)	6	(35.3%)	.59
SES (socioeconomic status)	2.6	(1.2)	2.6	(1.2)	.82
Age of onset (years)	10.9	(2.7)	10.1	(3.3)	.35
Length of illness (weeks)	14.4	(16.5)	26.6	(25.9)	<.05
Time to recovery (days)	65.5	(53.8)	76.4	(66.1)	.54
CDRS-R	57.3	(10.3)	56.8	(10.7)	.85
CGAS	45.9	(6.4)	46.5	(4.4)	.73
FGAS	65.8	(13.8)	66.4	(12.8)	.88
First episode of MDD	16	(53.3%)	7	(41.2%)	.79
MDD only	11	(36.7%)	3	(17.6%)	.35
Comorbid dysthymia	7	(23.3%)	7	(41.2%)	.37
Comorbid anxiety	12	(40.0%)	10	(58.8%)	.59
Comorbid behavior	10	(33.3%)	7	(41.2%)	.77

EFFECTS OF MEDICATION

As the follow-up period was not controlled, it is difficult to assess the impact of medication on recurrence or nonrecurrence. However, in an attempt to shed light on this question, a subsample of patients was selected who would have been considered to have entered a continuation phase of treatment. This group consisted of subjects who responded to treatment with fluoxetine and who had a minimum of 3 months of treatment. Thirty-five patients received fluoxetine for at least 3 months, and were then followed for 9 more months to determine their clinical outcome. Only ten patients remained on fluoxetine throughout the entire year.

Similar to the total group, 15/35 (43%) patients had a recurrence of MDD, eight of whom had a recurrence after discontinuing medication. Comparing the mean CDRS-R scores at the start of medication of those who had a recurrence versus those who did not recur, no significant difference was found between the two groups. Likewise, CDSR-R scores at the start of continuation (after 90 days) were similar between the 2 groups and were relatively asymptomatic for both groups (recurrers and nonrecurrers) 24.8 ± 5.4 vs. 24.0 ± 5.7.

A Cox proportional hazards regression was done to compare the risk of recurrence while on drug to the risk off drug. This analysis does not explicitly take into consideration the length of time the subject was on or off drug. The risk of recurrence when off drug is 2.3 times as great as when on drug (risk ratio 2.31, 95% CI 0.75–7.18).

The same analysis was repeated with age and beginning CDRS as covariates, but these had no effect on the risk of being off drug and were not significant predictors so they were not used. However, a larger sample may reveal predictors not found in the present smaller sample.

Next, a Cox regression was done where survival was measured from the time the subject was off drug until a recurrence occurred or the follow-up period ended. This analysis excluded subjects who were not discontinued from the drug or who had a recurrence while on drug (since the survival analysis is based on time until FIRST recurrence). This left 21 subjects. Time on drug was used as the predictor variable. The risk of recurrence when off drug decreases by 9% for each month the subject is on drug (risk ratio 0.93, 95% CI 0.66–1.31). Once again, this analysis was repeated with age and beginning CDRS score as covariates, but these had no effect on the risk ratio.

CONCLUSIONS

The results of the acute treatment were similar to adult studies with 56% of those randomized to fluoxetine responding, but only 33% having relative remission of symptoms. Similar to adults, the majority of patients were improved but not in remission at the end of an acute trial. Improvement, however, did occur during the continuation treatment.

Response of MDD in children and adolescents to fluoxetine was superior to placebo. Most (85%) patients recover from the episode within a year, but on average around 40% have a new episode within 12 months, which is a higher recurrence rate than that reported in adults (Keller et al., 1982).

Recovery appears to be associated with younger age, lower severity of depressive symptoms, higher family functioning, and fewer comorbid diagnoses, especially dysthymia.

Recurrence of depression occurs both off and on medication as in adults where 20% recurrence on fluoxetine has been reported (Montgomery et al., 1996). Of particular interest is that exposure to medication does not appear to induce further episodes with an equal number of recurrences occurring in those never exposed to medication. Clinically, there is little that differentiates those who will or will not have a recurrence. Some of the reasons for this apparent lack of predictor variables is the truncated design of the follow-up period. A much longer follow-up period is needed, as some patients in the nonrecurrence group can go on to have a recurrence at a later date. Also, the relatively small sample size hampers the ability to distinguish between group differences. As mentioned above, previously identified predictors of recurrence include psychotic depression (which is excluded from the sample), three of more previous episodes (which is not common in such a young sample), and double-depression (which was lower in the nonrecurrence group but not significant). One area not addressed in this paper is family history of recurrent depression, which was not obtained in this sample.

In conclusion, more research is needed in controlled studies of continuation and maintenance treatment including both psychotherapy and psychopharmacology. Effectiveness of both forms of treatment is beginning to be demonstrated in acute treatment and further work is needed on the relative effectiveness of psychopharmacology and psychotherapy, either separately or combined, in continuation and maintenance treatment.

Acknowledgments. This work was supported in part by grant MH39188 from the National Institute of Mental Health (NIMH), Bethesda, MD (Dr. Emslie), K07-MH01057-01A2 from NIMH (Dr. Kowatch), and contributions from Celeb C. and Julia W. Dula Education and Charitable Foundations, Mr. and Mrs. Woody Hunt, Cimmaron Foundation, Mr. and Mrs. Morton Meyerson, and the Azoulay Family (Dr. Weinberg).

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ORIGINAL ARTICLE

A Double-blind, Randomized, Placebo-Controlled Trial of Fluoxetine in Children and Adolescents With Depression

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Background: Depression is a major cause of morbidity and mortality in children and adolescents. To date, randomized, controlled, double-blind trials of antidepressants (largely tricyclic agents) have yet to reveal that any antidepressant is more effective than placebo. This article is of a randomized, double-blind, placebo-controlled trial of fluoxetine in children and adolescents with depression.

Method: Ninety-six child and adolescent outpatients (aged 7-17 years) with nonpsychotic major depressive disorder were randomized (stratified for age and sex) to 20 mg of fluoxetine or placebo and seen weekly for 8 consecutive weeks. Randomization was preceded by 3 evaluation visits that included structured diagnostic interviews during 2 weeks, followed 1 week later by a 1-week, single-blind placebo run-in. Primary outcome measurements were the global improvement of the Clinical Global Impressions scale and the Children's Depression Rating Scale—Revised, a measure of the severity depressive symptoms.

Results: Of the 96 patients, 48 were randomized to fluoxetine treatment and 48 to placebo. Using the intent to treat sample, 27 (56%) of those receiving fluoxetine and 16 (33%) receiving placebo were rated "much" or "very much" improved on the Clinical Global Impressions scale at study exit (χ^2=5.1, *df*=1, *P*=.02). Significant differences were also noted in weekly ratings of the Children's Depression Rating Scale—Revised after 5 weeks of treatment (using last observation carried forward). Equivalent response rates were found for patients aged 12 years and younger (n=48) and those aged 13 years and older (n=48). However, complete symptom remission (Children's Depression Rating Scale—Revised ≤28) occurred in only 31% of the fluoxetine-treated patients and 23% of the placebo patients.

Conclusion: Fluoxetine was superior to placebo in the acute phase treatment of major depressive disorder in child and adolescent outpatients with severe, persistent depression. Complete remission of symptoms was rare.

Arch Gen Psychiatry. 1997;54:1031-1037

DEPRESSION is a major cause of morbidity and mortality in children and adolescents.[1] School failure and school dropout are common outcomes for children and adolescents with depression,[2,3] and suicide remains one of the leading causes of death in adolescents.[4-6] The age of onset of depression is decreasing in those more recently born,[7] with the result that many individuals will experience their first episodes of depression during their adolescent years. Puberty marks a substantial rise in the overall prevalence of depression and is associated with a shift in the sex ratio, with a preponderance of females.

A meta-analysis of all available placebo-controlled trials (n=12) of tricyclic antidepressants (TCAs) in patients between the ages 6 and 18 years concluded that the difference between active treatment and placebo is too small to be clinically significant.[8] This lack of efficacy, as well as the prevalence of side effects of more noradrenergic antidepressants, has led to an increased interest in selective serotonin reuptake inhibitors.[9] Published articles about selective serotonin reuptake inhibitors in adolescent depression include 2 studies of "treatment-resistant" depression with fluoxetine[9,10]; 2 retrospective medical record reviews with fluoxetine[11] and sertraline treatment[12], and 1 negative, double-blind, placebo-controlled study of fluoxetine.[13] Despite the lack of evidence of effectiveness in randomized control trials, antidepressant medications continue to be prescribed widely in this age group primarily based on adult data. For adults, the efficacy of antidepressant medications for major depressive disorder (MDD) is well established.[14-16] No one antidepressant is clearly more effective than another, except that monoamine oxidase inhibitors are more effective than TCAs for depression with atypical features.[16,17]

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PATIENTS AND METHODS

PATIENTS

Child and adolescent outpatients (aged 7–17 years) who were self-referred or referred by other practitioners to our mood disorders program and who met *DSM-III-R* criteria for nonpsychotic MDD, single and recurrent. They were in good general medical health and of normal intelligence. Patients with bipolar I and II disorder, psychotic depression (lifetime), independent sleep-wake disorder, alcohol and other substance abuse (within the last year), anorexia nervosa or bulimia (lifetime), or previous adequate treatment with fluoxetine (20 mg/d for at least 3 weeks) were excluded. Any patient with at least 1 first-degree relative with bipolar I disorder (based on family history by a parent) was also excluded.

Possible patients for study were scheduled for a full evaluation after telephone screening for inclusion and exclusion criteria. Prior to the initial interview, the study was explained and written informed consent was obtained from the parent(s) and assent from the patient. The study was approved by the institutional review board at the University of Texas Southwestern Medical Center at Dallas. In addition to a structured psychiatric interview, the initial evaluation included a medical review of systems, a physical and neurological examination, and laboratory tests (blood chemistry study using an automated multiple analysis system, complete blood cell and differential cell counts, urinalysis, thyroid panel, and electrocardiogram). The evaluation was completed during a 3-week period.

METHODS

At the initial visit, each patient and parent(s) were interviewed separately using the Diagnostic Interview for Children and Adolescents,[25,26] a semistructured *DSM-III-R–based diagnostic interview to establish that the patient met DSM-III-R* criteria for MDD and to identify other concurrent and lifetime psychiatric disorders. The final diagnoses were based on information from interviews of the parent(s) and child. Additionally, criterion depressive symptoms and depressive symptom severity were assessed using the depressive items of the Kiddie Schedule for Affective Disorders and Schizophrenia[27] and the Children's Depression Rating Scale–Revised (CDRS-R),[28] respectively. Patients completed 2 self-report scales for depression, either the Children's Depression Inventory[29] (all patients ≤12 years) or the 21-item Beck Depression Inventory[30] (all patients ≥13 years), and the Weinberg Screening Affective Scale.[31] Overall functioning was assessed using the Children's Global Assessment Scale (CGAS).[32]

Following the initial diagnostic interview, the patients were seen for 2 additional follow-up interviews, 1 at visit 2 and 1 at visit 3. During the follow-up interviews, the patient and parent(s) were interviewed separately by 1 of 3 of us experienced in evaluating children and adolescents (G.J.E., W.A.W., and R.A.K.). The Diagnostic Interview for Children and Adolescents was reviewed. The Kiddie Schedule for Affective Disorders and Schizophrenia depressive items were scored for the past week and for the nadir of the present episode and were used primarily as a criteria measure at baseline. The CDRS-R and Brief Psychiatric Rating Scale–Children (BPRS-C),[33] a clinician-rated measure of general psychopathologic characteristics, were also completed. The course of illness, including the number, length, and timing of prior and current episodes, was established and the family history was reviewed.

Final consensus diagnoses were determined following visit 3 in a research conference that has been meeting weekly for the past 10 years. To enroll in the 1-week, single-blind, placebo run-in at visit 4 (3 weeks from initial interview), all patients had to continue to meet criteria for MDD, have a CDRS-R score greater than 40, and meet the previous inclusion-exclusion criteria. At the end of the placebo run-in week, the patients were randomized to either fluoxetine treatment or placebo if they still met all of the enrollment criteria, including a CDRS-R score greater than 40 the preceding week. Randomization was by a table of random numbers stratified for age and sex. Randomization was conducted by the pharmacy and clinicians, who remained *blind to assignment until the end of the study. Those patients* whose conditions improved (n=7) during the 1-week placebo run-in period continued to receive placebo for an additional week to determine if the symptoms returned. If the patients' conditions still improved, they were withdrawn from the study (n=7).

The possible reasons for the differences between adults and adolescents have been reviewed.[18,19] Ryan[19] noted that medications studied to date have been primarily noradrenergic or were metabolized quickly to noradrenergic metabolites. Based on limited animal studies, it is suggested that the noradrenergic system does not develop fully until early adulthood,[20,21] suggesting that serotonergic agents may be more effective in this age group.[19] Alternatively, high levels of hormones during puberty may decrease the effectiveness of TCAs.[19] Several articles have also commented on design issues,[22–24] small sample sizes, definitions of response, comorbidity, length of treatment, and large placebo response in children and adolescents. A primary concern is whether the populations studied are sufficiently homogeneous to allow a study of the efficacy of medication. The major concerns are that (1) the populations studied are abnormally treatment resistant (incipient bipolar, subjects with atypical depression, and substantial comorbidity), (2) the populations are overly treatment responsive, (3) the samples are too heterogeneous to detect medication effects, or (4) the wrong medications have been evaluated.

Our study was undertaken to evaluate the comparative efficacy, safety, and tolerability of fluoxetine treatment compared with placebo in child and adolescent outpatients with nonpsychotic MDD.

RESULTS

Five hundred eighty-three patients were screened by telephone during the course of the study (April 1, 1991 to January 31, 1995), 256 of whom were interviewed at least once. Of these, 106 patients completed the initial evaluation visits and enrolled in the placebo run-in period. Of the 150 ineligible patients, 34 (23%) refused to participate in the treatment study; 55 (37%) did not meet in-

OUTCOME MEASURES

Outcome was measured weekly. The Clinical Global Impressions (CGI) scale improvement rating and the CDRS-R were selected, a priori, as the major outcome measures. Additionally, the clinician completed the CGAs and the BPRS-C weekly. The patient completed the Beck Depression Inventory or Children's Depression Inventory and the Weinberg Screening Affective Scale at the beginning and the end of treatment. All subjects continued in the study for 8 weeks unless continued nonresponsiveness or adverse events dictated a change in treatment.

Following randomization, each patient was given 1 capsule of placebo or 20 mg of fluoxetine every morning. All patients were seen weekly for 8 consecutive weeks. Serum levels were collected on all patients at weeks 1, 2, 4, 6, and 8, approximately 8 hours after the last dose; however, results of blood chemistry levels were not provided to clinicians. Compliance was monitored by counting returned pills. New bottles were provided weekly, with 2 extra pills in the event of scheduling difficulties for the next visit. The pharmacy provided blinded medication based on the random assignment. Electrocardiograms and routine laboratory work (repeat of baseline studies) were repeated at weeks 4 and 8 (or at last visit) of the study.

STATISTICAL ANALYSIS

The data were computerized and managed using screen- and menu-guided Statistical Analysis System software (SAS, Cary, NC). Throughout our study, quality control procedures were in place to ensure accurate and complete data (eg, dual entry and multiple manual comparisons).

To assess interrater reliability specific for our study, the CGI scale and CDRS-R scores were assessed in the same interviews by 2 experienced clinicians during various stages of the evaluation and treatment phases of the study. Patients receiving dual assessments were selected solely on the availability of clinicians at the time of appointment, though patients were seen by 2 clinicians on completion of the study if at all possible. As the CGI scale improvement score is not completed during evaluation, paired scores are available for 48 patients for the CDRS-R and 41 patients for the CGI scale, 35 of which were performed at visit 8. The intraclass correlation[17] for the CDRS-R was 0.95 and the CGI improvement rating was 0.93. If the CGI scale improvement rating is used as a categorical variable[17] (ie, responder vs nonresponder), then $\kappa = 0.951$.

The primary outcome measures for the study were categorical. The proportion of patients who were randomized (intent to treat) who responded in each group (drug and placebo) as defined by a CGI scale improvement rating of 1 or 2 ("very much" or "much" improved, respectively) and dimensional (the group mean weekly CDRS-R scores). Secondary analyses to explore in more depth the pattern of response to fluoxetine treatment and placebo included a survival analysis of time to remission (defined as the first of 2 consecutive weekly CGI scale ratings of 1 or 2) and repeated-measures of analyses of variance using weekly CDRS-R scores *with the last observation carried forward* (LOCF).

However, the results of the LOCF method are not always reliable owing to the creation of "carried forward" data for weeks after discontinuation. This could bias the between-group comparison depending on how the pattern of dropouts varies between groups. Therefore, an additional method of analysis was used to obtain results based on all of the data but without the bias inherent in the LOCF method. For this analysis, the rate of change in the CDRS-R score was estimated for each patient (fluoxetine-treated or placebo) individually using all data available for that patient. The rates of change for all patients in each group (fluoxetine-treated or placebo) were averaged together. The averages for these 2 groups were then compared using a t test. The rate of change (or slope) was first estimated using linear regression (which also produces an estimated baseline CDRS-R score). Kraemer and Thieman[18] recommend analysis of linear regression slopes as an efficient method for use with "soft" data. As a check on the validity of this method, the average slope in each group and the variability of the average was estimated using the more sophisticated empirical Bayesian analysis described by Mori et al.[19] The empirical Bayesian analysis was selected because it adjusts for the correlation between the probability of dropout and the true unobservable rate of change (ie, informative right censoring). Such correlation can be tested[19] and was significant in our data ($P = .02$). Secondary outcome measures were compared based on the last available measurement using analysis of covariance with the baseline measurement as the covariate. All tests were 2-sided with $P < .05$ used for significance. Means are presented as ±SD.

clusionary criteria; 24 (16%) met exclusionary criteria; the condition of 22 (15%) improved during the evaluation, thereby, becoming ineligible, and 15 (10%) needed immediate treatment. Of the 106 patients enrolled in the placebo run-in period, 96 were randomized. Of the 10 not randomized, the condition of 7 improved, 2 refused further study, and 1 had significant side effects while receiving placebo. Of the 96 patients randomized, 48 received fluoxetine treatment and 48 received placebo.

As mentioned previously, the sample was stratified by age (≤ 12 years and and ≥ 13 years) and by sex. Of the 48 patients randomized to fluoxetine treatment, 24 were aged 12 years and younger and 24 were aged 13 years and older. Of those randomized to placebo, 24 were aged 12 years and younger and 24 were aged 13 years and older. The 2 groups, fluoxetine-treated and placebo, were not different in any demographic or clinical features, except that those assigned to fluoxetine treatment had a greater lifetime incidence of comorbid anxiety disorders ($\chi^2 = 4.2$, $df = 1$, $P = .04$). **Table 1** lists the demographic and clinical characteristics of these 2 groups (fluoxetine treatment and placebo).

Table 2 lists the timing and basis for patients not completing the 8-week trial. The most common reason for discontinuation was continued nonresponse (19 patients who were receiving placebo and 7 who were receiving fluoxetine). Side effects, as a reason for discontinuation, were minimal, affecting only 4 patients who were receiving fluoxetine and 1 who was receiving placebo. The side effects leading to discontinuation of fluoxetine treatment were in 3 patients in whom manic symptoms developed and 1 patient who developed a severe rash.

Based on a CGI scale improvement rating of 1 or 2 (very much or much improved) to define response, 27 (56%) of 48 patients receiving fluoxetine treatment and 16 (33%) of 48 patients on placebo responded to treatment at exit from the study ($\chi^2 = 5.097$, $df = 1$, $P = .02$). On the other hand, of

Table 1. Clinical and Demographic Characteristics

Features	Patient Group* Fluoxetine-Treated	Placebo
Demographics		
Age, y	12.2±2.7	12.5±2.6
(Range)	(7-17)	(8-17)
Female, No. (%)	22 (46)	22 (46)
White, No. (%)	35 (72.9)	41 (85.4)
Socioeconomic status, No. (%)†		
1-2	14 (29.2)	16 (33.3)
3	16 (33.3)	18 (37.5)
4-5	18 (37.5)	14 (29.2)
Clinical characteristics		
CDRS-R score‡	58.5±10.5	57.6±10.4
(Range)	(42-90)	(42-82)
Melancholic, *DSM-III-R* (%)	7 (14.6)	12 (25)
First episode, No. (%)	23 (47.9)	23 (47.9)
No. of episodes	1.7±0.7	1.8±0.8
(Range)	(1-3)	(1-4)
Duration, current episode, wk	14.6±9.7	13.7±7.5
(Range)	(4-56)	(4-32)
Length of illness, mo	18.8±20.9	18.0±19.7
(Range)	(1-84)	(1-72)
Age at onset, y	10.6±2.7	11.0±2.6
(Range)	(6-16)	(5-17)
Positive family history, No. (%)§	25 (52.1)	29 (60.4)
CGAS score‖	47.9±8.3	48.4±7.8
(Range)	(25-65)	(35-80)
Comorbid diagnoses, lifetime, No. (%)		
None	7 (14.6)	11 (22.9)
Dysthymia	20 (41.7)	14 (29.2)
Anxiety disorders	32 (66.7)	22 (45.8)
ADHD	16 (33.3)	13 (27.1)
Oppositional/conduct	13 (27.1)	16 (33.3)

*There were 48 patients enrolled in each group (mean±SD).
†Two-factor index (A. B. Hollingshead, unpublished data, 1975).
‡CDRS-R indicates Children's Depression Rating Scale–Revised; CGAS, Children's Global Assessment Scale, and ADHD, attention deficit hyperactivity disorder.
§A first-degree relative with affective disorder treated with either hospitalization or medication.
‖Based on average of scores during evaluation.

Table 2. Reasons for Discontinuation Following Randomization

Patient Group	Week 1	2	3	4	5	6	7	8	Total
Fluoxetine-treated									
Lack of efficacy	.	.	.	.	1	3	2	1	7
Side effects	.	.	.	1	2	.	1	.	4
Protocol violation*	.	.	1	.	1	1	.	.	3
Placebo									
Lack of efficacy	.	1	1	1	5	5	5	1	19
Side effects	.	.	.	1	.	.	.	.	1
Protocol violation	1	.	.	1	.	.	.	.	2
Total	**1**	**1**	**2**	**4**	**9**	**9**	**8**	**2**	**36**

*Protocol violations included taking nonstudy medications and missing appointments. Ellipses indicate no patients discontinued.

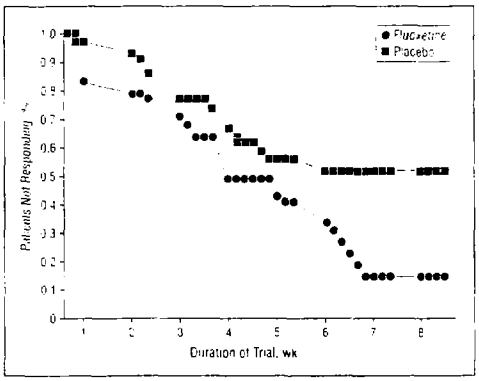

Figure 1. *Survival curve for time to response comparing fluoxetine and placebo. Response is Clinical Global Impressions scale (improvement) rating of 2 or less for 2 consecutive weeks.*

those who completed the entire 8 weeks of treatment 25 (74%) of 34 patients responded to fluoxetine treatment and 15 (58%) of 26 patients responded to placebo (χ^2=1.663, *df*=1, *P*=.20). This result is influenced by the differential dropout of nonresponders in the placebo group. While the condition of many patients improved during the study, only 15 (31%) of 48 patients of the fluoxetine-treated group and 11 (23%) of 48 patients of the placebo group had minimal symptoms (ie, a CDRS-R score ≤28) by end of the study.

To examine the pattern of change in the 2 groups, time to response was defined categorically as the first of 2 consecutive weeks when the CGI scale rating was a 1 or a 2 (much or very much improved). Kaplan-Meier survival curves[20] were compared using the log-rank test and were found significantly different (χ^2=5.96, *df*=1, *P*=.017) (**Figure 1**).

The other primary outcome measure, the weekly CDRS-R score, was examined as a continuous variable. **Figure 2** shows the traditional method of dealing with patient attrition during the course of the treatment (ie, weekly CDRS-R scores for each group are presented with the LOCF). The last available observation is filled in for the values for patients who discontinued study participation before 8 weeks. A repeated measure (analysis of variance) using all 96 patients showed a significant drug by time interaction (*F*=3.66; *df*=8, 752; *P*=.01). Age group by treatment interaction was also examined but was not significant (*P*=.76). Comparing the weekly CDRS-R scores for each treatment group using *t* tests, the first week that the groups were significantly different was week 5. At week 5, the mean CDRS-R score for the fluoxetine-treated group (39.8±13.2) was lower than the placebo group (46.8±16.6) (*t*=−2.28, *df*=94, *P*=.03).

To make the most efficient use of the available data[20] without resorting to a completion analysis or LOCF analysis, the rate of change (slope) and baseline CDRS-R score (intercept) were estimated from linear regressions on each patient and for each group. The estimated baselines were similar (54.2 for the fluoxetine-treated group vs 53.8 for the placebo group). However, the fluoxetine-treated group slope of −2.75±−2.52 was significantly different from the placebo group slope of −1.27±−2.86 (*t*=2.68, *df*=94, *P*<.001).

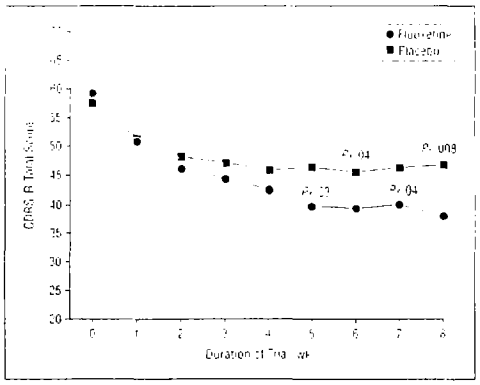

Figure 2. *Weekly Children's Depressive Rating Scale—Revised (CDRS-R) scores (last observation carried forward) for fluoxetine and placebo.*

These results may be interpreted as follows. The fluoxetine-treated group began with an average CDRS-R score of 54.2 and their scores improved by 2.75 U per week to end with an estimated week 8 score of 32.2. While placebo patients began with a similar average CDRS-R score (53.8), their score improved only 1.27 U per week to the end of the study with an estimated exit score of 43.6. Using the empirical Bayesian analysis of estimating slopes (intercept estimates were unavailable) gives an estimated slope of −2.60±2.36 for the fluoxetine-treated group and a significantly smaller slope of −1.32±3.56 for the placebo group (t=2.08, df=94, P=.04).

To further evaluate the effect of age and sex on response, regression lines were calculated for patients aged 12 years and younger and 13 years and older in each group. There were no significant drug by age interactions (F=0.12, df=1, 92, P=.73), though the younger patients independent of the treatment group started with lower CDRS-R scores (F=8.77, df=1, 92, P=.004). Similarly, if the sample is divided by sex, using the same analyses, there was no drug by sex interaction (F=.001; df=1, 92; P=.96).

Finally, for descriptive purposes, **Table 3** lists the initial and last available scores for all 96 patients on the clinician measures and self-report depression scales by groups. Fluoxetine treatment and placebo were associated with significant decreases between baseline and exit scores on these measures. As noted previously, improvement in the CDRS-R scores were greater in the fluoxetine-treated group (final CDRS-R score, 38.4±14.8) than in the placebo group (final CDRS-R score, 47.1±17.0) and the analysis of covariance (F=10.58, df=1, 93; P=.002). However, on measurements of general psychiatric symptoms (BPRS-C) and global functioning (CGAS), there were significant improvements in the condition of the patients in both groups during the course of the study, but the improvement in the fluoxetine-treated group was not significantly superior to the placebo group. Furthermore, self-reported depressive symptom measurements also showed improvement in both groups, but the between-group differences were not significant. However, given the wide variability of initial child self-reports, these findings are difficult to interpret.

Table 3. Baseline to Exit Outcomes

	Patient Group Scores*			
	Fluoxetine-Treated		Placebo	
Scale†	Baseline	Final	Baseline	Final
CDRS-R	58.5±10.5	38.4±14.8	57.6±10.4	47.1±17.0
(Range)	(42-90)	(19-71)	(42-82)	(17-78)
CDI/BDI	15.8±10.6	9.9±12.0	15.3±11.9	11.2±10.8
(Range)	(0-41)	(0-56)	(0-54)	(0-42)
WSAS	20.6±11.8	13.1±12.0	20.6±12.8	16.7±13.5
(Range)	(1-45)	(0-42)	(0-47)	(0-46)
BPRS-C	47.3±7.7	36.9±10.0	46.2±8.9	41.0±10.4
(Range)	(34-65)	(21-58)	(24-69)	(21-67)
CGAS	47.9±8.3	63.9±12.9	48.4±7.8	60.1±14.8
(Range)	(25-65)	(40-89)	(35-80)	(40-95)

*There were 48 patients enrolled in each group (mean±SD).
†CDRS-R indicates Children's Depression Rating Scale–Revised; CDI, Children's Depression Inventory; BDI, Beck Depression Inventory; WSAS, Weinberg Screening Affective Scale; BPRS-C, Brief Psychiatric Rating Scale–Children; and CGAS, Children's Global Assessment Scale.

COMMENT

Fluoxetine treatment was superior to placebo in relieving depressive symptoms. The difference between fluoxetine treatment and placebo was evident in clinician assessment of clinical global improvement (the CGI scale) and in weekly clinician depressive symptom severity ratings (the CDRS-R). Differences between fluoxetine treatment and placebo became statistically significant after 5 weeks.

There was no clear difference in patient responsiveness to either fluoxetine treatment or placebo based on age or sex. The overall rates of response were similar to those reported in adults for fluoxetine treatment and placebo using comparable analyses. For example, the Depression Guideline Panel[11] reports that a meta-analysis of all available double-blind studies of fluoxetine treatment, with intent-to-treat samples, reveals a 46% response rate to fluoxetine treatment and a 22% difference between fluoxetine treatment and placebo.

Despite improvements in depressive symptoms, relatively complete remission of depressive symptoms (a CDRS-R score ≤28) was uncommon, which is not dissimilar to adult data in 6- to 8-week efficacy trials. Differences between the fluoxetine-treated group and the placebo group were less evident in self-report scales (Children's Depression Inventory, Beck Depression Inventory, and Weinberg Screening Affective Scale) and in clinician ratings of general psychiatric symptoms (the BPRS-C) and global functioning (the CGAS).

COMPARISON WITH FINDINGS FROM PREVIOUS STUDIES OF CHILDREN AND ADOLESCENTS

Several factors may explain a positive result in our study compared with previous studies of children and adolescents. While depressed at baseline evaluation, as evidenced by CDRS-R scores, the sample as a whole was neither overly responsive (ie, the placebo response rate of 33%) nor treatment resistant (ie, the fluoxetine-treated group response rate of 56%).

In the study of 38 children by Puig-Antich et al,[39] 56% (9/16) of the children responded to imipramine therapy and 68% (15/22) responded to placebo. Four patients in the imipramine-treated group, but none in the placebo group, failed to complete the 5-week protocol. An open extension of this study suggested that in addition to the high placebo response rate, failure to achieve therapeutic levels of imipramine limited effectiveness.[40]

In part, as a result of this study, Geller et al[41] designed their study of nortriptyline in children to be longer (8 weeks) and controlled for blood chemistry levels. The randomization was preceded by a 2-week placebo washout phase. The patients had severe depression, had a chronic course, and had a high rate of comorbidity including family histories of bipolar disorder. Of the 50 children randomized, 30.8% responded to active treatment and 16.7% responded to placebo based on an earlier version of the CDRS. The mean unrevised CDRS scores at the end of the study for active and placebo were 32.9±11.4 and 32.0±9.8, respectively.

In adolescents, using the same design as for children, Geller et al[42] enrolled 52 patients, 35 of whom were randomized. Response was defined as a CDRS score of less than 25 and a Kiddie Schedule for Affective Disorders and Schizophrenia depressive items score of 2 or less, except concentration. One active treatment patient and 4 placebo patients responded despite mean nortriptyline levels for the active treatment group of 350±70 nmol/L. Kutcher et al[18] reported on a randomized, double-blind, placebo-controlled study of 750 nmol/L of desipramine per day in adolescent outpatients, which was an extension of an earlier report. Of 60 adolescents randomized, 18 dropped out before 6 weeks, 13 of whom were receiving desipramine. With response defined as a 50% or greater decrease in the Hamilton Depression Rating Scale, 48% responded to desipramine treatment compared with 35% to placebo, a difference that failed to reach significance.

Simeon et al[13] described 40 adolescent outpatients with MDD in a double-blind, placebo-controlled study of fluoxetine. All of the patients completed a 1-week, single-blind placebo run-in prior to randomization, though the length of time prior to enrolling in the single-blind placebo run-in was not described. Patients' dosages were titrated to 60 mg of fluoxetine by week 2 and studied for 6 weeks. Fifteen patients in each group completed the study. Simeon et al reported that 2 of every 3 patients showed mild to moderate improvement with either fluoxetine treatment or placebo. All clinical measures showed a greater improvement with fluoxetine treatment than placebo except sleep although none were statistically significant, perhaps owing to the relatively few patients tested. Similar to the study by Puig-Antich et al,[39] the placebo response rate was high.

The design of our study benefited from the experience of previous studies. Factors possibly contributing to a positive result included sample characteristics such as a relatively large sample, the exclusion of patients with psychotic depression, bipolar symptoms or a family history of bipolar disorder, and the recruitment of patients from a range of socioeconomic backgrounds, including those who were able to pay for treatment. All patients were self-identified patients. None were recruited by media methods. Methodologic issues included an extensive evaluation period (3 weeks) and a single-blind placebo period (1 week) prior to randomization.

The choice of the drug studied resulted in the ability to attain adequate levels of medication with few side effects. Also, previous studies, apart from Simeon et al,[13] have used medications that are more noradrenergic or metabolized to noradrenergic metabolites.

To our knowledge, there have been no studies in this age group comparing selective serotonin reuptake inhibitors and TCAs directly. However, in an open trial of 15 adolescents and young adults (aged 16-24 years) who had failed to respond to a TCA, Boulos et al[43] found a 64% response rate to fluoxetine treatment during a 6- to 7-week trial. Also, it has been proposed theoretically that differences in the rate of development of neurotransmitter systems could contribute to differences in response to antidepressants. Data from studies of nonprimates[20] and rhesus monkeys[21] suggest that the development of monoaminergic storage capacity and synthesis continues through childhood and is generally more rapid for serotonin than for catecholamines.

STUDY LIMITATIONS

The patients recruited evidenced relatively severe and persistent symptoms of depression and would not be representative of all children and adolescents with MDD. Of 150 patients who did not enroll in the treatment phase of the study following the initial interview, only 55 (37%) had not met MDD criteria initially. The rest improved, met exclusionary criteria, or refused enrollment in the study. Twenty-nine patients responded to the evaluation or single-blind placebo.

Following randomization, attrition during the study resulted in greater attrition from the placebo group because of failure to respond. Most patients had been seen weekly for at least 8 visits and discontinuation from the study came at the patient's or parent's request and it would have been unethical to continue studying these patients. Every effort was made to have the patients continue with the study as long as possible. It is impossible to know whether nonresponders at week 4 or later would have become responders if they had continued longer in the study in either group, which would effect the result of the χ^2 test of the CGI scale at exit. However, data in adults suggest that placebo responders are more likely to occur early in treatment and the placebo response rate in this study parallels adult findings and is not excessively low. Additionally, the analysis of the CDRS-R using slopes from individual regressions should not be effected much by attrition. Several simulation studies have shown that an unweighted average of individual slopes is subject to little bias owing to dropouts.[37,38] Also, an additional slopes analysis was performed using the procedure of Mori et al[37] that was designed specifically to adjust for nonrandom dropouts. Both of these analyses showed significant treatment effect.

Finally, the study may have been too short to demonstrate significant differences between the groups in global functioning (the CGAS) and, as comorbid disorders were frequent, measurements assessing other symptoms, not only depression (the BPRS-C), might change differentially as a function of treatment, although both

groups improved on both measurements. Self-report measurements for children and adolescents, as mentioned previously, did not significantly differentiate the 2 groups, presumably in part because of relatively poor reliability. For example, some patients rated themselves on self-report as having minimal or no symptoms, whereas on clinical interview, they met criteria for MDD.

CONCLUSION

These data indicate that fluoxetine at 20 mg/d is safe and effective in children and adolescents with MDD. Replication is needed to evaluate the certainty of this finding. In addition, whether long-term treatment would result in the amelioration of school, general functioning, or concurrent comorbidities is unknown. How long to continue fluoxetine treatment, assuming it is effective, deserves study. Subsequent analyses to evaluate predictors of response are planned.

Accepted for publication August 20, 1996.

This study was supported by grants MH-39188 (Dr Emslie) and MH-41115 (Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas) from the National Institute of Mental Health, National Institutes of Health, Bethesda, Md.

Presented in part at the annual New Clinical Drug Evaluation Unit Meeting, Orlando, Fla, June 2, 1995, and the Annual Meeting of the American Academy of Child & Adolescent Psychiatry, New Orleans, La, October 19, 1995.

We thank Kenneth Z. Altshuler, MD, Stanton Sharp Distinguished Chair and Chairman, Department of Psychiatry, for his administrative support; the staff of the Child and Adolescent Psychiatry Service at Children's Medical Center for their clinical assistance, Melody Brummett, for her secretarial support; and Christina Gullion, PhD, for design, management of the randomization procedures, and data management advice.

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Depressive Symptoms by Self-Report in Adolescence: Phase I of the Development of a Questionnaire for Depression by Self-Report

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Abstract

As the first step in validating a criteria-based, self-report depression questionnaire specifically for children and adolescents and to determine the prevalence of self-reported depressive symptoms, we studied 3,294 high school students of mixed ethnic background in a large urban school district. They completed the Weinberg Screening Affective Scale. The 21-item Beck Depression Inventory was also completed to allow comparison with a previous study. The prevalence of clinically significant depressive symptoms suggesting depression by self-report ranged from 18% on the Beck Depression Inventory to 13% on the Weinberg Screening Affective Scale. Hispanic females had the highest scores, while white males had the lowest. Being behind in school, female, and nonwhite predicted more self-reported depressive symptoms. (*J Child Neurol* 1989;3:114-121).

Adolescent depression and suicide are major mental health problems. Depression with or without learning disabilities is a common cause of school failure in normally intelligent young people.[1-3] In addition, school failure and school dropout are significant problems.[4] Depression is an identifiable condition that meets established systematic criteria. Recognition that affective illness is a cause of poor school performance requires systematic evaluation utilizing established criteria for depression, eg, *Diagnostic and Statistical Manual of Mental Disorders*, ed 3 (*DSM-III*),[5] Feighner et al,[6] Research Diagnostic Centers (RDC),[7] Weinberg et al[1] and Poznanski et al.[8] The Weinberg and Poznanski groups' criteria were developed specifically for school-aged populations. Useful adjuncts to clinical interviews are self-report measures.[9-11] However most self-report instruments are scored using cutoff scores and do not take into account the need for the presence of a cluster of symptoms to make a diagnosis of depression. There are no validated criteria-based questionnaires for depression specific to children and adolescents.

This study was undertaken as the first step in ongoing research into the Weinberg Screening Affective Scale,[12] a self-report questionnaire based on established criteria for depression in children and adolescents. Additionally the Beck Depression Inventory[13] was used to allow comparison with a previous study of a different population of high school students.[14] This paper will present preliminary data on (1) prevalence of self-reported depressive symptoms in a large sample of urban adolescents of mixed ethnic background by both instruments, (2) the demographic characteristics of adolescents self-reporting depressive symptoms, (3) the relationship between the two self-report measures of depressive

Received Nov 29, 1988. Received revised April 24, 1989. Accepted for publication May 3, 1989.

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Presented in part at the Annual Meeting of the American Academy of Child and Adolescent Psychiatry, October 1987, Washington, DC.

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symptoms in adolescents, and (4) whether different depressive symptoms differentiated depressed from nondepressed adolescents in various ethnic groups.

Kaplan et al[14] reported on 385 high school students and found that 8.6% scored in the moderate to severe range (16 or higher) on the Beck Depression Inventory. This population was 71% white and 22% black. They found no significant gender differences in scores when age and social class were controlled. Kandel and Davies[15] administered a 6-item self-report inventory to 4,204 adolescents ages 13 to 19 years. In this study, there were no age or socio-economic status differences, but females scored higher than males. In a study by Schoenbach et al[16] of 624 junior high students completing the Center for Epidemiological Studies Depression Scale (CES-D), overall persistent symptoms were reported more often by blacks than by whites, with black males being predominant in the high-scoring group.

Little information is available on mental health problems specific to Hispanic adolescents. Langner et al[17] studied 1,034 children aged 6 to 18 years selected from a cross-section of Manhattan households, 29% of which were Spanish speaking. Hispanic and black groups evidenced more behavioral difficulties than whites. In a study by Canino et al[18] comparing referred black and Hispanic children and adolescents in Manhattan with regard to 22 common mental health symptoms, Hispanics reported significantly more depression, sadness, and anxiety symptoms. Hoppe and Martin[19] compared patterns of suicide among Hispanics and non-Hispanics in Texas over a 20-year period (1960 to 1980). In the 15- to 24-year age group, an increase in suicide rates in both male and female Hispanics were noted. However, this increase was less than that for non-Hispanics.

Methods

We studied 3,294 high school students in a large metropolitan school district who were beginning the mental health section of their Health Education class. Health Education is a required course for one semester and is usually taken in the 10th grade, with about half the students taking it each semester. In the summer prior to the fall semester, we met with all the health education teachers in the district. The project was explained and the specific instructions to students for teachers was reviewed. Each high school principal sent a letter to the parents of adolescents enrolled in Health Education to explain the study and to request return notification if they did not want their child to participate. During the third week of the school year, the precoded questionnaires were sent in packets to each Health Education teacher for each class and then picked up 1 week later. Twenty-three of the 25 high schools in the district participated.

The timing of the study was chosen so that results would not be influenced by reports of grades, ie, it was done 1 to 2 weeks before the first marking period. The study was performed at the beginning of the mental health section of the Health Education classes so that the results would not be influenced by having spent several weeks talking about mental health issues. All students present in class on the day the questionnaire was handed out were given a form. Specific instructions were read by the teacher to the students, and the students were told their participation was voluntary.

The sample constituted 89% of those students enrolled in Health Education classes by school records. Of those students participating, 98% completed more than 90% of the questions on both forms. The sample was representative of the total high school population with regard to sex (50.7% male) and race: 1,825 or 55.4% were black, 783 or 23.8% were white, 599 or 18.2% were Hispanic, and 86 or 2.6% were "other," including Asian, American Indian, and Oriental. The mean age for the sample was 15.7 years (SD, 1.1; range, 13 to 20 years), with the median and modal grade being the 10th grade.

Measures

The two self-report measures of depressive symptoms used were: the 21-item Beck Depression Inventory[13] and the Weinberg Screening Affective Scale.[1,12]

The Beck Depression Inventory is a widely used, well-studied clinical and research measure of depressive symptoms. It has been utilized in adult and adolescent populations. It consists of 21 questions with four choices of answers giving scores of 0 to 3 for each item and a possible total score of 0 to 63. Cutoff scores used in previous studies that included adolescents for total Beck Depression Inventory score are 0 to 9, nondepressed; 10 to 15, mild depression; 16 to 23, moderate depression; 24+, severe depression. A total Beck Depression Inventory score of 16+ has been validated to be a cutoff score for major depressive disorder in adults,[20] college students,[21] and adolescents.[22]

In addition, the above cutoff scores were used to allow direct comparison with a similar study in a different adolescent population.[14] Recently, the use of the Beck Depression Inventory was reviewed by Kendall et al.[23] They clarified the use of the Beck Depression Inventory for syndromal assessment.

Those with Beck Depression Inventory scores of 16 or greater, when interviewed, comprise the following: those who do not meet criteria for depression, termed "dysphoric"; those meeting criteria for depression; and those with other predominant medical or psychiatric disorders, ie, a secondary depression.

The Weinberg Screening Affective Scale[1,11,12] consists of 55 statements that require yes or no responses and a 4th-grade reading level. Fifty of the 55 questions directly relate to the Weinberg Criteria for Depression[1] and the Bellevue Index of Depression.[24,25] The Weinberg Screening Affective Scale was used to assess whether by self-report the child or adolescent fulfilled an established set of criteria for the diagnosis of depressive syndrome. The Weinberg Criteria were developed specifically for school-age children and contain 10 major symptom categories.

Two categories are deemed essential (depressed mood and self-deprecatory ideation). The eight remaining categories are agitation, sleep disturbance, change in school performance, decreased socialization, change in attitude towards school, somatic complaints, decreased energy, and change in appetite or weight. For each symptom category, specific definitions and behaviors are delineated. The total number of items for the 10 categories is 40. Subsequently, the original 40 items (symptoms and behaviors) were developed by Petti into the Bellevue Index of Depression and were validated in hospitalized child psychiatry patients.[24] The Weinberg Criteria for Depression initially required the presence of the two essential categories (depressed mood and self-deprecatory ideation) plus two of the eight additional symptom categories. Petti found that 20 positive responses of the original 40 items by interview were diagnostic for depression.

Comparisons of the original criteria and other criteria for depression have been made.[8,26] In clinical populations, a requirement of two essential symptom categories plus four of the eight additional categories correlated better with major depression as defined by *DSM-III* in children and adolescents than did the previous method of requiring only two of the eight additional symptom categories.[27]

The Weinberg Screening Affective Scale is a self-report form that asks questions parallel to the Bellevue Index of Depression and Weinberg Criteria. There are more than 40 questions because some individual symptoms or behaviors previously published are asked with more than one question. The Weinberg Screening Affective Scale form consists of four to eight questions in each of the 10 major symptom categories. For this study, the Weinberg Screening Affective Scale was scored both as a total score and as a self-report criterion measure. A subject was scored as depressed if they met a diagnostic criteria of two essential symptoms (depressed mood and self-deprecatory ideation) plus at least four of the eight additional symptom categories. For a given symptom category to be scored positive, at least two of the self-report questions relevant to that symptom had to be answered in the affirmative, and the subject had to respond "yes" to the statement, "My answers are how I have been feeling most of the time."

Results

According to the Beck Depression Inventory, 597/3,294 (18.1%) of the students scored in the moderate to severe range (score of 16+), while 743/3,294 (22.6%) scored in the mild depressive range (10 to 15) (see Table 1). Significantly more females (368/1,624 or 22.7%) than males (229/1,670 or 13.7%) fell into the moderate to severe range ($\chi^2 = 43.8$, $P < .001$). Within the three major ethnic groups, Hispanic females had the highest proportion in the moderate to severe range (96/308 or 31.2%), while white males had the lowest representation (36/418 or 8.6%); ($\chi^2 = 59.1$, $P = .001$). The group comprising Asian, American Indian, and Oriental students was too small for meaningful comparisons.

Table 2 shows the results with the Weinberg Screening Affective Scale. Criteria for depressive syndrome by self-report as defined above were met by 440/3,294 (13.4%) of subjects. Hispanic females again evidenced the highest percentage with depression (69/308 or 22.4%), while white males had the lowest percentage (33/418 or 7.9%). Although proportionally more Hispanic females reported themselves as depressed than black females (22.4% v 17.5%), this was not significantly different ($\chi^2 = 0.3$, $P = .56$).

In combining males and females (Table 3), blacks and Hispanics had significantly more depression on both the Beck Depression Inventory and the Weinberg Screening Affective Scale than whites ($P < .01$).

To ascertain whether demographic factors differentiated depressed from nondepressed subjects, a stepwise discriminant function analysis was conducted. Variables included age, sex, race, and being behind in school (age minus grade). The factors that differentiated those who were depressed on the Beck Depression Inventory from the rest were, in order: behind in school, female, and nonwhite. These same three variables also discriminated the Weinberg Screening Affective Scale positive and negative

TABLE 1
Gender Differences of Levels of Depressive Symptoms on Beck Depression Inventory by Ethnic Group

Race	Beck Depression Inventory Scores* ≤ 9, % (n = 1,954)	10–15, % (n = 743)	≥ 16, % (n = 597)	χ^2	P
Black (N = 1,826)					
Female	49.9	28.4	21.7†		
Male	64.7	21.8	13.6	42.5	< .001
White (N = 783)					
Female	62.7	21.4	15.9†		
Male	76.8	14.6	8.6	19.12	< .00007
Hispanic (N = 599)					
Female	44.8	24.0	31.2†		
Male	63.2	17.9	18.9	21.08	< .00002
Other (N = 86)					
Female	43.6	15.4	41.0		
Male	40.4	29.8	29.8	3.18	< .204
Total (N = 3,294)					
Female	51.7	25.7	22.7†		
Male	66.8	19.5	13.7	81.87	< .001

* ≤ 9 = not depressed; 10–15 = mild depression, ≥ 16 = moderate to severe depression.
† Significantly more depression in females than males in designated ethnic group ($P < .05$).

TABLE 2
Gender Differences of Depression on Weinberg Screening Affective Scale by Ethnic Group

Race	% Depressed	χ^2	P
Black (N = 1,826)			
Female (n = 912)	17.5*	18.19	.00001
Male (n = 914)	10.5		
White (N = 783)			
Female (n = 365)	9.6*	.51	.476
Male (n = 418)	7.9		
Hispanic (N = 599)			
Female (n = 308)	22.4*	10.51	.001
Male (n = 291)	12.0		
Other (N = 86)			
Female (n = 47)	18.0	.35	.556
Male (n = 39)	10.6		
Total (N = 3,294)			
Female (n = 1,624)	16.7*	30.12	.001
Male (n = 1,670)	10.1		

* Significantly more depression in females than males in designated ethnic groups ($P < .05$).

TABLE 3
Prevalence of Depression by Ethnic Group

Race	BDI, %	WSAS, %
Black (n = 1,826)	17.6	14.0
White (n = 783)	12.0	8.7
Hispanic (n = 599)	25.2	17.4
Other (n = 86)	34.9	14.0

BDI = Beck Depression Inventory; WSAS = Weinberg Screening Affective Scale.

groups. However, for both analyses, only 2% of the variance was accounted for by those three variables.

Figure 1 demonstrates there was a large number of subjects who were positive only on one of the measures. However, the group that was positive for depression on both measures had the highest scores on both measures (Table 4). The mean total Beck Depression Inventory score for the group positive only on that scale was 22.3 (SD = 6.4) compared to the Beck Depression Inventory total score in the group positive on both measures of 26.2 (SD = 7.8) ($t = 6.6$, $df = 595$, $P < .001$). The mean total Weinberg

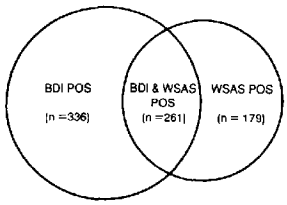

FIGURE 1
Number of students meeting criteria for depression by Beck Depression Inventory (BDI) and/or Weinberg Screening Affective Scale (WSAS). Of 776 students, 336 were positive (POS) for depression on BDI only, 179 were positive for depression on WSAS only, and 261 had positive scores on both tests.

Screening Affective Scale score in the group positive only on that scale was 21.8 (SD = 4.3) compared to 25.7 (SD = 5.7) in the group positive on both scales (t = 8.2, df = 438, $P < .001$).

Finally, we were interested to know if different symptoms would differentiate depressed from nondepressed adolescents in different ethnic groups. Table 5 lists the top 10 Beck Depression Inventory symptoms for whites using a stepwise discriminant function analysis that predicted those subjects whose Beck Depression Inventory scores were ≥ 16. Similarly, Table 6 lists the Weinberg Screening Affective Scale symptoms that differentiated depressed from nondepressed in a similar analysis.

On the Beck Depression Inventory, while statements relating to self-dislike, for example "I am disgusted with myself," was the first symptom in whites and Hispanics, it was not significantly discriminatory in blacks. Unattractiveness was less meaningful in Hispanics than in both whites and blacks. Withdrawal and crying discriminated depressed from nondepressed blacks and Hispanics but not whites. Self-accusation was ranked fairly high in Hispanics but not in the other two major groups. The top 10 symptoms in blacks, whites and Hispanics accounted for 63%, 65%, and 69% of the variance, respectively, and little more was gained by additional symptoms

On the Weinberg Screening Affective Scale, the statement "I am lonely too much of the time" discriminated depressed and nondepressed whites but not blacks or Hispanics. The statements "My friends don't like me anymore," "It seems like some part of my body always hurts me," and "This is not a good world," discriminated depressed and nondepressed blacks but not whites or Hispanics. "I have many bad moods," and "School makes me feel sick," discriminated depressed and nondepressed Hispanics but not whites and blacks. The first 10 symptoms on the Weinberg Screening Affective Scale in blacks, whites and Hispanics accounted for 44%, 47%, and 53% of variance, respectively. The total variance accounted for by all variables included were 51%, 51%, and 58%, respectively.

In the Weinberg Screening Affective Scale, if there is a pattern distinctive of each group, it would appear that whites were more likely to endorse self-punitive symptoms (eg, "I am lonely too much of the time," "I cause trouble for everybody"), while blacks tended to report complaints more related to a negative view of their immediate interpersonal world (eg, "School makes me nervous," "This is not a good world"). Hispanics had a mixture of negative views of themselves and their interpersonal relationships. All three groups reported 2 to 3 somatic symptoms, though they were different for each ethnic group. By Beck Depression Inventory and Weinberg Screening Affective Scale, all three groups were very likely to endorse school difficulties, sad mood, feelings of failure, indecision, and guilt or self-dislike.

Discussion

The prevalence of depression by self-report in adolescents from a large metropolitan school district of mixed ethnic background ranged from 13% to

TABLE 4
Severity of Depression Scores in Students Meeting Criteria for Depression*

	BDI = Positive (n = 336)	WSAS = Postive (n = 179)	Both Positive (n = 261)
BDI total score	22.3 ± 6.4	9.2 ± 4.1	26.2 ± 7.8
WSAS total score	15.2 ± 5.6	21.8 ± 4.3	25.7 ± 5.7

BDI = Beck Depression Inventory; WSAS = Weinberg Screening Affective Scale.
* Mean ± SD

TABLE 5
Rank Order of Beck Depression Inventory Items Predicting Score ≥ 16 by Ethnic Group

Symptoms	White	Black	Hispanic
G. Self-dislike	1	—	1
A. Sadness	2	7	5
M. Indecisive	3	1	2
N. Unattractive	4	2	14
P. Insomnia	5	13	16
D. Dissatisfaction	6	14	15
K. Anorexia	7	9	3
F. Punishment	8	3	12
C. Failure	9	8	7
O. Work Effort	10	12	11
L. Withdrawal	—	—	8
J. Crying	13	—	6
E. Guilt	—	—	—
I. Suicidal	—	—	—
H. Self Accusation	—	—	4
B. Pessimism	—	—	9
K. Irritability	—	—	10

18%. Hispanic females showed the highest scores, while white males the lowest. Being behind in school and female and nonwhite status predicted more depression by self-report. For the total group, these figures are somewhat higher than previously reported for adolescents.[14] By Beck Depression Inventory, whites in our sample were closer to the previous study, which was predominantly white (12% *v* 8.6%). The school district studied is predominantly lower socioeconomic status, which may be a factor in the higher rates, in addition to or separate from ethnic background. In this school district, student dropout is a significant problem, particularly in Hispanics. Clearly, those students who are behind in school had higher depression scores. Whether depression leads to falling behind in school or vice versa is unclear. In such a population, social disadvantage may lead to feelings of hopelessness and helplessness. Specific factors leading to minority student dropout bears further study.

In contrast to the previous study in adolescents

TABLE 6
Rank Order of Weinberg Screening Affective Scale Predicting Depressed Versus Nondepressed by Ethnic Group

Questions	White	Black	Hispanic
16. I feel lonely too much of the time	1	—	—
45. I cause trouble for everybody	2	—	16
24. I don't want to go to school anymore	3	6	2
37. I have too many aches and pains in my muscles	4	23	—
53. I can't have fun anymore	5	27	1
3. I can't do my homework anymore	6	25	—
41. It's hard to fall asleep and that bothers me	7	10	—
20. I am not as good as other people	8	14	20
6. Sometimes I wish I were dead	9	29	—
18. Nothing is ever done the way I like it	10	30	—
42. My friends don't like me anymore	—	1	—
49. School makes me nervous	16	2	—
27. It seems like some part of my body always hurts me	—	3	—
10. I can't do my school work anymore, it's too hard	20	4	17
47. Everybody picks on me	11	5	—
32. I'm too hard to get along with	12	7	—
14. This is not a good world	—	8	—
21. It seems like I'm always in trouble for fighting and that is not fair	—	9	10
13. I have too many bad moods	—	—	3
5. I can't do anything right	18	22	4
31. My friends don't want to be with me anymore	—	15	5
34. I daydream too much in school	—	28	6
12. School makes me feel sick	—	—	7
22. I have gained too much weight	17	24	8
43. When I wake up at night, it is hard to go back to sleep	—	—	9

using the Beck Depression Inventory,[14] our sample showed more depressive symptoms in females. Although we were unable to control for socioeconomic status, another factor might be that this sample was predominantly an older adolescent age group, when most males and females are postpubertal. Age is probably not a factor in this study because the design limits the age range studied, predominantly to one grade level.

As to whether self-reported measures are actually indicative of major depressive disorder is dependent on the ability to study the same population with structured interviews. It is expected that a number of subjects would meet criteria for "caseness" of major depressive disorder as in the study by Kashani et al,[28] while others would have symptoms but without clear disorder. Studies assessing the actual prevalence of depression in adolescents using interview and specific criteria for caseness and diagnosis are limited. Kashani and colleagues[28] interviewed a representative sample of 150 adolescents attending public school in Missouri and found that seven (4.7%) had major depressive disorder and five (3.3%) had dysthymic disorder by *DSM-III* criteria. Depressive symptoms sufficient for meeting criteria for major depressive disorder and dysthymic disorder were present in another 33 (22%) adolescents but these were not considered cases because (1) insufficient duration of symptoms, (2) treatment was not necessary, or (3) the depressive symptoms resulted in minimal dysfunction. Finally, 28 (19%) reported dysphoric mood for at least 2 weeks but did not meet criteria for depression. This left 77 (51%) not reporting any dysphoric mood.

While there is no evidence to date that the rate of actual depressive disorder is different between ethnic groups, this is the first study to report significant self-reported depressive symptomatology differences between ethnic groups in adolescents. While the diagnosis of depression cannot be made based only on self-report measures, there is substantial evidence that higher scores correlate with dysfunction, both current and future.[29-33]

The two self-report measures used identified different populations, with overlap between the groups. However, the group that was positive by both measures seemed significantly more depressed than either group alone. If one assumes that clinical depression is most likely in adolescents who are positive on both measures, then 261/3,294 (7.9%) may be judged likely to be clinically depressed, which is similar to prevalence rates obtained by interview.[28]

With regard to differences in depressive symptoms reported by different ethnic groups, black adolescents' tendency to externalize their depression by blaming their environment and others often leads to their depression manifesting in conduct problems. The depressed Hispanic adolescents seem to internalize their depression, blame themselves, feel hopeless, withdraw, and drop out. Since all conceptualizations of depressive symptoms and criteria have been determined in whites, it is important to examine the different presentations of depression in different ethnic groups.

Depression as a disease, having the same psychological and vegetative symptoms across ethnic groups, may manifest differently in various ethnic groups. It is important to consider depression as a primary disease entity in adolescents doing poorly in school, at home, or with free time, independent of their ethnic group. These two self-report measures can be useful in screening for depression and as adjuncts to clinical evaluation.

In summary, this study presents preliminary data on an instrument designed specifically for children and adolescents to recognize depression by self-report using established criteria. This initial study is intended as a first step in developing such an instrument. The next phase of validating this instrument includes interviewing a random sample of a screened population and is currently in progress.

Acknowledgments

This study was supported in part by a grant from NIMH (MH-39188) (GJE), by NIMH Mental Health Clinical Research Grant (MH-4115) (AJR), the Caleb C. and Julia W. Dula Educational and Charitable Foundation, Mr and Mrs Woody Hunt, Mr Robert McBride, Mr and Mrs Morton Myerson, Mr and Mrs Michael Quigley, and Phi Delta Kappa National Education Fraternity.

The authors thank Dr K. Z. Altshuler, Stanton Sharp Professor of Psychiatry, for administrative support, Ms Ann McLean and Linda Parkin-Feigenbaum for assistance in carrying out the study, David Savage for data entry, the high school principals, Health/Science Departments and students of the Dallas Independent School District for their participation and support of the project.

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Effect of Fluoxetine on the Electrocardiogram

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The effects of fluoxetine on the ECG were compared to those of placebo, imipramine, amitriptyline, and doxepin. ECG tracings at the beginning and end of several drug studies were evaluated retrospectively, without knowledge of the drug to which patients had been assigned. Mean changes in heart rate revealed a statistically significant decrease in the fluoxetine group. Active control drugs increased heart rate: increases were significant for imipramine and amitriptyline but not doxepin. Intraventricular conduction delays were noted in 5 patients who received imipramine and 1 patient who received amitriptyline: 4 of these patients developed left bundle branch block. No intraventricular conduction delays were noted in fluoxetine-treated patients.
(J Clin Psychiatry 46 [3, Sec. 2]:42-44, 1985)

The purpose of this study was to evaluate the effect of fluoxetine, a new antidepressant, on cardiac function as measured by the ECG. Fluoxetine is a straight chain phenylpropylamide and is not structurally related to the tricyclic antidepressants. Its effects on the ECG are compared in this study to those of the tricyclics imipramine, amitriptyline, and doxepin, as well as placebo.

Alteration of the electrophysiologic properties of the heart and the ECG as a result of the administration of tricyclic antidepressants has been recognized since these drugs were first introduced in the 1950s. The ECG changes include prolongation of the PR, QRS, and QT_c intervals and alteration of the ST segment and T waves. In toxic doses, life-threatening arrhythmias and a wide variety of conduction defects have been documented.[1-3]

METHOD

In this retrospective study, the ECG records from patients with major depressive disorder who had participated in double-blind fluoxetine studies were evaluated. Each patient had received fluoxetine, imipramine, amitriptyline, doxepin, or placebo for up to 6 weeks. The active study drugs were administered at therapeutic doses, with daily maintenance doses ranging from 40 to 80 mg of fluoxetine and 150 to 300 mg of imipramine, amitriptyline, or doxepin. For patients who participated in a geriatric study, the daily maintenance dose of doxepin ranged from 75 to 200 mg.

To be included in this analysis, the patient's baseline ECG had to have been obtained not more than 2 days before admission to the study, and the endpoint ECG had to have been obtained within 2 days of the patient's discontinuation of the study. In addition, the patient was required to have taken the study drug for at least 2 weeks.

The following observations were made for each ECG: heart rate, RR interval, PR interval, QRS complex, QT interval, QT_c, ST segment, T-wave amplitude (if outside the normal range), and any evidence of conduction abnormalities. These observations were compared for each baseline and endpoint ECG. The evaluation was performed without knowledge of the study drug the patient had received.

Also recorded were the patient's age, sex, weight, height, blood pressure on the date the ECG was recorded (or the most recent blood pressure before the ECG was recorded), and any concomitant medication(s). After interpretation of the ECGs, the name and dosage of the study drug, the duration of study drug treatment and, if applicable, the time interval (1 or 2 days) between the last dose of the study drug and the recording of the ECG were added to each patient's ECG record.

Statistical Analysis

The statistical analysis consisted of a two-tailed Wilcoxon signed-rank test of the changes from baseline to endpoint.

TABLE 1. Sex and Age Distribution of Subjects

Drug	Number of Patients		Age (Years)	
	Male	Female	Mean	Range
Fluoxetine	89	223	45.6	19-79
Placebo	64	102	41.1	18-67
Imipramine	53	112	42.6	18-69
Amitriptyline	15	39	44.8	24-67
Doxepin	27	29	60.9	23-88

RESULTS

A total of 1506 electrocardiograms from 753 patients met the inclusion criteria established in the study; 312 of the 753 patients had taken fluoxetine, 166 placebo, 165 imipramine, 54 amitriptyline, and 56 doxepin. The age and sex distribution by treatment groups is shown in Table 1.

Evaluation of the ECG tracings showed that the fluoxetine-treated patients had a reduction in the mean heart rate, whereas imipramine and amitriptyline treatment produced a significant increase in the heart rate (Table 2). Doxepin also increased the heart rate, but the difference was not significant. The placebo group remained unchanged.

There was an increase in PR intervals during amitripty-

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TABLE 2. Mean Changes (Δ) Recorded During the Study (Poststudy – Baseline)

	Heart Rate (bpm)		PR (msec)		QT_c (msec)		QRS (msec)	
Drug	Δ	p	Δ	p	Δ	p	Δ	p
Fluoxetine (N = 312)	−3.3	<.001	−1	.342	+2	.150	0	.293
Placebo (N = 166)	−0.3	>.5	−2	.028	−2	.313	0	>.5
Imipramine (N = 165)	+11.6	<.001	+5	.003	+12	<.001	+2	.001
Amitriptyline (N = 54)	+10.9	<.001	+6	.032	+11	.014	+3	.079
Doxepin (N = 56)	+2.3	.083	−1	>.5	+3	.140	+1	.395

TABLE 3. Percentage of Patients with Various Degrees of QRS Changes

Change	Fluoxetine	Placebo	Imipramine	Amitriptyline	Doxepin
Increase					
From 80 to 100 msec	2.9	6.0	7.3	7.4	5.4
From 80 to 120 msec	—	—	1.2	—	—
From 80 to 140 msec	—	—	0.6	—	—
From 80 to 160 msec	—	—	—	1.9	—
From 100 to 120 msec	0.3	—	—	—	—
From 120 to 160 msec	—	—	—	—	1.8
Total	3.2	6.0	9.1	9.3	7.2
Decrease					
From 100 to 80 msec	5.1	3.6	0.6	1.9	3.6
From 120 to 80 msec	—	0.6	—	—	—
Total	5.1	4.2	0.6	1.9	3.6

line and imipramine treatment and an insignificant decrease during fluoxetine, placebo, and doxepin therapy. Amitriptyline and imipramine also increased the mean QT_c interval. No significant changes in these measurements were seen with fluoxetine, placebo, or doxepin (Table 2).

On the average, QRS duration did not change during fluoxetine or placebo treatment and increased only from 1 to 3 msec during tricyclic antidepressant therapy. A more meaningful analysis of the percent of patients whose QRS duration changed during the study period is shown in Table 3. The only significant QRS prolongations, from 80 to 120, 140 or 160 msec, were during imipramine and amitriptyline treatment.

Intraventricular conduction delays were diagnosed in five patients who had received imipramine and one patient who had received amitriptyline. These ECG changes required discontinuation of the study drug in 4 of these patients (3 imipramine and 1 amitriptyline), all of whom had developed left bundle branch blocks. In 2 of the patients, the ECG tracings returned to normal shortly after discontinuation of imipramine therapy. The ECG of the third imipramine patient did not revert to normal. No follow-up information is available on the patient who had received amitriptyline. All 3 imipramine patients were crossed over to fluoxetine for 1 year after discontinuation of imipramine. No significant ECG changes were noted during their treatment with fluoxetine. Intraventricular (bundle branch) conduction remained normal.

Geriatric Studies

Of the 753 patients, 76 had participated in a geriatric study. Their ages ranged from 64 to 88 years. These patients had received either fluoxetine, 20–80 mg/day (N=42) or doxepin, 75–200 mg/day (control group, N=34). The mean ages were 70 years for the fluoxetine treatment group and 71 years for the doxepin group.

Prestudy ECGs showed abnormal findings in 13 (31%) fluoxetine patients and 7 (21%) doxepin patients. There were no ECG changes from normal to abnormal during up to 6 weeks of therapy with fluoxetine or doxepin.

DISCUSSION

The results of the study indicate that fluoxetine differs from imipramine and amitriptyline in its effect on heart rate. While fluoxetine decreases heart rate, imipramine and amitriptyline increase it. The difference is statistically and clinically significant. With the exception of this effect on heart rate, fluoxetine in therapeutic doses had no significant clinical effect on the ECG. In fact, the ECG remained normal in a patient who ingested 1000 mg of fluoxetine and another who ingested 200 mg of fluoxetine with 15 ounces of rum. The slowing of the heart rate and absence of conduction abnormalities in man is in keeping with similar observations made in dogs studied over a 12-month period, including periods during which toxic doses of the drug were administered (data on file, Lilly Research Laboratories).

Significant prolongation of the PR interval, left bundle branch block, and left anterior divisional block appeared in 3, 4, and 1 patients, respectively. The appearance of left bundle branch block was associated with acceleration of the heart rate and thus may represent acceleration-dependent bundle branch block, rather than a direct depressing effect of the drug. Such a mechanism would explain the fact that left bundle branch block was not recorded with fluoxetine, which slows the heart rate.

The significance of ECG changes produced by the tricyclics, and the relationship of these changes to cardiac dysfunction, is controversial.[44] If these changes are related to any deleterious effect, one can only conclude that fluoxetine is safer since it had no appreciable effect on the ECGs of 312 depressed patients who had received therapeutic

doses of fluoxetine. The experience with toxic doses of fluoxetine is limited, and no conclusions can be drawn at this time. However, the first two reports of overdose without subsequent ECG changes appear promising.

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Epidemiology of Childhood Depressive Disorders: A Critical Review

JAN E. FLEMING, M.D., AND DAVID R. OFFORD, M.D.

Abstract. The methodology of 14 recent epidemiological studies of childhood and adolescent depressive disorders was critically reviewed and findings summarized for prevalence, comorbidity, correlates, risk factors, and outcome. Shortcomings in sampling and considerable inconsistency in the measurement of depression in the studies made it difficult to draw firm conclusions about the prevalence and correlates of depression in young people. Nonetheless, it is likely that major depressive disorder is relatively uncommon in prepubertal children, increases in frequency in adolescents, and is significantly associated with such variables as family dysfunction and low self-esteem. Comorbidity of depression with other psychiatric disorders was also high in these nonpatient samples and it will be important in future work to assess the implications of this for the etiology, treatment, and prognosis of depressive disorders in children and adolescents. *J. Am. Acad. Child Adolesc. Psychiatry*, 1990, 29, 4:571–580.
Key Words: depressive disorders, epidemiology, children, adolescents.

The 1980s saw major advances in research into childhood and adolescent depressive disorders. There were new and promising developments in the areas of epidemiology (Angold, 1988; Costello, 1989; Rutter, 1989), biological correlates (Puig-Antich, 1987), natural history (Kovacs et al., 1984a,b), the influence of parental affective disorders (Weissman, 1988), and pharmacotherapy (Ambrosini, 1987), to name but a few. Contributing to these advances has been the use of a common approach to diagnosis, with the almost exclusive use by investigators, of either Research Diagnostic Criteria (RDC) (Spitzer et al., 1978), or *DSM-III* and *DSM-III-R* criteria (APA, 1980, 1987).

A review of epidemiological studies of childhood and adolescent depressive disorders, defined by current nosology, seemed timely for two reasons. First, although the area has recently been reviewed in part, the reviews have either not included several of the larger, most recent studies (Angold, 1988) or have not been directed specifically at depressive disorders (Costello, 1989). Second, while prevalence and measurement aspects of epidemiology have been emphasized, other important aspects, such as sampling, comorbidity, correlates, risk factors and outcome have not been. A better understanding of all aspects of the epidemiology of depression in young people is important for the planning of services, for generating and testing hypotheses about etiology, and eventually for launching effective preventive efforts.

Accepted March 20, 1990.

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Dr. Fleming is supported by an Ontario Mental Health Foundation Research Fellowship. Dr. Offord is supported by a National Health Scientist Award from Health and Welfare Canada. Dr. M. Boyle provided helpful comments on the manuscript.

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Search Methods and Inclusion Criteria

The methods used to locate studies included computer searches of the literature from 1980 to 1989 and verbal or written contact with experts in child psychiatric epidemiology regarding recently completed studies or manuscripts awaiting publication. Studies were included for review if nonpatient samples of children aged 6 to 19 were used, if prevalence of depressive disorders was assessed, and if operational diagnostic criteria were used. There were two exceptions to these criteria: one study that used a pediatric primary care sample was included because it was one of only a few studies to provide extensive correlate data (Costello et al., 1988), and another study that did not use diagnostic criteria for depression was included because it was one of only two community-based studies to provide data on the outcome of childhood depressive disorders (Kandel and Davies, 1982, 1986). Studies of preschool children were not included.

Findings

Fourteen studies meeting the above criteria were located (four of children, six of adolescents, four of both age groups) and will be summarized under the following headings: sampling, measurement, prevalence and comorbidity, outcome, correlates, and risk factors. For the purpose of this paper, 6- to 11-year-olds are referred to as children and 12- to 19-year-olds as adolescents with some minor exceptions (Table 1).

Sampling

To assess the adequacy of a sample, the reader should be provided information about the sampling frame, unit, and method; there should be sample size justification, usually determined according to the degree of confidence required by the investigator for the accuracy of the prevalence estimates; and statement of the response rate. The latter should be expressed as the number of participants divided by the number of subjects eligible for the study. The denominator should not be limited to eligible subjects who were actually available or contacted, as this could render deceptively high response rates. Also, to help understand

TABLE 1. *Summary of Selected Sample Characteristics of the Studies Reviewed*

Study	Age(s)	Stage[a]	*N*	Sampling Frame	Response Rate(%)[b]
I. Children					
1. Kashani et al. (1983)	9	1	641	Children born at one hosp.	56[c]
		2	189	in a New Zealand city between	88[d]
2. Anderson et al. (1987)	11		792	Apr. '72 and March '73	70[c]
3. Costello et al. (1988)	7–11	1	789	Families attending two	73
		2	300	HMO pediatric clinics	74
4. Kashani and Simonds (1979)	7–12		103	Children born at and families attending a family practice clinic at one medical center	?
II. Adolescents					
5. Deykin et al. (1987); Levy and Deykin (1989)	16–19		424	Two colleges (one, all female)	42
6. Kashani et al. (1987a,b)	14–16		150	Adolescents attending public schools in one city	72
7. McGee and Williams (1988); Frost et al. (1989)	13		762	As for studies 1, 2, above	70[c]
8. Schoenbach et al. (1982)	12–16		384	Students attending one junior high school	81[c]
9. Garrison et al. (1989)	11–17		677	As above (3 yrs. later)	89
10. Kandel and Davies (1982)	13–19[e]		8206	Students attending 20 high schools in New York State	81
III. Children and adolescents					
11. Bird et al. (1988)	4–16	1	777	Households in Puerto Rico	92
		2	386		88
12. Fleming et al. (1989); Boyle et al. (1987)	6–16		2852	1981 Census for province of Ontario	91
13. Velez et al. (1989)	9–18		776	Households in two upstate counties of New York	68[c]
14. Kashani et al. (1989)	8, 12, 17		210	Public school lists in one county	77

[a] For studies with more than one assessment stage.

[b] Numerator = number of subjects who participated; denominator = number of eligible children at the study inception, rounded to nearest whole number.

[c] Recalculated using above definition of response rate.

[d] For screen positives; not stated for screen negatives.

[e] 32 subjects were age 19 or more.

potential sources of bias in the prevalence estimates, information should be provided about significant differences between participants and nonparticipants on sociodemographic characteristics or any other relevant variables. Some of the sampling characteristics of the studies reviewed are summarized in Table 1, which demonstrates the considerable variation in the types and sizes of the samples. Information about sampling unit and method is not included in the table, but they were generally well described in the studies. It should be noted that four studies used the household as the sampling unit, three of them using one randomly selected child per household (Bird et al., 1988; Costello et al., 1988; Velez et al., 1989) and the fourth studying all children per household (Fleming et al., 1989). Selecting one child per household will tend to underestimate the prevalence of conditions that cluster within sibships. However, it is not known the extent to which this occurs for childhood affective disorders. In the authors' sample (Fleming et al., 1989), there was no clustering of depression within sibships (unpublished data, 1990). It should also be noted that just under half of the studies used school samples, which, because they exclude school dropouts and those with poor attendance, probably underrepresent children with depressive disorders.

Response rates were less than 75% in over half of the studies (Table 1). Compounding this problem, information about nonparticipants was usually inadequate, although in some cases census data were used to demonstrate similarities between participants and the population at large. Levy and Deykin (1989) were able to obtain information about depressive symptomatology for about 10% of their nonparticipants, finding for them a "slightly greater" level of symptoms than for participants. At this point, it can only be speculated that depressive symptoms in adolescents may contribute to nonresponse in surveys, leading to underestimation of the true prevalence of disorder.

While the majority of studies used a one-stage design for assessment, three studies used an initial screening stage (Stage 1) to select a smaller sample of children for more intensive interviewing (Stage 2). In one of these studies, nonrespondents at Stage 2 were more likely than respondents to have screened positive for psychopathology at Stage 1 (Costello et al., 1988), whereas in another, they were more likely to have screened negative for psychopathology at Stage 1 (Bird et al., 1988). These conflicting findings may reflect cultural differences in willingness to be involved in research (Pennsylvania and Puerto Rico were the two sites).

TABLE 2. *Measurement of Depressive Disorders*

Study Number[a]	Stage	Instrument(s)[b]	Informant(s)[c]	Diagnostic System	Definition of "Caseness"[d]
1.	1	Depressive symptom checklist	P, C	*DSM-III*	C,RS
	2	K-SADS-E	C	RDC	C,RC
		Rutter Child Scales (RCS) A,B	P,T		
2.		DISC	C	*DSM-III*	C, 4 levels of "caseness"[e]
		RCS A, B[e]	P,T		
3.	1	CBCL	P		Score in "clinical range"
	2	DISC	P,C	*DSM-III*	C,RS
4.		Clinical interview	P,C	*DSM-III*	C,RC
5.		DIS	A	*DSM-III*	C
6.		DICA	A,P	*DSM-III*	C plus impairment & need for treatment, RC[g]
7.		DISC (modified)	A	*DSM-III*	C by adolescent plus confirming symptoms by P/T
		RBPC	P		
		RCS B	T		
8.		CES-D	A	RDC	C
9.		CES-D	A	*DSM-III*	C
10.		6-item scale	A		Different cutoffs
11.	1	CBCL	P,T		Score in clinical range—RS
	2	DISC. CGAS	P,C,A	*DSM-III*	C plus CGAS < 61 = definite; C plus CGAS 61-71 = possible; RC
12.		SDI	P,T,A[h]	*DSM-III*	C,RS 3 levels of "caseness"[i]
13.		DISC	P,C,A	*DSM-III-R*	C plus depression scale score — 3 levels of caseness[j] — RC
14.		CAS	P,C,A	*DSM-III*	C,RS

[a] As in Table 1.

[b] Schedule for Affective Disorders and Schizophrenia for school-aged children—epidemiological version (K-SADS-E); Diagnostic Interview Schedule for Children (DISC); Child Behavior Checklist (CBCL); Diagnostic Interview Schedule (DIS); Diagnostic Interview for Children and Adolescents (DICA); Revised Behavior Problem Checklist (RBPC); Center for Epidemiologic Studies — Depression Scale (CES-D); Clinical Global Assessment Scale (CGAS); Survey Diagnostic Instrument (SDI-based on CBCL); Child Assessment Schedule (CAS).

[c] P = parent, C = child, T = teacher, A = adolescent.

[d] C = meets diagnostic criteria; RC = information from informants combined; RS = information from informants kept separate.

[e] Two additional sets of behavioral items relating to attention deficit disorder and depression were completed by parents.

[f] Based on pervasiveness of symptoms across sources.

[g] Adolescent responses only used for diagnosis; parent and adolescent responses used for "caseness."

[h] P & T for age 6-11, P & A for age 12-16.

[i] High, medium, and low "diagnostic certainty" based on symptom severity.

[j] Mild = C only; moderate = C plus one SD above mean on depression scale; severe = C plus 2 SD above mean.

Only one study mentioned sample size justification (Boyle et al., 1987). This omission can be understood in part by the fact that only for a minority of the studies was the original sample selected for the main purpose of determining prevalence estimates of psychiatric disorders in children (Kashani and Simonds, 1979; Boyle et al., 1987; Kashani et al., 1987a,b; Costello et al., 1988). For example, three studies (Kashani et al., 1983; Anderson et al., 1987; McGee and Williams, 1988) took their samples from an ongoing longitudinal study of New Zealand children, the major aims of which were to study various aspects of developmental disorders in children (McGee and Silva, 1981). Two studies used one high school that was originally chosen for a study of "biosocial factors in adolescent sexual behavior" (Schoenbach et al., 1982, 1983; Garrison et al., 1989). Finally, two of the larger studies (Bird et al., 1988; Velez et al., 1989) drew their samples from earlier surveys, the first from a study of adult psychiatric disorders (Canino et al., 1987) and the second from a survey designed to evaluate a set of "quality of child life indicators" (Kogan et al., 1977).

Measurement

From Table 2, we can see that five different structured diagnostic interviews and numerous checklists, alone or in conjunction with diagnostic interviews, were used to measure depressive disorders. For most studies, some information was provided about the psychometric properties of the instruments used and about methods of interviewer training. As might be expected, techniques for determining such parameters as reliability and validity were as numerous and varied as were the types of instruments. Although the Diagnostic Interview Schedule for Children (DISC) (Costello et al., 1984) was the most commonly used interview sched-

TABLE 3. *Prevalence of Depressive Disorder*

	Study Number	Time Frame	Informant[a]	Prevalence(%) of Disorder[c] MDD	DD	Other
I. Children						
						(minor depression)
	1	Current		1.8		2.5
		Past		1.1		9.7
	2	Past year		0.5[d]	1.7[d]	
						(cyclothymia)
	3	Past year	Parent	0	0.6	0.2
		Past year	Child	0.4	0.6	0.4
	4	Child		1.9		
	11	Past 6 mos.		2.5	("moderate" cases)	
	13	Past 6 mos.	Parent	0.5	("medium" cases)	
			Teacher	2.2		
	14	Current	Parent	0.7	ages, 8,12	
			Child	1.4		
II. Adolescents						
	5	Lifetime		8.3		
	6	Current		4.7	8.0	
	7	Current		0.4	1.6	
	8	Current		2.9		
	9	Current		4.4		
	10	Current				15–28[e]
	11	Past 6 mos.		3.7, 2.5, 3.1[f]		
	13	Past 6 mos.	Parent	1.0		
			Adolescent	6.4		
	14	Current	Parent	2.9		
			Adolescent	5.7		
III. Ages combined						
	12	Past 6 mos.		5.9		

[a] As in Table 1.
[b] Indicated for studies reporting estimates separately by informant.
[c] MDD — major depressive disorder, DD — dysthymic disorder, Other — as indicated.
[d] Combining all levels of "caseness."
[e] 15%, 18%, and 28% corresponding to cutoffs of 23, 21.8, and 19.5.
[f] For ages 13-18, 11-14, 15-20, respectively.

ule, variation across studies was introduced through use of different versions of the instrument, different types of interviewers (lay versus clinician), different informants (child only versus parent and child), and use of the same, as opposed to different interviewers for different informants.

Of the three studies that used Stage 1 "screening" questionnaires, one found the measure to be ineffective, identifying many children as depressed who were not depressed by the Stage 2 structured interview (false positives) (Kashani et al., 1983), and two others used the Child Behavior Checklist (CBCL) (Achenbach and Edelbrock, 1983) to screen for overall psychiatric disturbance but did not assess its accuracy in screening for depressive disorders (Bird et al., 1988; Costello et al., 1988).

From Table 2 it can be seen that the majority of studies used more than one informant, although studies of adolescents tended to rely on self-report only. Teachers, in general, were underrepresented as informants.

Finally, despite the consistent use of *DSM-III*, *III-R* or RDC criteria in all studies for making diagnoses, such consistency was not seen for defining "caseness." Studies differed in how data were combined from different informants, in whether criteria for "caseness" in addition to diagnostic criteria were required, in what particular additional criteria were required, and in whether or not differing "levels" of caseness were used. Methods used to combine data from different informants ranged from use of a computer algorithm (Velez et al., 1989) to use of clinical judgment (Kashani et al., 1983; 1987a,b; Bird et al., 1988). Studies that relied solely on checklist data to measure "RDC-like" or "*DSM-III*-like" syndromes also differed in how diagnostic criteria were applied to the checklist items (Schoenbach et al., 1982; Fleming et al., 1989; Garrison et al., 1989). These three studies were at a particular disadvantage because the instruments they used were not originally intended to measure depressive syndromes defined by current nosology. As a result, certain criteria relating to duration and intensity of symptoms were not well covered.

Prevalence and Comorbidity

Prevalence data for depressive disorders are summarized in Table 3. Confidence intervals were provided for many studies but were omitted here in order to simplify the presentation of data. Given the vast differences in sampling and

TABLE 4. *Comorbidity of Depression with Other Psychiatric Diagnoses*

Study Number[a]	Respondent	% of Depressed Sample with Particular Diagnosis[c]						
		Any	Anxiety	ADD/ADDH[b]	Conduct	Opp.	Alcohol Abuse	Drug Abuse
I. Children								
2		79	71	57	79			
3	Parent	50	0	50	50	0		
	Child	67	50	0	17	0		
II. Adolescents								
5							23	23
6		100	75	8	33	50	25	25
7		33						
III. Children & Adolescents								
11		68	32	31	52			
12[d]		63	45	23	22			

[a] As in Table 1.
[b] ADD/ADDH — attention deficit disorder with or without hyperactivity, OPP — oppositional disorder.
[c] Conduct or oppositional disorder.
[d] For "medium" cases, data from respondents combined.

measurement among studies discussed earlier, it is not surprising that the prevalence rates vary as much as they do.

For children, there are three points worth noting: (1) by any informant, the prevalence of major depressive disorder (MDD) in children is not high (< 3%); (2) two studies present preliminary evidence that MDD is more frequently identified by children than by parents; and (3) teacher-identified depression was reported in only one study which found that teachers identified more MDD for children than did their parents. In the two studies that reported on agreement among informants, there was generally little overlap among children identified by different informants (Costello et al., 1988; Fleming et al., 1989).

For adolescents, there are also three points worth noting from Table 3: (1) rates of adolescent-identified MDD range from 0.4% to 6.4% and are generally higher than rates reported for children; (2) parents identify less MDD for their adolescents than adolescents identify for themselves; and (3) the rates of depression were high when cutoff scores were applied to a self-report checklist (Kandel and Davies, 1982). This latter finding has also been reported with other self-report questionnaires (Angold, 1988; Fleming et al., 1989).

Only about half of the studies measured comorbid, nonaffective diagnoses (Table 4), finding that "pure" depression in children and adolescents is a rare entity. As would be expected, anxiety tended to be the most common comorbid diagnosis, but externalizing diagnoses and substance abuse were also common.

Outcome

Three of the reviewed studies were longitudinal and two of them have published data on the outcome of childhood or adolescent depression. McGee and Williams (1988) followed 121 children from the New Zealand cohort who were diagnosed at age 9 with current depression (CD) (N = 17), past depression (PD) (N = 23), or as not depressed (ND) (N = 81). They found that the CD group had more depressive disorder and more emotional and behavioral symptoms at ages 11 and 13 than did the PD and ND groups. In the CD group, 31% of the children had persistent depressive disorder at one or both follow-up assessments. Weaknesses of this study are fivefold: (1) inconsistencies in the measurement of depression and definition of "caseness" at all three ages; (2) lack of blind follow-up for all cases at age 13; (3) failure to assess comorbid diagnoses at age 9; (4) failure to assess outcomes other than psychopathology; and (5) follow-up of only a small proportion of the original sample. That is, slightly less than half of the 9-year-olds who were administered the structured interview were included in the follow-up study. This, in turn, represents only 13% of the 955 eligible children at age 9.

Kandel and Davies (1986) also followed a small subsample (12%) of adolescents from their original survey 9 years later. They found that those scoring "highly depressed" at ages 15 and 16 were more likely than those scoring "not highly depressed" to experience a variety of adverse psychological and social outcomes in young adulthood. There were some minor sex differences, with depressed girls experiencing more difficulty later in their family roles and boys in their work roles. The major weakness of this study was that diagnostic criteria were not used to measure depression. Instead, three different cutting points for the 6-item scale were explored, yielding a range of prevalence estimates (Table 3). The cutoff chosen to categorize subjects as "highly" or "not highly" depressed for the follow-up study was found in an earlier validation study to have a sensitivity of only 50% in indentifying adolescents with a psychiatrist-diagnosed *DSM-III* depressive disorder (specificity not stated). Therefore, the results of this study cannot be generalized to adolescents with depressive disorders. Also, because there was oversampling of homerooms with high marijuana use for follow-up, the cohort selected is not likely to be representative of the original sample.

Correlates and Risk Factors

Eleven variables were found which were measured cross-sectionally in two or more studies. The same kinds of inconsistencies in measurement seen for diagnosis and "caseness" existed for these correlates. Different measures, respondents, and cutoff values were used in assessing most of the correlates. There was also considerable variation in the type of dependent measure used (categorical versus continuous) and the type of analysis (univariate versus multivariate). Stronger associations are usually found using continuous measures and univariate analyses.

For only two of the eleven variables was there a consistent lack of association with depression: (1) low IQ (Kashani et al., 1983; Williams et al., 1989); and (2) poor physical health (Costello et al., 1988; Bird et al., 1989), although it should be noted that each variable was measured in only two studies. A consistently significant association with depression was found for four variables: (1) Age—adolescents had significantly more depressive disorders than children in studies that included both age groups (Bird et al., 1988; Fleming et al., 1989), with one exception—Kashani et al. (1989) found mean self-report ratings of depressive symptoms, but not prevalence of depressive disorders, to be significantly higher in 17-year-olds than in 8- and 12-year-olds; (2) Family dysfunction—four studies, all using different measures of both depression and family functioning, found depression to be significantly associated with some aspect of family dysfunction (Kandel and Davies, 1982; Garrison et al., 1985; Bird et al., 1988; Kashani et al., 1988); (3) Low self-esteem—this was significantly associated with depression in three studies (Kandel and Davies, 1982; Kashani et al., 1983; Williams et al., 1989); and (4) Stressful life events—these were significantly associated with depression in one of the combined age group studies (Bird et al., 1989), with child- but not parent-identified depression in one of the child studies (Costello et al., 1988), and for white but not black students in one of the adolescent studies (Garrison et al., 1985).

Findings for the remaining five variables were generally inconsistent across studies: (1) Gender—in children, depressive disorder was just as common in girls as in boys in three studies (Kashani et al., 1983; Fleming et al., 1989; Velez et al., 1989) and more common in boys than girls in two studies (Anderson et al., 1987; Costello et al., 1988), although in the latter study this was for child-identified depression only. For adolescents, the findings were less consistent. Five studies found more depression in girls than boys (Kandel and Davies, 1982; Deykin et al., 1987; Kashani et al., 1987a; Garrison et al., 1989; Velez et al., 1989), and another found significantly more depression for girls, using the lowest threshold for disorder but not for two higher thresholds (Fleming et al., 1989). There were more boys than girls with depression in one study of 13-year-olds (McGee and Williams, 1988) and no sex effect in three studies (Schoenbach et al., 1982; Bird et al., 1988; Kashani et al., 1989), the latter two studies including both children and adolescents; (2) Parental psychopathology—there was a small but significant association between adolescent and parental depressed mood for a subsample of adolescents in one study (Kandel and Davies, 1982). A significant association between childhood and adolescent depressive disorder and maternal history of psychiatric problems was found in one study (Bird et al., 1989), while no association with a measure of family adversity (which included family psychiatric history) was found in another (Costello et al., 1988); (3) Race—depression was not more prevalent in whites compared to blacks in one study of children (Costello et al., 1988). It was more common in black than white adolescent males in one study (Schoenbach et al., 1982) and more common in black than white adolescent females in another (Garrison et al., 1989). There were no race effects in two studies (Kandel and Davies, 1982; Kashani et al., 1988); (4) School performance—measures of poor academic performance were not significantly associated with depression in four studies (Kandel and Davies, 1982; Kashani et al., 1983; Costello et al., 1988; Williams et al., 1989), whereas, there was a significant association in three (Bird et al., 1989; Fleming et al., 1989; Garrison et al., 1989), although in the latter study this was true only for white males and black females; and (5) Socioeconomic status (SES)—low SES, variably defined, was not significantly associated with depression in children (Kashani et al., 1983; Costello et al., 1988; Williams et al., 1989). For adolescents, parental education was not a significant correlate of depression (Kandel and Davies, 1982; Schoenbach et al., 1982; Kashani et al., 1988; Garrison et al., 1989), whereas low family income was (Kandel and Davies, 1982; Schoenbach et al., 1982). For children and adolescents combined, there was significantly more depression in the lower compared to the middle and upper SES levels in one study (Bird et al., 1988) and no association with SES in another (Kashani et al., 1989).

Two of the three longitudinal studies reported on predictors of the course of depressive symptoms (Kandel and Davies, 1986) and risk factors for new cases of depression (Velez et al., 1989). Using multiple regression analyses, Kandel and Davies (1986) examined the influence of numerous background and psychosocial variables, as well as events occurring between the initial and follow-up assessments ("intervening events") as predictors of depressed mood in young adulthood. The only positive predictors for both males and females that retained their significance when controlling for other variables were initial level of depression and two intervening events—total months of cigarette use and number of periods of unemployment.

Velez et al. (1989) used logistic regression to examine long- and short-term risk factors for major depressive disorder. For the first analysis, risk factors were measured when the cohort was aged 1 to 10 years and disorder was measured 8 years later. Significant relative risks (controlling for age, sex, and SES where relevant) were obtained for low maternal education and parents never having been married, while other measures of SES, race, religion, parental sociopathy, and pregnancy problems were not significant. For the second analysis, risk factors were measured at ages 9 to 18 and disorder 2 years later. Significant relative risks were obtained for gender (greater risk for females), presence of stepfather, maternal emotional problems, history of school

failure, and history of receiving mental health treatment. Numerous other factors, including age, SES, stressful life events, paternal emotional problems, and parental sociopathy were not significant. While the authors of this study note that low prevalence of depression (Table 3) reduced the statistical power for evaluating risk factors, it would also appear that children with depressive disorders at ages 9 to 18 were not removed from the analyses of short-term risk factors which would tend to inflate the degree of association found with depressive disorders 2 years later.

Discussion

Sampling

Overall, there were three major sampling problems identified for the studies: (1) lack of sample size justification; (2) small and/or nonrepresentative samples (i.e., schools); and (3) low response rates with inadequate information for understanding potential biases.

There was, in short, a conspicuous paucity of large, representative samples (including children and adolescents) chosen for the express purpose of determining precise estimates of the prevalence of depressive disorders (and other psychiatric disorders) and their correlates. It will be essential in future studies to ensure the validity of the findings that more attention be paid to these sampling issues.

Measurement

There was marked inconsistency in the measurement of depressive disorders; in the types of instruments, in the way similar instruments were used, in the number and types of informants, and in case determination—inconsistencies that have been identified before (e.g., Angold, 1988; Costello, 1989). One effect of inconsistent case determination was demonstrated by Kazdin (1989) who showed that different methods of defining depression in the same sample led to the selection of different children as depressed and to the identification of different correlates for each group. He pointed out that, depending on selection criteria, one could draw different conclusions about the nature of depression in children.

The authors did not critique the psychometric properties of the instruments used in the studies, as many of them have been reviewed in detail elsewhere (e.g., Gutterman et al., 1987; Costello and Angold, 1988; Edelbrock and Costello, 1988), but suffice it to say that difficulties with reliability and validity still need to be worked out. Similar reviews of instruments used for correlate identification would be welcome. Fortunately, measurement problems are currently being addressed by a major NIMH initiative to develop reliable and valid measures of childhood psychiatric disorders and correlates suitable for use in large scale epidemiological studies (NIMH, 1989).

Finally, although the authors are encouraged by the now routine use of standard diagnostic criteria in assessing depression in young people, there is still, as succinctly put by Winokur et al. (1988), "the insidious problem of intercenter inconsistencies in criteria interpretation and application" (p. 684).

Prevalence and Comorbidity

Because of the methodological inconsistencies in sampling and measurement discussed above, it would be premature to draw any firm conclusions about prevalence, other than that MDD appears to occur in less than 3% of children and increases in frequency in adolescence. There is some suggestion that DD and minor depression may be more prevalent than MDD but only a minority of studies have included these diagnoses. Other affective diagnoses such as adjustment disorder with depressed mood and subtypes of MDD (with psychotic features, melancholic, seasonal) (APA, 1987) still need to be assessed in community samples.

High comorbidity of depressive and nondepressive disorders, including overlap with both anxiety and behavior disorders, was clearly evident. The next task is to understand the etiological treatment and prognostic implications of this comorbidity, a task that has been addressed to some extent with clinical samples. For example, there is preliminary evidence to suggest that comorbid anxiety has little impact on biological correlates, familial aggregation of depressive disorders, and outcome and response to treatment in children referred for depression (see Puig-Antich and Rabinovich, 1986). It is unclear, though, if this would apply for nonreferred children or those referred, but not specifically, for depressive symptomatology. There has been less attention paid to comorbid conduct disorder, but one study found that it neither affected recovery from a depressive episode nor contributed to recurrence in children referred for depression (Kovacs et al., 1988). There is, though, some interesting speculation that comorbid conduct and possibly attention deficit disorders may predict a bipolar outcome (Carlson and Kashani, 1988; Kutcher et al., 1989). While comorbid substance abuse was measured in only two community samples (Deykin et al., 1987; Kashani et al., 1987b), the findings from these studies of substance abuse in about a quarter of depressed adolescents, supported by evidence from clinical samples (DeMilio, 1989), suggests that this will be an important association to explore additionally.

Finally, both Fleming et al. (1989) and Kashani et al. (1987b) found that comorbidity increased as the severity of depression increased. One implication of this finding is that differences in outcome which might be attributed to comorbid conditions (e.g., depression only, better outcome than depression plus another disorder) may have less to do with the comorbid condition than with increased levels of depression. It will, therefore, be important to consider severity of depression when examining the impact of comorbidity in future outcome studies.

Outcome

Only two studies, with major methodological limitations, addressed the outcome of childhood and adolescent affective disorders. Nonetheless, their findings are consistent with those of other follow-up studies of clinical samples (Kovacs et al., 1984a,b; Asarnow et al., 1988; Garber et al., 1988) and of children of parents with affective illness (Apter et al., 1982; Laroche et al., 1987; Keller et al., 1988) in showing that depressive symptoms and disorders are per-

sistent and associated with poor psychosocial outcomes. Attention must be paid in future longitudinal studies to minimizing sample loss, to assessing the impact of comorbid disorders, and to assessing a wide range of outcomes.

Correlates/Risk Factors

Results were inconsistent across studies for about half of the correlates studied, probably due to method variance in sampling, measurement (of correlates and of depression), and in analytic techniques. Of particular interest are the inconsistent findings for gender in adolescents. Because there is substantial evidence that depression is more prevalent in adult women than men (Weissman and Klerman, 1977; Weissman et al., 1984), the challenge is to determine the age of onset of this gender effect and the factors of puberty or social role development related to its onset. There are some preliminary data available from the New Zealand cohort that suggest that the onset of a female preponderance of depression occurs between the ages of 13 and 15 (R. McGee, personal communication, June, 1989).

Findings from the reviewed studies confirm earlier evidence that the prevalence of depression increases from childhood to adolescence (e.g., Rutter et al., 1970). Still, little is known about the reasons for this increase or about the nature of any differences between prepubertal- and adolescent-onset depression. Preliminary findings have suggested that prepubertal-onset depression may be associated with a greater familial loading of depression (Strober et al., 1988; Weissman et al., 1988; Puig-Antich et al., 1989).

Psychosocial variables such as family dysfunction, low self-esteem, and stressful life events were also found to be associated with depressive disorders. These findings are also supported by similar results from clinical samples (e.g., Goodyer et al., 1985; Asarnow and Bates, 1988), other school-based studies (e.g., Tolor and Murphy, 1985; Friedreich et al., 1988; Reynolds and Rob, 1988), and "high-risk" studies (e.g., Hammen, 1988). More careful investigation of these variables as risk or perpetuating factors will require longitudinal approaches.

Three additional points about correlates and risk factors deserve mention. First, most of these studies did not examine the correlates of depression occurring as a single disorder, which, as we saw earlier, occurred infrequently. Only Frost et al. (1989) examined "pure" depressives in the New Zealand cohort at age 13 and found that they did not differ from normals on neuropsychological correlates, whereas a group with multiple disorders (25% with depression) was significantly impaired. Anderson et al. (1989), studying the New Zealand cohort from ages 5 to 11, combined those with "pure" depression and "pure" anxiety and found this combined group did differ significantly from normals on several cognitive and social correlates, but the group with multiple disorders (56% with depression) was particularly impaired. Also, the "pure" anxious-depressed group was not distinguishable on most variables from the "pure" conduct and "pure" attention deficit disorders groups. Clearly, the contribution of comorbid disorders in understanding the correlates of childhood depression warrants careful study. Second, Offord et al. (1989) found that the correlates of "pure" disorders (conduct disorder, hyperactivity, emotional disorder, and somatization) differed in important ways by informant. Of the studies reviewed here, only Costello et al. (1988) looked at correlates separately by informant and found, for example, that gender and stressful life events were significant for child- but not parent-identified disorder. Third, Offord et al. (1989) point out that assessment of correlates is also complicated when the source for disorder is the same as the source for correlate identification. For example, in three of the four studies that measured family functioning, adolescents served as informants both for this correlate and for depression. It would be important to know if independent assessment of family dysfunction by a clinician, for example, would also yield a significant association with depression.

In closing, the introduction in the 1980s of a common nosology for diagnosing depression in young people and instruments to assess it have contributed to advances in our understanding of the epidemiology of this important condition. The challenge for investigators in the 1990s will be to address the important methodological issues that have been identified here, and thus help move the field a step further toward our ultimate goal—prevention.

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Preliminary Data on the Relationship Between Nortriptyline Plasma Level and Response in Depressed Children

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Twenty-two subjects 6–12 years old who met Research Diagnostic Criteria and DSM-III *criteria for major depressive disorder received a fixed daily dose of nortriptyline during an 8-week protocol. Weekly plasma levels were measured; the raters performing behavioral assessments were blind to these levels. There was a highly significant difference between the mean steady-state plasma levels and the milligram-per-kilogram doses of the responders and nonresponders. The data suggest that the lower limit of the therapeutic range of nortriptyline in children (over 60 ng/ml) is similar to that reported for adults. The disadvantages of the use of a milligram-per-kilogram dose rather than a pharmacokinetic approach are discussed.*

(Am J Psychiatry 143:1283–1286, 1986)

Geller et al. have previously reported on the similarity of the pharmacology of nortriptyline in adult and pediatric age groups with respect to single-dose kinetics to predict steady-state plasma levels and dose (1), pharmacokinetic factors (2), serial monitoring and the time to achieve steady-state plasma levels (3), and the interaction with chlorpromazine (4). In this article we report on the preliminary data at midpoint from an ongoing study of the relationship between mean nortriptyline steady-state plasma levels and response in children. Data from similar studies in adult samples suggest that response is most likely to occur at 50–150 ng/ml (5). We chose to investigate the lower limit of the pediatric therapeutic range. The upper limit was not studied because of the high probability of cardiotoxicity in adults at plasma levels of 150–170 ng/ml (6) and the likelihood that this would also be true for children because of the other pharmacological similarities between the two age groups.

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The authors acknowledge the technical assistance of Patti Hollis.
Supported in part by NIMH grant MH-40273.

METHOD

Subjects were boys and girls 6–12 years old who met Research Diagnostic Criteria (RDC) and *DSM-III* criteria for major depressive disorder, had a Children's Depression Rating Scale (7) score of 40 or more, were in good physical health, and had been ill for at least 2 months. Subjects were excluded if they had an IQ less than 75, had been taking psychotropic medication during the prior month, or had other *DSM-III* axis I psychiatric disorders except the associated features (8) or major medical or neurological disorder. Delusional subjects were excluded due to the poor response to conventional doses of tricyclic antidepressants in delusional adults (9). Baseline assessments included the pediatric version of the Schedule for Affective Disorders and Schizophrenia-Present Episode version (Kiddie-SADS) (10), administered to the mother and child separately; the Children's Depression Rating Scale, administered to the mother and child together; the modified Asberg Side Effects Scale (11) (items 1 and 2 modified for children; see appendix 1); a physical examination; Tanner staging for puberty; and a complete blood count, SMA-18, and urinalysis. A baseline ECG and blood pressure measurement (with the subject recumbent and after standing for 1 minute) were also obtained. All scales were administered by raters with established interrater reliability.

All subjects were outpatients; the families of suicidal subjects elected to institute precautions at home. Informed consent was obtained from the parent and child assent from the child (for children over age 7) after the procedures had been fully explained. These subjects also participated in the pharmacokinetic and diagnostic studies reported elsewhere (1–4, 8, 12). No other treatments were given during the protocol.

Following baseline assessment, each subject was kept medication free for a 2-week period. At the end of the 2 weeks, a repeat Children's Depression Rating

Scale was administered, and the 23 subjects who had a score of 36 or more entered the drug protocol.

The fixed daily doses were based on the open pilot data (13). A twice daily regimen was used because of the mean±SD half-life β phase of nortriptyline of 17.6±3.7 hours (range=13.6–24.1) in prepubertal children (2). Because there is a five- to sevenfold variation in the rate of nortriptyline metabolism in 6–12-year-olds (1–3), baseline single-dose kinetics (1) were performed to determine the subjects' rate of metabolism; these data were also used to develop tables to predict optimal dose (1). Slow metabolizers were those subjects with a diminished rate of nortriptyline elimination evidenced by a 24-hour nortriptyline plasma level of over 30 ng/ml after a single dose (1, 3). These subjects were administered the 20-mg dose to ensure that their steady-state plasma levels would not exceed 150–170 ng/ml, the adult toxic range (6).

Subjects 6–9 years old and subjects 10–12 years old who were very slow metabolizers were administered a fixed daily dose of 20 mg, given in a twice-daily dose of 10 mg at 7:00 a.m. and 10 mg at 7:00 p.m. Other subjects 10–12 years old were administered a 50-mg fixed daily dose, given in a twice-daily divided dose of 25 mg at 7:00 a.m. and 25 mg at 7:00 p.m., or a 20-mg dose if their 24-hour nortriptyline level after a single dose was over 30 ng/ml.

Each subject received the following weekly assessments by raters who were blind to the single-dose kinetics and to the weekly plasma levels: the Children's Depression Rating Scale, the modified Asberg Side Effects Scale, an ECG tracing, blood pressure with the subject recumbent and after standing for 1 minute, and nortriptyline plasma level. Each subject was maintained at the fixed daily dose for 8 weeks. The rationale for the 8-week protocol has been described elsewhere (13). A Children's Depression Rating Scale score of 20 or less, with a rating of 2 or less on all *DSM-III* criteria items, is the optimal response. A Children's Depression Rating Scale score of 21–25 indicates doubtful depression, and, therefore, subjects with a score of 25 or less did not have their dose increased and were considered responders.

Plasma samples were drawn into glass oxalated tubes with non-plasticizer-containing caps (14) 9–11 hours after the 7:00 a.m. dose (4:00–6:00 p.m.), coded, and separated and stored at −20°C before weekly shipment on dry ice to the Nathan S. Kline Institute for blind duplicate assay by gas chromatography (15).

Pills were given to the family once a week in the exact amount they would need for that week, plus four extra pills given at the beginning of the study in case a pill was accidentally lost. Each subject was instructed to place the pills in a weekly pill minder, which has slots for each day of the week. At each weekly visit there was a pill count and a check of the pill reminder. Noncompliance was defined as the child having missed more than one dose in a week or more than one dose in 2 consecutive weeks.

RESULTS

Twenty-three subjects entered the study, and 22 completed the protocol (table 1). One subject was dropped due to noncompliance. There were 16 boys and six girls 6–12 years old (mean±SD=9.23±1.74). Social class distribution (16) was as follows: classes I and II, 41% (N=9); III, 32% (N=7); and IV, 27% (N=6). Duration of illness was as follows: 2 years or less, 18% (N=4); 3 or 4 years, 32% (N=7); and 5 years or more, 50% (N=11). Twenty subjects met the RDC for endogenous depression. Fourteen subjects responded to treatment, and eight subjects did not respond.

There were no significant differences between responders and nonresponders with respect to age ($t=.24$, $df=19.6$, $p=.810$), sex ($\chi^2=.033$, $df=1$, $p=.856$), weight ($t=-.36$, $df=20$, $p=.726$), social class ($\chi^2=.496$, $df=3$, $p=.920$), duration of illness ($\chi^2=3.199$, $df=2$, $p=.202$), baseline Children's Depression Rating Scale score ($t=-.41$, $df=20$, $p=.686$), or week 2 Children's Depression Rating Scale score ($t=.66$, $df=20$, $p=.513$).

The mean±SD milligram-per-kilogram doses of the responders (1.02±0.21, range=0.64–1.57) and of the nonresponders (0.82±0.51, range=0.40–2.01) were significantly different ($Z=3.83$, $p=.0001$, Wilcoxon rank sum test; 95% confidence interval .09, .52). Milligram-per-kilogram doses correlated significantly with the week 8 scores on the children's depression scale (Spearman's $r=-.44$, $p=.042$) (see figure 1), with the differences between baseline and week 8 depression scores (Spearman's $r=.46$, $p=.331$), and with mean nortriptyline steady-state plasma levels (Spearman's $r=.56$, $p=.007$).

The mean±SD nortriptyline steady-state plasma levels of the responders (60.31±20.90 ng/ml, range=18.8–111.5) and nonresponders (30.86±17.64 ng/ml, range=12.0–54.3) were significantly different ($Z=2.87$, $p=.004$, Wilcoxon rank sum test; 95% confidence interval 6.0, 51.1). Mean nortriptyline steady-state plasma levels correlated significantly with the week 8 depression scores (Spearman's $r=-.47$, $p=.026$) (see figure 1) and with the difference between baseline and week 8 depression scores (Spearman's $r=.48$, $p=.022$).

In summary, 12 of the 13 subjects with a dose of 0.89 mg/kg or more were responders. In addition, all nine subjects who had mean nortriptyline steady-state plasma levels of 60 ng/ml or more were responders. Four of the seven subjects who had mean nortriptyline steady-state plasma levels of 40–59 ng/ml also responded.

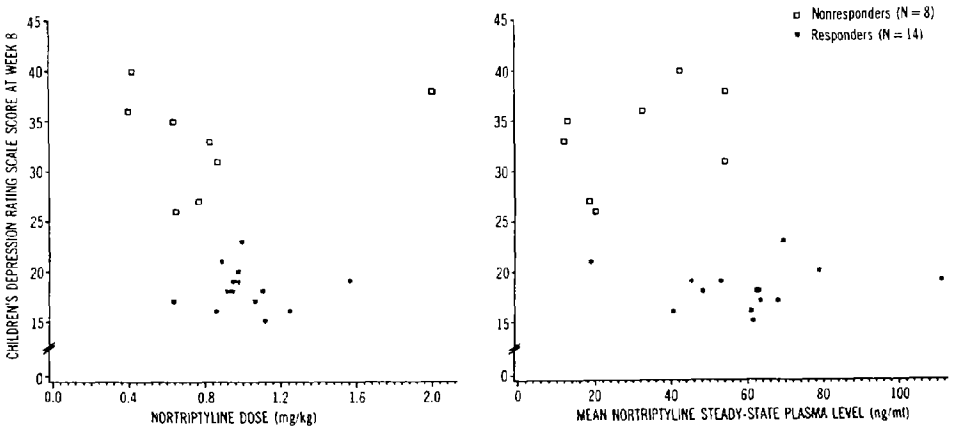
This was a fixed-dose protocol. However, after the protocol ended, seven of the eight nonresponders (subjects 1, 7, 13, 15, 16, 17, 21) improved when their dose was increased to achieve mean nortriptyline steady-state plasma levels of 60–100 ng/ml; this was done according to previously developed predictive tables based on their 24-hour level after a single dose

TABLE 1. Nortriptyline Treatment and Depression Scores for 22 Children With Major Depressive Disorder

Child	Age (years)	Nortriptyline: Fixed Dose (mg/day)	Nortriptyline: Dose by Weight (mg/kg)	Plasma Level (ng/ml): Mean	Plasma Level (ng/ml): SD	Children's Depression Rating Scale Score: Baseline	Children's Depression Rating Scale Score: Week 2[a]	Children's Depression Rating Scale Score: Week 8[b]
1	8	20	0.65	20.1	1.81	52	43	26
2	6	20	1.12	61.3	6.67	51	45	15
3	11	50	0.86	40.4	4.31	51	48	16
4	12	50	1.07	63.5	10.68	45	40	17
5	6	20	1.00	69.6	12.39	48	48	23
6	8	20	0.77	18.5	1.51	45	48	27
7	10	50	0.87	54.1	6.77	49	40	31
8	11	50	0.93	62.3	11.41	57	51	18
9	10	50	1.25	60.8	9.45	53	38	16
10	10	20	0.64	68.1	14.23	50	47	17
11	8	20	0.92	48.3	8.33	56	47	18
12	8	20	0.95	45.3	8.86	49	52	19
13	9	20	0.64	12.8	1.58	53	49	35
14	7	20	0.89	18.8	2.66	43	37	21
15	10	20	0.42	42.5	5.78	45	44	40
16	10	20	0.40	32.6	3.42	47	36	36
17	10	50	2.01	54.3	5.60	60	39	38
18	10	50	1.57	53.0	6.32	48	46	19
19	8	20	0.98	79.0	10.94	52	42	20
20	11	50	1.11	62.5	8.14	50	42	18
21	8	20	0.83	12.0	3.23	56	49	33
22	12	50	0.98	111.5	17.08	48	40	19

[a]After subject was drug free for 2 weeks.
[b]After 8 weeks at a fixed daily dose of nortriptyline.

FIGURE 1. Relationship Between Nortriptyline Dose and Nortriptyline Steady-State Plasma Level and Depression Scores in 22 Children With Major Depressive Disorder



(1). Subject 14 relapsed 3 days after the protocol ended and then responded when his dose was increased, according to the predictive tables, to achieve plasma levels over 60 ng/ml.

ECG tracings were all within published guidelines for nortriptyline in prepubertal children (12). Side effects were minimal and transient.

DISCUSSION

These results suggest that prepubertal children with major depressive disorder who receive sufficient nortriptyline to obtain steady-state plasma levels of 60–100 ng/ml will have a good clinical response and will not experience adverse ECG or other side effects.

Although it was not in a controlled design, seven of the eight nonresponders recovered after the protocol ended when their plasma levels were increased to 60–100 ng/ml.

These were outpatients whose plasma levels, monitored over the 8 weeks, had a mean±SD coefficient of variation of 13.8%±3.4% (range=8%–21%), indicating excellent compliance (3).

Both a milligram-per-kilogram dose and mean nortriptyline steady-state plasma levels correlated with response. However, the main concerns with the use of a milligram-per-kilogram dose for a drug like nortriptyline, which has a low toxic to therapeutic ratio (6) and a wide genetic variation in rate of metabolism (1), are that children who are slow metabolizers might develop toxic or nontherapeutic plasma levels and that children who are rapid metabolizers might be at subtherapeutic plasma levels. For example, subject 21 in this study had his dose adjusted after the protocol ended to achieve mean nortriptyline steady-state plasma levels over 60 ng/ml. To obtain these plasma levels he required 3 mg/kg; had he received 0.89 mg/kg, he would have had subtherapeutic plasma levels. A 41-kg subject we entered on another protocol needed 10 mg every other day to obtain a mean nortriptyline steady-state plasma level of 55 ng/ml. If he had received 0.89 mg/kg (35 mg daily) (assuming linearity of nortriptyline kinetics [2]), his mean nortriptyline steady-state plasma level would have been 385 ng/ml, i.e., in the toxic range. Therefore, the clinician using milligram-per-kilogram dose would need to perform ECGs daily for the first 4 days, as was done in our open pilot study (13), to be sure the child's plasma levels are in a safe range.

On the basis of the previously cited studies and other relevant publications (1–4, 12), we strongly recommend administering an age-appropriate single dose, obtaining a nortriptyline plasma level 24 hours later, and then adjusting the dose according to the pediatric suggested dose tables (1) to obtain mean nortriptyline steady-state plasma levels of 60–100 ng/ml. These mean steady-state plasma levels are most likely to produce a safe response (12). Since children's plasma levels are stable over time (3), an ECG need only be performed at baseline and once at steady-state (3, 12). The effect of fever, aspirin, acetaminophen, and minor intercurrent illness on elevating children's nortriptyline plasma levels has been discussed elsewhere (3). We do not recommend beginning any child at a fixed maintenance dose of nortriptyline unless the child has first received the single-dose, 24-hour plasma level procedure and has had his or her suggested maintenance dose determined through the predictive table (1).

Finally, the Food and Drug Administration has approved the use of nortriptyline in children only for investigational purposes, and, therefore, clinicians should so inform families.

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APPENDIX 1. Items Modified for Children on the Asberg Side Effects Scale

1. Physical tiredness
   - None (0)
   - Feels tired, no naps (1)
   - Head on desk at school or after school naps (2)
   - Sleeping 1–2 hours longer than usual at night (going to bed earlier or awakening later, or with great difficulty) (3)
2. Sleep disturbance
   - Normal sleep (0)
   - Difficulty falling asleep (1)
   - Early awakening (2)
   - Less than 3 hours' sleep (3)

VOL. 26, NO. 1, 1990

Double-Blind Placebo-Controlled Study of Nortriptyline in Depressed Adolescents Using a "Fixed Plasma Level" Design[1]

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Abstract

We performed a random assignment, double-blind, placebo-controlled study of nortriptyline (NT) in postpubertal 12- to 17-year-olds with Research Diagnostic Criteria (RDC) and *DSM-III* major depressive disorder. The protocol included a 2-week placebo washout phase and an 8-week double-blind, placebo-controlled phase with weekly plasma level monitoring. Active subjects had their plasma level placed at 80 ± 20 ng/ml by using previously developed tables to determine the starting dose from a plasma level drawn 24 hours after a single dose administered at baseline. The study population was severely depressed and had a chronic, unremitting course prior to study; a high percentage of family histories with affective disorder, alcoholism, and suicidality; and a high rate of comorbidity. Of the 52 subjects enrolled, there were 17 placebo washout responders, 4 dropouts, and 31 completers (12 active and 19 placebo). Only one active subject responded; therefore, the study was terminated early. The mean NT plasma level was 91.1 (18.3 SD) ng/ml. The two treatment groups had similar postprotocol severity ratings. Subjects on active drug did not evidence the anticholinergic side effects reported in adult samples. The negative outcome in this study is similar to the findings in our previously reported NT study in prepubertal 6- to 12-year-olds.

[1]This research was supported by USPHS Grant MH-40646 to B.G. from the National Institute of Mental Health.

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Background

This work, similar to our previous report on nortriptyline (NT) in depressed children (Geller et al. 1989), was based on the findings from the Puig-Antich and colleagues (1987) prepubertal imipramine study which suggested that future studies of antidepressants in pediatric depression include a placebo washout phase and control for plasma levels. Based upon these recommendations, the NT studies were designed to include a 2-week placebo washout period and to control for plasma levels by using a fixed-plasma level, instead of fixed-dose, design.

Methods

Inclusion and Exclusion Criteria

Subjects were boys and girls 12 to 17 years old who were postpubertal and who met Research Diagnostic Criteria (RDC; Spitzer et al. 1977) and *DSM-III* (American Psychiatric Association 1980) criteria for major depressive disorder (MDD), nondelusional type. *DSM-III-R* (American Psychiatric Association 1987) was not available when this study was initiated. Delusional depressives were excluded based on data from studies of adults suggesting that conventional doses of tricyclics were not effective in delusional depressives (Glassman & Roose 1981). Subjects needed a duration of illness of at least 2 months. They were excluded if any of the following conditions existed: IQ less than 75; Tanner Stage (Katchadourian 1977) less than III; autism or childhood onset pervasive developmental disorder; other major medical, psychiatric, or neurological illnesses; psychotropic drug use in the past month; substance use disorders; pregnancy; or excessive fear of venipuncture.

Assessment Instruments

The Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-P), 1978 Version, Present Episode (Puig-Antich & Chambers 1978), was used to establish MDD, and the Kiddy Global Assessment Scale (GAS) and the Children's Depression Rating Scale (CDRS), 1979 Version (Poznanski et al. 1979), were used to assess severity. Other scales used are described elsewhere (Geller et al. 1989).

Study Design

At baseline, subjects received a single dose of 50 mg of NT and a plasma level was obtained 24 hours later. From tables previously developed, subjects were begun at a dose based on their 24-hour plasma level that would ensure steady-state NT plasma levels of 80 ± 20 ng/ml (Geller et al. 1985).

The design of the study included a 2-week, single-blind, placebo washout phase and an 8-week, double-blind, placebo-controlled phase. Each day, subjects received two pillminders: one containing the a.m. doses and one the p.m. doses. Each slot of the pillminder contained four capsules: two the size of 10 mg and two the size of 25 mg of Pamelor. Therefore, subjects received exactly the same capsules each day of the study. Capsules contained either all placebo or sufficient active drug to comprise a dose range of 10 mg to 140 mg daily (Geller & Fetner 1989). Subjects were considered noncompliant if they missed two doses in 1 week. Subjects were seen between 4 p.m. and 6 p.m. and were instructed to take their capsules at 7 a.m. and 7 p.m. Therefore, the NT plasma levels were drawn 9 to 11 hours after the a.m. dose and were blindly coded prior to shipment to the Nathan Kline Institute for analysis by methodology previously described (Cooper et al. 1976; Suckow & Cooper 1982). Each week, subjects received the CDRS, the Asberg Side Effects Scale (Asberg et al. 1970), an electrocardiogram (EKG), blood pressure lying and after standing for 1 minute, and had a plasma level drawn.

Criteria of Response

Subjects needed a score of 30 or less on the CDRS at the end of Week 1 or Week 2 to be considered a placebo washout responder. At the end of the 8-week, double-blind, placebo-controlled phase, subjects needed a CDRS score of 25 or less and a score less than or equal to 2 on *DSM-III* criteria items on the K-SADS-P, except the concentration item, which could be less than or equal to 3. We selected a higher cut-off for response at the end of the placebo washout phase based on the reasoning that if a subject had a score of 30 or less at the end of Week 1 or Week 2, he or she was likely to go on to full response. We used a higher score on the concentration item based on our experience that subjects who had severe difficulties in school due to chronic depression were unlikely to improve on this item within 2 months.

Findings

Fifty-two subjects were enrolled; 17 subjects were placebo washout responders at the end of Week 1 or Week 2. Twelve subjects were randomized to active medication and 19 subjects to placebo; 4 subjects were dropouts. Of these 4 dropouts, 1 subject developed a rash during Week 3 of study, and when the blind was broken, he was on active medication. One subject needed emergency hospitalization for escalating suicidality between Weeks 2 and 3 of study. Two subjects were dropped due to noncompliance.

Table 1 shows the rate of categorical response when 31 subjects had completed the double-blind, placebo-controlled phase. Based on this very low rate of response, statistical analyses were performed to estimate the probability of our finding a significant difference between active and placebo groups had the study continued to complete the total population of 60 (30 active, 30 placebo) that were in the initial design. Using the multinomial distribution statistic, there was less than a 1 in 10,000 chance that a statistically significant difference would be found had we continued the study.

Subject Characteristics

Due to the large number of placebo washout responders, Table 2 includes the placebo washout responder (PWR) group. The subjects in this study were largely Caucasian; suburban; from small, two-parent households; and middle and upper class.

Severity, Chronicity, Melancholia and Comorbidity

Table 3 shows the baseline severity assessed by the CDRS and the GAS. These scores place all the subjects in the severe range of pathology. Eighty-three percent of subjects had a duration of illness of at least 2 years and 50 percent had a duration of 5 years prior to the start of the protocol.

TABLE 1. Percent Response.

	Nortriptyline (n = 12)	Placebo (n = 19)
Response	8.3 (1)	21.1 (4)
Nonresponse	91.7 (11)	78.9 (15)

NOTE: Fisher's exact, p = .342.

TABLE 2. Demographic Characteristics.

	PWR (n = 17)	Active (n = 12)	Placebo (n = 19)	Total (n = 48)
Mean age (SD) (years)	14.2 (1.4)	14.0 (1.7)	14.4 (1.6)	14.3 (1.5)
Sex (%)				
M	35.3	75.0	42.1	47.9
F	64.7	25.0	57.9	52.1
Ethnicity (%)[a]				
Caucasian	70.6	83.3	100.0	85.4
Black	29.4	16.7	0.0	14.6
Residence (%)				
Urban	5.9	8.3	0.0	4.2
Suburban	88.2	75.0	89.5	85.4
Rural	5.9	16.7	10.5	10.4
Household (%)				
Two parents	58.8	75.0	84.2	72.9
Other	41.2	25.0	15.8	27.1
Family size (n)	3.9 (1.1)	3.8 (1.1)	4.1 (1.1)	3.9 (1.1)
SES class (%)[b]				
I	0.0	0.0	10.3	4.2
II	23.5	16.7	26.3	22.9
III	58.8	58.3	26.3	45.8
IV	11.8	25.0	31.6	22.9
V	5.9	0.0	5.3	4.2

[a]Chi-square = 6.3, p = .04.
[b]Class I is the highest and class V is the lowest (Hollingshead and Redlich 1958).

TABLE 3. Severity, Chronicity, Melancholia and Cormorbidity.

	PWR (n = 17)	Active (n = 12)	Placebo (n = 19)	Total (n = 48)
Baseline CDRS and GAS scores (SD)				
CDRS[a]	51.4 (3.9)	51.3 (4.4)	51.4 (3.7)	50.8 (4.3)
GAS[b]	38.2 (3.8)	37.6 (3.8)	38.6 (3.9)	38.1 (3.6)
Duration of MDD prior to study (%)[c]				
< 1 yr	11.8	0.0	5.3	6.3
1–2 yrs	11.8	0.0	15.8	10.4
2–5 yrs	35.3	33.3	31.6	33.3
> 5 yr	41.2	66.7	47.4	50.0
Melancholia and comorbidity (%)[d]				
RDC endogenous	100.0	100.0	89.5	95.8
DSM-III melancholia	76.5	58.3	63.2	66.7
Separation anxiety	47.1	58.3	52.6	52.1
Antisocial behavior	47.1	50.0	36.8	43.8

[a]One-way ANOVA comparing the three groups F = .63, p = .54.
[b]One-way ANOVA comparing the three groups F = .32, p = .73.
[c]Chi-square = 4.41, p = .62.
[d]Chi-square comparisons n.s.

The subjects were largely endogenous and melancholic and had high comorbidity. Family histories (Andreasen et al. 1977) were positive for affective disorders in 85.4 percent, for alcoholism in 81.1 percent, for suicidality in 48.7 percent, and for mania in 59.9 percent.

NT, 10-OH-NT Plasma Levels, and Total Daily Dose

Table 4 shows the mean steady-state NT and total, trans, and cis 10-OH-NT plasma levels. All subjects had all blood samplings, and the mean was based on at least 4 weeks at stable dose i.e., after any initial adjustments in order to obtain a plasma level within the study range. All subjects on active drug had NT plasma levels within the study range of 80 ± 20 ng/ml. Because there was only 1 active responder, statistical comparisons would not be meaningful. However, the plasma level ranges for the 1 responder and the 11 nonresponders are presented to show that the responder was within the range of the total sample.

As anticipated, due to the wide genetic variation in the rate of metabolism of NT (Geller et al. 1985), the range of total daily dose was 45 mg to 140 mg [mean dose 85 mg/day (31.9 SD)]. The responder received 140 mg daily as did 3 of the active nonresponders.

There was a significant correlation between NT plasma levels and final CDRS scores (r = .79, p = .002), that is, subjects were worse at higher plasma levels because a higher CDRS score indicates more severe pathology. There were no significant correlations between 10-OH-NT (total, trans, or cis) and final CDRS scores.

TABLE 4. Mean NT and 10-OH-NT Plasma Levels [ng/ml (SD)] and Mean Total Daily Dose [mg (SD)].

	Responder (n = 1)	Nonresponder (n = 11)	Total (n = 12)
NT	73.0	92.8 (18.2)	91.1 (18.3)
Range		67.3–121.3	
Total 10-OH-NT	131.8	73.9 (37.0)	78.7 (39.0)
Range		18.3–138.3	
Trans 10-OH-NT	119.3	65.1 (34.2)	69.6 (36.2)
Range		11.7–122.3	
Cis 10-OH-NT	12.5	8.8 (4.5)	9.1 (4.5)
Range		0.0–16.0	
NT Dose	140.0	80.0 (28.1)	85.0 (31.9)
Range		45.0–140.0	

Side Effects, EKG, and Blood Pressure Measures

Table 5 shows the items on the Asberg Side Effects Scale that were rated at baseline and at each week of the study. The comparison presented is between Weeks 1 and 2, when all subjects were on placebo, and between Weeks 6 and 9, when all active subjects were at a stable dose of NT. This comparison uses multiple time points on placebo and on active medication. For a side effect to be counted, there

TABLE 5. Comparison of Percentage of Side Effects.[a]

	Weeks 1–2[b]		Weeks 6–9[c,d]	
Item	Active (n = 12)	Placebo (n = 19)	Active (n = 12)	Placebo (n = 19)
Tired	16.7	47.4	25.0	21.1
Sleep	16.7	26.3	33.3	15.8
Headache	—	10.5	16.7	5.3
Vertigo	—	—	—	—
Orthostatic	—	10.5	8.3	5.3
Palpitation	—	5.3	—	5.3
Tremor	—	—	—	—
Perspiration	—	—	8.3	5.3
Dry Mouth	—	—	—	—
Constipation	—	—	—	—
Micturition	—	—	—	—

[a] Modified Asberg Side Effects Scale.
[b] Rating of 2 or 3 at both Weeks 1 and 2 when all subjects were on placebo.
[c] Rating of 2 or 3 for any 2 consecutive weeks between Weeks 6-9.
[d] All statistical comparisons were nonsignificant using the chi-square test.

had to be a rating of 2 (clearly present) or 3 (clearly present and with impairment) for 2 consecutive weeks to obviate side effects from subclinical intercurrent infections.

There was an absence of the anticholinergic side effects commonly reported in adults. No subject had dry mouth, constipation, or micturition disturbances. Further, the most common side effects at Weeks 1 to 2 and Weeks 6 to 9 were those that are also symptoms of depression: tiredness, sleep disturbances, and headaches.

The EKG and blood pressure measurements to obtain multiple baseline and treatment points were also compared between Weeks 1 and 2, when all subjects were on placebo, and Weeks 6 to 9, when all subjects on active medication were at a stable dose and plasma level. Multiple time points are important due to the known wide intrasubject variation in pediatric heart rate and blood pressure (Nelson et al. 1979). Repeated measures multivariate analyses of variance (MANOVAs) comparing the means of EKG and blood pressure variables at Weeks 1 to 2 to Weeks 6 to 9 showed that there was a significant increase in heart rate ($F = 81.7$, $p < .001$). This increase corresponded to a mean increase in heart rate of 20 beats per minute, which did not produce any known clinical symptomatology. There were no significant differences in the other EKG variables or in the blood pressure measurements between Weeks 1 to 2 and Weeks 6 to 9.

Outcome

Figures 1 and 2 show that the PWR and the two treatment groups had similar baseline CDRS and GAS scores, respectively. There were no significant differences in the final CDRS or GAS scores between the active and placebo groups.

Followup Post-protocol

Post-protocol, 13 of the 17 placebo washout responders relapsed; 9 of the 13 relapsed within 1 to 4 weeks. The 1 active responder later went on to have a bipolar course.

Another part of the design of this study had been to raise the plasma level of active nonresponders to 130 ± 10 ng/ml following the completion of the double-blind, placebo-controlled protocol. This was to be a single-blind phase, that is, the raters knew that the plasma level was being raised, the families did not. This procedure was followed for the first 2 active nonresponders, who had a worsening of their pathology. This part of the study was therefore discontinued.

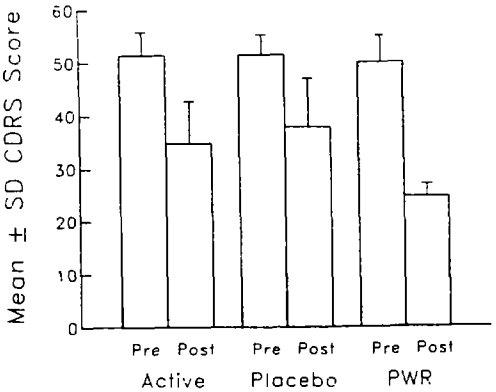

FIGURE 1. Pre- and post-treatment CDRS scores for active, placebo, and placebo washout responder (PWR) groups. Final CDRS scores (SD) for active and placebo groups were 34.7 (7.8) and 37.8 (9.1). They were not significantly different ($t = .98$, $p = .33$). Mean (SD) of Week 1 or Week 2 scores for the PWR group was 24.6 (2.3).

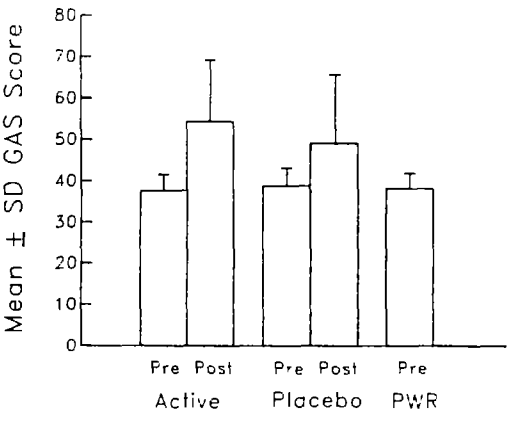

FIGURE 2. Pre- and post-treatment GAS scores for active, placebo, and placebo washout responder (PWR) groups. Final GAS scores (SD) for active and placebo groups were 54.2 (14.9) and 48.9 (16.2). They were not significantly different ($t = .96$, $p = .40$) and were in the range of clinically significant psychopathology.

Summary of Child and Adolescent NT Studies

In both of our pediatric NT studies, the subjects had a chronic, unremitting course of years in contrast to the cyclic course with episodes of 6 to 9 months reported in adults (Hamilton 1979). They also had severe MDD; high comorbidity; high percentage of family histories for mood disorders, alcoholism, and suicidality; poor response to NT; and low anticholinergic side effects, unlike the pattern reported for adults. The adolescents showed a worsening of their pathology at higher NT plasma levels.

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ECDEU ASSESSMENT MANUAL FOR PSYCHOPHARMACOLOGY Revised, 1976

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Public Health Service
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This publication was supported by NIMH grant MH-22019,
from the Psychopharmacology Research Branch,
Division of Extramural Research Programs.

DHEW Publication No. (ADM) 76-338
Printed 1976

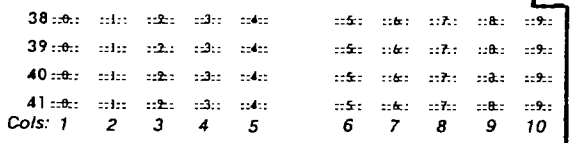
028 CGI CLINICAL GLOBAL IMPRESSIONS

CLINICAL GLOBAL IMPRESSIONS

INSTRUCTIONS: *Mark these items on General Scoring Sheet coded 01.*

Complete Item 1 – SEVERITY OF ILLNESS at the initial and subsequent assessments.
Items 2 and 3 may be omitted at the initial assessment by marking 0 – "Not Assessed".

Mark on the left half of the scoring sheet on rows 38 – 41.



ROW NO.	CLINICAL GLOBAL IMPRESSIONS
38	**1. SEVERITY OF ILLNESS** Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? 0 = Not assessed 1 = Normal, not at all ill 2 = Borderline mentally ill 3 = Mildly ill 4 = Moderately ill 5 = Markedly ill 6 = Severely ill 7 = Among the most extremely ill patients
	THE NEXT TWO ITEMS MAY BE OMITTED AT THE INITIAL ASSESSMENT BY MARKING "NOT ASSESSED" FOR BOTH ITEMS
39	**2. GLOBAL IMPROVEMENT – Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.** Compared to his condition at admission to the project, how much has he changed? 0 = Not assessed 1 = Very much improved 2 = Much improved 3 = Minimally improved 4 = No change 5 = Minimally worse 6 = Much worse 7 = Very much worse
40 & 41	**3. EFFICACY INDEX – Rate this item on the basis of DRUG EFFECT ONLY.** Select the terms which best describe the degrees of therapeutic effect and side effects and record the number in the box where the two items intersect. EXAMPLE: Therapeutic effect is rated as "Moderate" and side effects are judged "Do not significantly interfere with patient's functioning". Record 06 in rows 40 and 41.

THERAPEUTIC EFFECT	SIDE EFFECTS: None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED – Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
MODERATE – Decided improvement. Partial remission of symptoms	05	06	07	08
MINIMAL – Slight improvement which doesn't alter status of care of patient	09	10	11	12
UNCHANGED OR WORSE	13	14	15	16
Not Assessed = 00				

Clinical Global Impressions (CGI), developed during the PRB collaborative schizophrenic studies,consists of 3 global scales (items) formatted for use with the General Scoring Sheet. Since the items are "universal", the CGI is included in both the Pediatric and Adult packets. Two of the items, Severity of Illness and Global Improvement, are rated on a 7-point scale; while the third, Efficacy Index, requires a rating of the interaction of therapeutic effectiveness and adverse reactions.

APPLICABILITY	For all research populations
UTILIZATION	For Severity of Illness: Once at pretreatment and at least one post-treatment assessment. Additional ratings are at the discretion of the investigator. For Global Improvement and Efficacy Index: No pretreatment (baseline) assessment is required. At least one post-treatment assessment should be made. Additional post-treatment ratings are at the discretion of the investigator.
TIME SPAN RATED	For Severity of Illness: Now or within the last week. For Global Improvement: Since admission to the study. For Efficacy Index: Now or within the last week.

CARD FORMAT - ITEMS CARD 01 = (19x, 2I1, I2)

Item	Column
Severity of Illness	20
Global Improvement	21
Efficacy Index	22 - 23

SPECIAL INSTRUCTIONS

The contexts under which the 3 CGI items are to be rated have been modified to increase the reliability and precision of the items. Veteran ECDEU raters should be alert to these new contexts.

Item 1 - Severity of Illness - For this item, the modification for rating context is:

OLD	**Considering your total clinical experience, how mentally ill is the patient at this time?**
NEW	**Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?**

The old version asked the rater to judge the severity of illness of a given subject in the context of that rater's total experience with all types of patients; i.e., regardless of diagnosis, chronicity, age, etc. The present version restricts the judgment within the range of the specific population under study. Thus, an anxious neurotic subject is judged in the context of the rater's experience with anxious

neurotics - not, as was the case in the past - against a clinical background which may have included schizophrenics, brain damaged, and depressive subjects as well as anxious ones.

Item 2 - Global Improvement - The modification here involves the relationship between this item and Efficacy Index (Item 3). In the past, no distinction between TOTAL clinical improvement and that portion of the TOTAL which, in the opinion of the rater, is the direct result of the drug administered. The present contexts are:

Global Improvement

GLOBAL IMPROVEMENT – Rate total improvement whether or not, in your judgment, it is due entirely to drug treatment.

Efficacy Index

EFFICACY INDEX – Rate this item on the basis of DRUG EFFECT ONLY.

In many studies, of course, TOTAL improvement and improvement due to drug will be one and the same; nevertheless, the new contexts allow a distinction to be made when it is present.

Raters are cautioned to observe the unique time span rated for Global Improvement. For most other ECDEU items, the time span to be rated is either a specified number of days or since the last rating. The time span for Global Improvement - at each and every rating - is "since admission to the project (study)" - NOT from the last rating period.

Item 3 - Efficacy Index - In addition to the contextual modification mentioned above, the matrix of therapeutic vs. side effects has been changed as follows:

THERAPEUTIC EFFECT	SIDE EFFECTS			
	None	Do not significantly interfere with patient's functioning	Significantly interferes with patient's functioning	Outweighs therapeutic effect
MARKED – Vast improvement. Complete or nearly complete remission of all symptoms	01	02	03	04
MODERATE – Decided improvement. Partial remission of symptoms	05	06	07	08
MINIMAL – Slight improvement which doesn't alter status of care of patient	09	10	11	12
UNCHANGED OR WORSE	13	14	15	16
Not Assessed = 00				

The new matrix has been made symmetrical (4 x 4) by combining 2 therapeutic categories, "Unchanged" and "Worse" into one category. Category 4 of Side Effects has also been reworded.

Efficacy Index is an attempt to relate therapeutic effects and side effects. Therapeutic effect is regarded as gross profit; side effects as cost. The index, then, is analogous to net profit. The index is derived by dividing therapeutic effect score by side effect score as follows:

	Side Effects			
Therapeutic Effect	None 1	No Significant Interference 2	Significant Interference 3	Outweighs 4
4 Marked	4.00*	2.00	1.33	1.00
3 Moderate	3.00	1.50	1.00	0.75
2 Minimal	2.00	1.00	0.67	0.50
1 Unchanged or Worse	1.00	0.50	0.33	0.25

* Example: $\frac{\text{Therapeutic Score (4)}}{\text{Side Effect Score (1)}}$ = Efficacy Index (4.00)

The transformation procedure for Efficacy Index (EI) is:

Number Encoded	Transformed Score	EI
01	41	4.00
02	42	2.00
03	43	1.33
04	44	1.00
05	31	3.00
06	32	1.50
07	33	1.00
08	34	0.75
09	21	2.00
10	22	1.00
11	23	0.67
12	24	0.50
13	11	1.00
14	12	0.50
15	13	0.33
16	14	0.25
00	00	0.00

Employing the cross tabulation scheme (page 478) to interpret EI, indices falling on the diagonal CB would indicate that the therapeutic and toxic effects of a treatment are equivalent. Those in the upper left quadrant would indicate some degree of "profit" - the profit increasing as pole A is approached. The converse is true of indices falling in the lower right quadrant and, in fact, in all of the last column. The treatment with the greatest efficacy fills the cell at Pole A; the worst at Pole D. The cell at Pole C contains the "inert" treatment. Pole B represents a paradoxical and "theoretical" cell - not one likely to be encountered in the real world.

DOCUMENTATION

a. Raw score printout
b. Means and standard deviations
c. Frequencies and crosstabulations
d. Variance analyses

British Journal of Psychiatry (1988), **153** (suppl. 3), 87–98

Cardiovascular Effects of Antidepressant Medications

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Antidepressants are associated with a variety of side-effects, ranging in severity from the merely annoying to those with significant morbidity and even potential mortality. Prominent among the latter are cardiovascular effects, which have provided much of the impetus for the development of newer antidepressants such as fluoxetine. In this paper, we will review these cardiovascular effects, but as this has been previously undertaken elsewhere (e.g. Glassman & Bigger, 1981; Marshall & Forker, 1882; Glassman, 1984*a*), our consideration will be selective, with emphasis on methodological issues of relevance to the evaluation of new antidepressants. Since mechanisms of cardiac side-effects are best understood in relation to tricyclic antidepressants (TCAs), these will be a major focus, and will provide a background for the consideration of newer agents.

While less is known regarding the side-effects of the newer antidepressants, examination of the evolution of knowledge and opinions regarding their safety is particularly pertinent in that it illustrates the waxing and waning of enthusiasm that typically accompanies the introduction of new therapeutic agents. We review below the growing body of data regarding fluoxetine and some of the other serotonin-selective antidepressants, as well as discussing serotonergic effects on the cardiovascular system and their implications for the clinical use of these agents. Since the interactions between antidepressants and drugs used to treat cardiovascular disorders have been reviewed by Risch *et al* (1982) and Glassman & Salzman (1987), these will not be considered here.

The cardiovascular side-effects of antidepressants in current clinical use include electrocardiogram (ECG) and cardiac rate changes, as well as conduction disturbances and orthostatic hypotension, which are more clinically important. These effects are also prominent in overdoses and a major factor in determining their lethality. However, several antidepressants may have beneficial antiarrhythmic properties. Contrary to earlier reports, it now appears that depression of cardiac pump function is insignificant at therapeutic drug levels.

Tricyclic antidepressants

Effects on cardiac conduction

The cardiac impulse originates in the sinoatrial node, depolarises the atria, and travels through the atrioventricular node and the common His bundle, which divides into the left and right bundles. The bundles terminate as purkinje fibres on the endocardial surface of the ventricles. The PR interval, as measured by the ECG, reflects conduction through these segments. His bundle recordings (an invasive procedure requiring cardiac catheterisation to obtain intracardiac electrical recordings) allows estimation of the duration of both nodal conduction (AH interval) and His bundle conduction (HV interval). This technique allows localisation of defects to the proximal (AV node) or distal (bundle or purkinje fibres) sections, and was first used in the study of antidepressants by Vohra *et al* (1975).

The TCAs are associated with an increased heart rate, largely mediated through their anticholinergic effect. Non-specific ST-T changes and diminished height of T waves are the most common abnormalities observed on the ECG; in addition, the duration of the PR and QT intervals and the QRS complex are increased (Glassman & Bigger, 1981). His bundle recordings have indicated that the delays involve the distal part of the conduction system, i.e. the HV interval (Vohra *et al*, 1975). The mechanisms of the conduction defects (and related ECG changes) are probably among the best understood cardiac effects of TCAs.

Studies of cultured cardiac cells *in vitro* indicate that TCAs exert major effects on the inward sodium current, which is responsible for the phase zero depolarisation of the cardiac action potential. This effect is associated with both an increase in the action potential duration and a prolongation of the refractory period and QT interval (Rawling & Fozzard, 1979; Weld & Bigger, 1980). Such observations, when taken together with the nature of ECG changes associated with TCAs, allow these drugs to be classified as Type Ia (quinidine-like) anti-arrhythmic agents (Bigger & Hoffman, 1985). These effects have been demonstrated most conclusively for nortriptyline, imipramine, and desipramine, but have also been documented for amitriptyline. Early studies with nortriptyline indicated that ECG changes and prolonged HV intervals were consistently found at plasma levels >200 ng/ml, while at levels <200 ng/ml most, but not all individuals had normal findings (Vohra *et al*, 1975). While the former levels are

now known to be above the therapeutic range for nortriptyline, the studies are of interest in that they demonstrate that cardiac changes regularly appear at blood levels of the drug slightly above therapeutic range for most patients, but may also occur at therapeutic ranges in certain individuals. Inter-individual heterogeneity was also found in His bundle studies of normal subjects who were given an acute dose of imipramine (Brorson & Wennerblom, 1978). Since levels >200 ng/ml are regularly obtained with TCAs other than nortriptyline, this may explain the observations that while ECG changes are found most frequently at supra-therapeutic blood levels of nortriptyline, they are commonly found at therapeutic levels of imipramine, desipramine, and amitriptyline (Glassman & Bigger, 1981). Doxepin was initially described as having less prominent cardiovascular effects, but this probably reflects, in part, a diminished bioavailability and lower plasma levels (Luchins, 1983).

Both inter-individual variation and the dose-response effects are likely explanations of the variations in degree of ECG abnormalities reported in different clinical studies. Therefore, data presented in terms of the proportion of subjects with altered ECG intervals are a valuable complement to data presented as inter-group comparisons of average ECG interval duration.

In healthy subjects, these effects on heart rate and ECG are probably of little clinical significance. The elevations in pulse rate are modest, have been reported to decrease with time (as have the ECG changes) in some but not all studies (Burckhardt *et al*, 1978; Glassman & Bigger, 1981), and are most prominent in subjects with slower pre-treatment rates (perhaps because of higher vagal tone). The ECG intervals rarely increase beyond normal range. The benign nature of the changes accounts for the general clinical practice of not requiring baseline ECG for healthy younger individuals prior to commencing antidepressant therapy.

While a prolongation of the QRS duration by 25% is considered a sufficient reason to decrease antidepressant doses in most cases, there are no systematic studies to support this approach. Clinical prudence also dictates careful attention to prolongation of the QT interval (rate corrected), which may serve as a warning of impending toxicity. Despite these potential problems, when carefully monitored, TCAs are generally quite safe in subjects with a normal ECG, although development of 2:1 heart block has occasionally been reported in such cases (Roose *et al*, 1987*b*).

The cardiac effects of TCAs are of serious clinical significance in subjects with underlying conduction abnormalities. This was first indicated by a number of anecdotal reports of complete heart block (e.g. Kantor *et al*, 1975) occurring during the use of TCAs in subjects with pre-existing cardiac disease. Such cases led to the systematic studies of effects of TCAs on cardiac conduction which are detailed below.

Tricyclic antidepressants and arrhythmias

At doses comparable to those used for depression, both nortriptyline and imipramine are effective anti-arrhythmic agents for patients with ventricular premature contractions in the presence (Giardina *et al*, 1979) or absence (Giardina *et al*, 1985) of depression. This observation is consistent with the TCAs' quinidine-like action. Thus, TCAs may be the agents of choice for simultaneous control of depression and certain arrhythmias in subjects with both disorders. Conversely, combined therapy with quinidine-like (Type Ia) anti-arrhythmic agents and a TCA may be associated with toxicity; it is therefore contra-indicated. Similar considerations require the avoidance of such anti-arrhythmics in the treatment of cardiac complications of TCA overdoses.

Despite their anti-arrhythmic action, TCAs, like other anti-arrhythmic agents, can also cause or exacerbate arrhythmias (Giardina *et al*, 1983). This phenomenon is well known in the case of the usual anti-arrhythmic agents, including quinidine. While most commonly seen at toxic levels, dangerous arrhythmias (including ventricular fibrillation) may occur from quinidine at 'therapeutic' levels, may be unassociated with 'warning' ECG changes, and may be an important potential cause of cardiac arrests in ambulatory out-patients with arrhythmias (Ruskin *et al*, 1983). While the issue is not resolved of whether an increased incidence of sudden death is associated with the use of antidepressants (Coull *et al*, 1970; Moir *et al*, 1972; Boston Collaborative Drug Surveillance Program, 1972), such arrhythmias or complete heart block resulting from quinidine-like effects of TCAs are potential causes of sudden death.

Tricyclic antidepressants and orthostatic hypotension

Orthostatic hypotension is the major side-effect of antidepressants; the public health dimension of this problem is enormous. A community-based survey of the number of hip fractures in a community sample of elderly subjects found a strong association between such fractures and usage of TCAs (Ray *et al*, 1987), while in a study of patients treated with imipramine, Glassman *et al* (1979) reported a 4% incidence of lacerations or fractures. In addition, it has been observed that orthostatic hypotension may

precipitate myocardial infarction or cerebrovascular accidents (Muller *et al*, 1961; Thayssen *et al*, 1981). Orthostatic hypotension is also an important cause of drop-out from treatment in both clinical trials and clinical practice. While imipramine is the best studied of the TCAs with regard to this side-effect, amitriptyline, desipramine, and doxepine also produce orthostatic hypotension (Nelson *et al*, 1982; Glassman, 1984*a*). The correlation between orthostatic hypotension and age is not entirely clear, but older subjects who are particularly susceptible to cerebrovascular accident, myocardial infarction, or hip fractures are more at risk from morbidity resulting from orthostatic hypotension (Thayssen *et al*, 1981).

Pre-treatment orthostasis is perhaps the best predictor of treatment-induced orthostasis. Orthostatic hypotension appears at subtherapeutic doses and has been reported to reach its maximum effect at these levels for most patients (Glassman *et al*, 1979), leading to the suggestion that if a patient can tolerate the orthostasis occurring at such subtherapeutic doses (e.g. 75 mg of imipramine), imipramine may be increased to therapeutic ranges with little increment in orthostasis. This must be done cautiously however, because, at least in some patients, a dose-response effect continues at higher doses (Rabkin *et al*, 1985).

There is disagreement as to whether orthostatic hypotension diminishes with time. Using an extremely stringent definition (50-point drop in systolic pressure on three separate days and/or symptoms of dizziness that prevented patient from standing) Roose *et al* (1987*b*) reported orthostatic hypotension in 7% of patients with normal ECGs who were treated with imipramine. In contrast, however, 30% of subjects with conduction abnormalities receiving imipramine (with or without congestive heart failure) developed orthostatic hypotension, requiring them to discontinue the medication. Overall, it has been estimated that in approximately 20% of subjects treated with imipramine, orthostatic hypotension is a substantial side-effect and/or leads to alteration in therapy (Glassman *et al*, 1979).

Pioneering studies by Freyschuss *et al* (1970) first suggested that nortriptyline is associated with less orthostatic hypotension than other agents. While it is clear that orthostatic hypotension can be caused by nortriptyline, the magnitude and morbidity of nortriptyline-induced hypotension is less than that seen with imipramine (Roose *et al*, 1981; Thayssen *et al*, 1981; Roose *et al*, 1987*b*).

Considering the importance of this problem, surprisingly little is known about its mechanism. Originally, orthostatic hypotension was attributed to the α-adrenergic blocking effects of the TCA, but doubt has been cast on this because of the observation that despite being associated with a greater degree of orthostasis (Glassman, 1984*a*), desipramine has a lower affinity for α_1-adrenergic receptors than does nortriptyline (U-Prichard *et al*, 1978). However, since α_1 affinity was measured in brain rather than peripheral tissues, the relevance of the α-blocking effect is still uncertain. As noted below, a TCA-induced decrease in cardiac pump efficiency has been virtually excluded as the explanation of the development of orthostatic hypotension, although pre-treatment cardiac disease is a definite predisposing factor (Glassman *et al*, 1983; Roose *et al*, 1987*b*). The increase in cardiac rate observed with TCA would be expected to preserve blood pressure by increasing cardiac output.

It has recently been suggested that in depressed patients treated with TCAs, a disease-drug interaction may play a role in the development of orthostatic hypotension. This was based on the observation that depressed subjects receiving imipramine have a higher incidence of orthostatic hypotension than non-depressed cardiac patients who are being treated with imipramine for arrhythmias (Giardina *et al*, 1985). A further link between depression and orthostatic hypotension is suggested by observations that the latter may predict a good response to treatment either with TCAs (Jarvik *et al*, 1983; Schneider *et al*, 1986) or monoamine oxidase inhibitors (Davidson & Turnbull, 1986). While these results require replication and may reflect various non-specific factors such as dehydration or loss of muscle tone (which may be secondary to depressive symptomatology), they may also be the result of alterations in adrenergic function associated with the pathophysiology of depression. Indeed, Prange *et al* (1967) have demonstrated that subjects with depression may have a weaker pressor response to infused norepinephrine, and we have recently shown (Wilner *et al*, 1987) that while depressed subjects have a normal increase in catecholamines in response to standing (postural challenge test), they have a blunted β_1-mediated chronotropic response. Further investigation of central and/or peripheral mechanisms leading to orthostatic hypotension are clearly of importance, both on practical and theoretical grounds.

Lack of an efficacious treatment for orthostatic hypotension reflects the poor understanding of its mechanisms. Volume expansion by salt-retaining steroids has shown variable results, but is clearly unsuitable for subjects with compromised cardiac function, in whom orthostatic hypotension effect is particularly incapacitating and dangerous. Mechanical measures to increase venous return have generally

been disappointing: caffeine or thyroid supplementation has been suggested, and these treatments have recently been reviewed by Pollock & Rosenbaum (1987). Reports of yohimbine reversal of antidepressant-induced orthostatic hypotension (Lecrubier *et al*, 1981; Hyatt & Messer, 1986) are intriguing in that they point to a central α-receptor-mediated mechanism.

As is the case for ECG effects, there is considerable variation in results between studies, with respect to orthostatic hypotension. This reflects the different criteria for its definition and different techniques for measuring it (having the patient lie down prior to standing vs standing from a sitting position) and the frequency of measurement (three times a day in Glassman's studies vs the weekly measures in the typical out-patient studies). In addition, out-patients and in-patients are likely to have very different cardiovascular tone and susceptibility to orthostatic hypotension. Therefore, meticulous attention to such details is necessary to identify the magnitude and frequency of orthostatic hypotension in a new agent.

Tricyclic antidepressants and ventricular function

Reports of impaired ventricular function in overdoses, together with the known quinidine-like action of the TCAs, led to concern that these agents, even in therapeutic doses, might cause impaired ventricular function. These fears were strengthened by reports that the systolic time intervals (time between commencement of QRS and ventricular mechanical events) were prolonged by therapeutic levels of TCAs. However, the systolic time interval is increased by the prolongation of the QRS associated with the TCA (Giardina *et al*, 1983). Controlled studies involving direct assessment of left ventricular function, using radionuclide scan measurements of ejection fractions (ventricular emptying), have found no evidence of impaired ventricular function. This has been demonstrated in subjects with cardiac disease, with markedly diminished ejection fractions. While the first report was based on patients treated with slightly lower than usual doses (by American standards) of medication (Veith *et al*, 1982), this finding has recently been confirmed in patients who were treated with higher doses of imipramine or nortriptyline (with levels of both in the therapeutic range) and who had markedly abnormal ejection fractions (≤ 0.3 compared with the normal mean of 0.65) (Glassman *et al*, 1983; Roose *et al*, 1986, 1987*a*). Re-examination of data from patients who had taken overdoses of TCAs also indicates the relative preservation of ventricular function in most cases (including studies involving cardiac catheterisation and Swann-Ganz readings).

Tricyclic antidepressants in patients with cardiac disease

The first systematic study of the effects of the TCAs imipramine and nortriptyline in subjects with documented conduction defects has recently been published (Roose *et al*, 1987*b*). One of 150 subjects with a normal ECG developed 2:1 heart block, while three of 24 patients with bundle branch block developed a heart block. Interestingly, none of 11 patients with first-degree block showed progression of heart block. This is consistent with the major effect of TCAs being on the distal conduction system, whereas first-degree heart block most frequently results from AV nodal disease.

Surprisingly, orthostatic hypotension was more of a problem than conduction defects in this group of patients with cardiac disease (Roose *et al*, 1987*b*). Twelve of the 35 subjects with conduction abnormalities (with or without congestive failure) who had been treated with imipramine for depression developed orthostatic hypotension requiring the discontinuation of this medication. However, only one out of 20 subjects with cardiac disease (including some who were crossed-over from imipramine because of orthostatic hypotension) treated with nortriptyline developed orthostatic hypotension. In another study, 50% of subjects with congestive heart failure treated with therapeutic levels of imipramine developed orthostatic hypotension, despite the fact that their ejection fractions were not further decreased by the TCA (Glassman *et al*, 198?).

Worsening or the onset of new arrhythmias have been reported in depressed subjects treated with TCAs for depression (Giardina *et al*, 1979), and exacerbations have been reported in non-depressed patients treated with TCAs for arrhythmias (Connolly *et al*, 1984).

Recently, a report has appeared describing TCA treatment in patients with ventricular pacemakers (Alexopolous & Shamoian, 1982). The authors point out that the pacemaker protects against the consequences of development of higher degrees of heart block, but it would not necessarily protect against arrhythmias. They also present one of the few examples of TCA-induced tachycardia (which overrode the demand pacemaker) causing cardiac compromise.

Summarising the results for patients with cardiac disease, it appears that TCAs do not decrease ventricular function, which was thought to be a major potential source of cardiotoxicity. This effect does not occur even in subjects with diminished baseline ventricular ejection fraction (i.e. with congestive heart failure). Somewhat surprisingly,

orthostatic hypotension is more prominent than exacerbation of conduction defects, even in patients with abnormal ECG. While nortriptyline appears to be advantageous with respect to orthostatic hypotension, like other TCAs, it can increase the degree of heart block. Despite their anti-arrhythmic action, TCAs may be associated with increased ventricular ectopy. Hence, there is an urgent need to develop new antidepressant agents for use in cardiac patients. These considerations in part motivated the development of the second-generation antidepressants, to be discussed below.

The studies described above involved an integrated team of cardiologists, pharmacologists, and psychiatrists, and allowed systematic evaluation of effects of TCAs on diseased hearts. Aside from the value of their results, these studies are important as a model for a systematic approach to determining the nature of drug–cardiovascular system interaction, rather than an approach relying on the often confusing data obtained from case reports, overdoses, and incidental results of efficacy studies.

Cardiac effects of tricyclic antidepressant overdoses

Overdoses with antidepressants are a major public health problem. Although TCA overdoses affect multiple organ systems, cardiovascular affects are a major cause of death; these overdoses have been the focus of several recent reviews (Crome, 1982; Marshall & Forker, 1982; Callaham & Kassel, 1985; Frommer *et al*, 1987). In TCA overdoses widening of the QRS complex is frequent; it has been suggested that the degree of widening may be predictive both of cardiovascular and CNS compromise, and in fact a more reliable indicator of toxicity than blood levels (Boehnert & Lovejoy, 1985). An anticholinergically mediated increase in rate is common initially and may progress to a superventricular tachycardia, but as would be anticipated from the quinidine-like action of TCAs, both ventricular tachyarrhythmias and asystole may occur. Vohra & Burrows (1974) pointed out that the increase in rate, together with the drug-induced widening of the QRS, may lead to an ECG pattern of rapid bizarre beats that resembles a ventricular tachyarrhythmia, leading to inappropriate and dangerous treatment. Hypertension may be present in milder overdoses, perhaps resulting from an increase in catecholamine levels (Preskorn & Irwin, 1982), but hypotension is a more ominous development (Frommer *et al*, 1987).

Most patients with serious overdoses show evidence of cardiotoxicity within hours of admission, and current data indicate that the development *de novo* of serious cardiovascular problems after 12–24 hours have elapsed is unusual (Callaham & Kassel, 1985). This is in contrast to several earlier reports in which arrhythmias developed and sudden death occurred several days after apparent recovery (*reviewed in Callaham & Kassel, 1985*). These anecdotal reports probably reflected lack of vigorous lavage and charcoal treatment, allowing delayed absorption of the drug (which is slowed by local anticholinergic effects). However, they underline the necessity for careful consideration of each overdose with respect to amount of TCA ingested, efficacy of lavage and installation of charcoal, and the nature of ECG changes prior to the transfer of the patient to a psychiatric facility, where medical monitoring may be less intensive.

Treatment of cardiovascular side-effects is still somewhat controversial, and because of the wide variety of potential cardiac effects, must be on an individual basis. Systemic alkalinisation (by hyperventilation or bicarbonate administration) has been reported to be helpful in reversing hypotension and even in narrowing the QRS (Frommer *et al*, 1987). Considerable attention has been given to the use of phenytoin (Hagerman & Hanashiro, 1981), a type Ib anti-arrhythmic, but this is not universally accepted. While initially recommended, the value of physostigmine is presently unclear, in part due to its potential induction of dangerous bradyarrhythmias (Frommer *et al*, 1987). The cardinal principles in management of TCA overdoses are careful observation and conservative supportive treatment of mild cases, awareness of the possible development in a rapid fashion of a 'catastrophic deterioration' (Callaham & Kassel, 1985), and very aggressive management in certain patients, including electroconversion and cardiac pacing.

Monoamine oxidase inhibitors

Quinidine-like effects are not exhibited by monoamine oxidase inhibitors (MAOIs), and these agents may actually speed conduction. Their use has been associated with cardiac slowing, which is of modest proportions and has not been associated with clinical complications (Robinson *et al*, 1982; Goldman *et al*, 1986; McGrath *et al*, 1987). Therefore that they have been proposed as a possible treatment for depressed subjects with conduction defects. They are, however associated with orthostatic hypotension; in contrast with that associated with TCAs, the orthostatic hypotension with MAOI treatment may be of more gradual onset and correlated with therapeutic dose levels, so that it may have a different mechanism (Kronig *et al*, 1983). In addition, MAOIs (unlike

TCAs) can also lower supine blood pressure, which may mask orthostatic hypotension (Goldman *et al*, 1986). Thus, comparison of pre-treatment and post-treatment standing blood pressure may be the most sensitive means for detecting orthostatic hypotension in these and other agents which have similar effects. It is likely that the physiological effects of supine and orthostatic hypotension respectively are additive, since symptoms of orthostatis and falls are not infrequent with these agents (Robinson *et al*, 1982; Rabkin *et al*, 1985; Goldman *et al*, 1986). While MAOIs have been used in patients with cardiovascular disease (e.g. Lippman *et al*, 1985), there has been no systematic comparison of their propensity to induce orthostatic hypotension in cardiac as compared with non-cardiac patients.

In contrast to the TCAs, symptoms of 'pure' MAOI overdose are generally delayed for at least 12 hours after ingestion, and may involve a hyperthermic delirium in addition to cardiovascular effects. The major cardiovascular manifestations are hypertension and/or hypotension (Guzzardi, 1983). As might be anticipated by the drug interactions associated with MAOIs, management of these overdoses may be difficult. The hypertension is most frequently treated with α-adrenergic receptor blockers, e.g. phentolamine, but these agents or the MAOI itself may lead to hypotension, which is ideally treated by postural manipulations and/or volume expansion. In certain instances of severe hypotension, adrenergic agonists of the type often considered to be contraindicated with concurrent MAOI administration may be used cautiously. The major guidelines for the treatment of cardiovascular effects of MAOI overdose include individual monitoring and treatment based on the emerging symptom complex. Thus, the use of MAOIs is also limited by cardiovascular effects, although the pattern of these differs from that of TCAs, particularly with regard to the absence in MAOIs of a quinidine-like action and their dose-dependent effects on blood pressure.

Second-generation antidepressants

Currently, four second-generation antidepressants are clinically available in the USA: trazodone, maprotiline, amoxapine, and fluoxetine. Buproprion was voluntarily withdrawn by its manufacturer because of its possible association with seizures, but is currently undergoing testing and may be re-released. While it was hoped that these agents would be safer in overdose and be associated with fewer cardiovascular effects, this claim is not proven for trazodone, and is not true for maprotoline and amoxapine. Reviews have recently been published of the side-effects (Glassman, 1984*a*; Robinson, 1984) and effects of overdoses of the newer antidepressants available in the USA (Kulig, 1986; Wedin *et al*, 1986). Fluoxetine was released for clinical use while this review was being prepared, and will be discussed below.

Buproprion does appear to be free of adverse cardiac effects – ECG changes, orthostatis, and decrease in ejection fraction – even in patients with cardiac disease (Roose *et al*, 1987*b*). Hence, results of re-evaluation of its seizure potential will determine its future clinical availability.

Maprotoline has a cardiovascular profile essentially similar to the TCAs: it has quinidine-like effects on the ECG (Burckhardt *et al*, 1978; Edwards & Goldie, 1983) and has been shown to be effective for the treatment of arrhythmias (Raeder *et al*, 1979). Maprotoline can cause orthostatic hypotension and anticholinergic effects; dangerous ventricular arrhythmias have been associated with both its use at therapeutic levels (Herrmann *et al*, 1983) and after overdose (Curtis *et al*, 1984). In addition, its propensity to cause seizures, particularly at higher doses, has limited its use (Dessain *et al*, 1986). As is true for a number of newer antidepressants, it is currently unclear to what extent the arrhythmias seen in patients treated with maprotoline reflect the patients' underlying cardiac disease, a drug effect *per se*, or an interaction between the drug and cardiac disease.

Particular attention has been given to the potential of amoxapine to cause extrapyramidal symptoms and to the intractable nature of the seizures associated with overdoses of this drug. However, it is clear that amoxapine may affect the cardiovascular system through its anticholinergic and orthostatic hypotensive effect. While most studies of this agent have not demonstrated ECG changes, there have been some contrary reports. Amoxapine has been associated with arrhythmias after overdose (Dugas & Weber, 1982; Jue *et al*, 1982). In summary it may have a somewhat narrower spectrum of cardiovascular side-effects than many of the other agents, but is not devoid of these effects. Its propensity to cause intractable seizures after overdose, as well as its neuroleptic-like side-effects, have decreased acceptance of this agent.

The nature of the cardiovascular side-effects of trazodone is particularly puzzling. When it was first released for clinical use, extensive animal (Gommol & Byrne, 1981) and human studies (Himmelhoch, 1981) indicated that it was essentially free of anticholinergic and cardiac effects except for orthostatic hypotension (probably due to α-adrenergic receptor blocking properties). Furthermore, it was

predicted, in part because of this profile and the results of animal studies, that trazodone would be safe in overdose. This prediction has held true and at present there have been no reports of serious cardiac toxicity or deaths from overdoses of trazodone as a single agent (Gamble & Peterson, 1986). However, starting in 1983 (Janowsky *et al*, 1983), there have been scattered reports of a variety of diverse cardiac rhythm disturbances attributed to this drug, which include increases in degree and severity of pre-existing ventricular ectopy (Janowsky *et al*, 1983; Pohl *et al*, 1986), reversible dose-related AV block (Irwin & Spar, 1983), and the development of angina associated with ventricular ectopy (Aronson & Hafez, 1986). Most of these have occurred in elderly patients with cardiac disease who are being treated with a variety of forms of cardiac medication. While the reporting of such cases performs the laudable function of alerting the psychiatric community to the need to monitor cardiovascular effects of 'safe' agents in patients with cardiovascular disease, some of the cases are extremely difficult to evaluate. For example, one patient who 'developed' complete heart block following a single dose of trazodone had a previous history of unexplained syncope (Rausch *et al*, 1984). There have been several other reports of complications occurring virtually on the institution of trazodone, which is of interest in view of the report of ECG abnormalities in normal subjects who are given acute doses of trazodone (Burgess *et al*, 1982), in contrast to the paucity of changes found in subjects on chronic treatment. While some of the cases of increased ectopy associated with the use of trazodone are more convincing, they may in some cases reflect loss of the antiarrhythmic effect of the TCA that was withdrawn prior to institution of trazodone (Pohl *et al*, 1986), and represent isolated case reports rather than systematic controlled studies. Himmelhoch *et al* (1984), in an attempt to determine the arrhythmogenic potential of trazodone, studied subjects being treated with trazodone with 'mild' cardiac disease including 'stable arrhythmias', and failed to find an increase in arrhythmias. They suggested the possibility of a reporting bias. However, new case reports continue to appear in the literature, so that at present, the indications and contraindications for the use of trazodone in patients with cardiac disease are unclear, despite the animal and human studies which have made the drug appear so attractive for treatment of these patients.

Mianserin is widely used in Europe, but unlikely to be released in the USA because of its purported association with blood dyscrasias. Most studies have found that it has no effects on either cardiac rate or on the electrocardiogram (Edwards & Goldie, 1983; Montgomery, 1983), but transient prolongations in QT (rate-corrected) have been reported (Burgess *et al*, 1979). The absence of an increase in heart rate with mianserin is consistent with its lack of anticholinergic properties (Ghose *et al*, 1976; Kopera, 1983). One of the few studies of mianserin performed in the USA confirmed its lack of effect on heart rate and ECG findings (McGrath *et al*, 1987). Results of His bundle studies performed in ten depressed patients prior to and after 3 weeks of therapeutic (and clinically effective) doses of mianserin were identical; neither the AH nor HV intervals were altered (Burrows *et al*, 1979). This study provides direct support for the conclusion, based on ECG findings, that mianserin does not alter cardiac conduction. Orthostatic hypotension is infrequent in normal subjects (Kopera, 1983) or depressed in-patients (Pichot *et al*, 1978) or out-patients (Burrows *et al*, 1979) at usual therapeutic levels when the dosage of mianserin is raised gradually, but has been reported (Eklund *et al*, 1985). However, acute administration of 60 mg (generally considered to be the average therapeutic dose) to normal subjects has been shown to have profound hypotensive effects (Macquire *et al*, 1982), indicating that careful attention must be paid to the rate at which dosage is adjusted.

Data from overdose cases are consistent with mianserin's lack of cardiac effects. There is one report of a mianserin overdose (in which moderate amounts of benzodiazepines were taken) apparently leading to first-degree heart block; this was not associated with compromised cardiac function, and resolved uneventfully within hours with supportive treatment. In a review of 44 cases of overdose in which mianserin was the sole agent ingested, the major cardiovascular side-effect was hypertension (nine cases), while no arrhythmias or ECG abnormalities were reported. These overdoses were associated with benign clinical courses, drowsiness being the major symptom in the majority of cases (Crome, 1982). The association of hypertension with mianserin overdoses contrasts both with the hypotensive effects of an acute dose of 60 mg on normal subjects and the hypotension frequently associated with overdoses of the TCAs. It is possible that the hypertension might be related to the α_2-adrenergic receptor blocking properties of this drug, since a similar effect has also been reported for other α_2-adrenergic antagonists such as yohimbine.

Mianserin has also been reported to be safe in subjects with cardiac disease including congestive heart failure and cardiomyopathies (Coppen & Kopera, 1978); in patients with 'gravely disturbed electrocardiograms' it apparently did not lead to

further abnormalities (Kopera & Schenck, 1977). However, detailed reports of these studies are not available in the English-language literature.

Thus, mianserin, in contrast to the TCAs, has a benign profile with respect to cardiovascular effects. This has been well established for ECG effects and overdoses and is likely to be true with respect to orthostatic hypotension and in patients with cardiovascular disease. Though more complete documentation of these two aspects of mianserin use would be desirable, mianserin is likely to be well tolerated by subjects with cardiovascular disease. For this reason and because of mianserin's lack of anti-cholinergic effects, it has been advocated as being particularly useful in elderly subjects (Eklund *et al*, 1985; Magni, 1987).

Cardiac effects of fluoxetine

Fluoxetine, a selective serotonin-reuptake inhibitor, has only been available for clinical use in the USA since February 1988. It has been studied far less than the TCAs and MAOIs, but there are some data available regarding its cardiovascular effects and those of other serotonergic agents. Unlike many of the other antidepressants, fluoxetine is associated with a diminished pulse rate (Fisch, 1985). It shares this feature with trazodone (Himmelhoch *et al*, 1984), fluvoxmine (Roose, 1983), and zimeldine (Pottage & Groschinsky-Grind, 1983), which are also agents with mainly serotonergic profiles. It is unclear whether this reflects a serotonergic effect or lack of anticholinergic effect.

Analysis of ECG data from 312 patients treated with fluoxetine in a multi-centre trial revealed a slightly decreased pulse rate, but no significant changes in mean PR, QRS, or QT duration (Fisch, 1985). Simultaneously-studied patients who were on TCAs showed the expected increases in PR, QRS, and QT intervals and pulse rates. The few patients whose QRS changed significantly (to $\geqslant$120 ms) were confined to the tricyclic-treated population. Also of importance was the observation that 'intraventricular conduction delays' were found in five patients in the TCA-treated group prior to treatment: these progressed to left bundle branch block during TCA treatment in four cases. Three of these four patients were then crossed over to fluoxetine, resulting in *reversal* of the TCA-induced conduction changes, and they maintained stable ECGs during a one-year follow-up. No ECG changes were reported in geriatric patients with normal ECGs who were given fluoxetine (Feighner & Cohn, 1985). The results of acute experiments with dogs are consistent with fluoxetine's apparent lack of effects on cardiac conduction in man: high doses of fluoxetine had no effect on AH or HV conduction, while amitriptyline prolonged HV conduction time (Steinberg *et al*, 1986).

In several cases of overdose of fluoxetine, no ECG changes were observed (Fisch, 1985). The benign cardiovascular effects of several other overdoses are reported in the paper by Cooper in this issue.

Orthostatic hypotension has not been reported as a major problem with selective serotonin-reuptake inhibitors such as zimeldine (Claghorn *et al*, 1983; Pottage & Groschinsky-Grind, 1983) and fluvoxamine (Roos, 1983). However, orthostatic changes, often of significant magnitude, have been reported to occur with fluvoxamine in medically healthy subjects in several studies (e.g. Lapierre *et al*, 1987), although their frequency has been lower than that observed with the simultaneously tested standard antidepressants. Fluoxetine's potential to induce this side-effect, however, has not been studied as systematically as has that of imipramine, certain other TCAs, and the MAOIs.

Similar considerations hold for fluoxetine. Orthostatic changes do not appear to be prominent with this drug (Wernicke, 1985). In a review of 185 subjects treated with fluoxetine (Stark & Hardison, 1985), dizziness was reported by 9% of patients, compared with 23% of patients treated with the other antidepressants (mainly TCA), and by 5% of placebo-treated patients. Dizziness should not necessarily be equated with orthostatic hypotension: this point is exemplified by Chouinard (1985), who found that in most cases, dizziness but not orthostasis was reported for fluoxetine-treated patients, while both were more often found in imipramine-treated patients. Nevertheless, the precise relative frequency of orthostatic hypotension in fluoxetine-treated patients is not entirely settled.

In summary, it appears that fluoxetine may be relatively free of cardiovascular side-effects both at therapeutic levels and in overdose; these observations are consistent with findings with other selective serotonergic agents.

However, the majority of patients studied with fluoxetine and the other selective serotonergic agents were physically healthy (and in many cases out-patients). Such patients are less prone to orthostatic hypotension, and as emphasised above, results with physically healthy out-patients cannot be extrapolated to cardiac patients or more severely depressed in-patients.

The favourable results obtained with fluoxetine and related agents make this a class of drugs with exciting potential for the treatment of depression in

cardiac patients, and indicate that consideration should be given to systematic clinical trials in patients with well characterised cardiac disease, together with evaluation of the cardiovascular effects in more severely depressed in-patients.

Serotonergically mediated effects on the cardiovascular system: implications for serotonin reuptake-inhibitor antidepressants

In experimental animals, alterations in both peripheral and central serotonin have been shown to mediate a variety of effects on the cardiovascular system (Kuhn *et al*, 1980). The effects of serotonin depend on the brain region in which it is altered. We have only an incomplete understanding of the effects of a selective serotonin reuptake-inhibitor such as fluoxetine on brain serotonin levels and of net synaptic transmission as a function of time of drug treatment. Thus, the complexity of these effects make precise prediction of the effects of serotonergic agents on cardiovascular function difficult.

Fluoxetine in the presence of 5-hydroxytryptophan, and to a minimal extent when administered alone, has been shown to have hypotensive effects in hypertensive rats (Fuller *et al*, 1979). While no similar data have been reported in humans, it would be of interest to assess this possibility in hypertensive depressed subjects. A potential, but entirely speculative beneficial side-effect is suggested by Lown's hypothesis that an elevation in central nervous system serotonin levels may diminish susceptibility to arrhythmia-mediated sudden death (Lown & Lampert, 1985). This hypothesis is based on studies indicating that treatment of dogs with MAOI, tryptophan (which presumably elevated brain serotonin), and carbidopa (to prevent peripheral increase of serotonin) can increase the ventricular threshold for electrical induction of coupled premature ventricular beats.

A question which may be raised is whether fluoxetine will alter peripheral serotonin and whether this could exert effects on cardiovascular function. Most serotonin is contained in whole blood in platelets; free plasma serotonin is difficult to measure precisely because of platelet fragility. As detailed by Lemberger *et al* (1985), fluoxetine inhibits platelet uptake of serotonin and with time depletes platelet serotonin. Thus, one might predict a time-dependent effect on free serotonin, reflecting a balance between diminished release (secondary to depletion of platelet serotonin) and diminished reuptake by platelets. This in turn might have effects on vasospasm in critical vessels such as coronary arteries. These considerations are purely speculative, however, and non-selective agents such as desipramine also affect (although to a lesser degree) central nervous system serotonin levels and platelet serotonin uptake (Aberg-Wistedt *et al*, 1982). Important and potentially interesting information may however result from careful examination of the cardiovascular effects of agents such as fluoxetine which have specific well-defined effects on the serotonin system.

Conclusions

Cardiovascular side-effects represent major limitations in the use of TCAs. These side-effects include conduction disturbances, orthostatic hypotension, and arrhythmias. In addition, cardiovascular effects are prominent in overdoses. The hope that the newer drugs would have less cardiotoxicity than the older ones has not been borne out for those currently available in the USA. Buproprion and mianserin appear to be relatively free of cardiac side-effects, but their role in the therapeutic armamentarium is presently uncertain, due to their other side-effects. While the cardiovascular side-effects of maprotoline are consistent with clinical and pre-clinical studies, data on side-effects for trazodone have come largely from case reports and may reflect its initially enthusiastic use in patients with severe cardiac illness. Overdose case data and case report data, while of interest, can be misleading. Overdoses often involve multiple drugs and of course are associated with major pathophysiological changes such as anoxia, which may be indirect causes of cardiovascular effects. It is difficult in many case reports to determine the relative contributions of drug effect *per se*, underlying cardiac disease, and the interaction of the two in the genesis of the final clinical picture. Moreover, once a medication has been 'labelled' as having certain effects, the undertaking of prospective clinical trials is discouraged because of ethical constraints. These considerations are arguments for early intensive systematic testing of drugs likely to be free of cardiac effects (on the basis of pre-clinical studies and studies on healthy subjects) on patients with cardiac disease, in medical-psychiatric units under the combined supervision of a psychiatrist and cardiologist.

The selective serotonin inhibitor fluoxetine appears to have an extremely favourable cardiovascular side-effect profile, but the above considerations indicate the necessity for continued careful evaluation of its cardiovascular side-effects and a systematic extension of studies to include patients with cardiac disease. In addition, in analogy with TCAs being introduced as treatments for intrinsic cardiac disease, unanticipated and even beneficial 'side-effects'

of fluoxetine on the cardiovascular system may emerge.

Acknowledgements

This work was partly supported by US Public Health Service Grant MH 37907, by the Readers Digest Psychiatry Research Fellowship (JPH) and an Irma T. Hirschl Trust Research Scientist Award (JJM). We gratefully acknowledge the secretarial skills of Mrs Jennifer Mulligan and Ms Mary Ruth Goodley.

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NEUROPSYCHOPHARMACOLOGY 1994–VOL. 10, NO. 2

The Effects of Fluoxetine on the Polysomnogram of Depressed Outpatients: A Pilot Study

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The effects of fluoxetine (FLU) and its active metabolite, norfluoxetine (NFLU), on the polysomnogram (PSG) of nine depressed outpatients (eight with major depression; one with bipolar II, depressed phase disorder) were investigated by contrasting PSG values prior to treatment and during administration of FLU. The PSG changes were correlated with daily dose, cumulative dosage, single serum concentrations, and the total area under the serum concentration curve (AUC) of both FLU and NFLU. Fluoxetine clearly increased both stage 1 sleep time and rapid-eye-movement (REM) latency and decreased both percent REM and REM density. With a few exceptions, the cumulative dosage of FLU and the AUC of FLU and NFLU were better predictors of the changes in awake and movement time in the PSG than single-sample concentrations of FLU and NFLU taken at the time of PSG assessment. [Neuropsychopharmacology 10:85-91, 1994]

KEY WORDS: *Fluoxetine; Norfluoxetine; Polysomnography; Serotonin; Depression*

Fluoxetine (FLU)–a potent, specific, serotonin reuptake inhibitor–is an effective treatment for major depression (for a review, see Depression Guideline Panel, 1993). Serotonin affects the regulation of the sleep–wake cycle. It plays a role in the induction and maintenance of sleep as well as the character of sleep-stage macroarchitecture and rapid-eye-movement (REM) sleep expression (Jouvet et al. 1989).

Fluoxetine reportedly causes a shift toward lighter sleep that is reflected in increases in sleep latency and percentage of non-REM stage 1 sleep and decreases in total sleep time, sleep efficiency, and percentage of non-REM stages 3 and 4 sleep (Nicholson and Pascoe 1986; Pastel and Fernstrom 1987; Kerkhofs et al. 1990; Keck et al. 1991; Keck and McElroy 1992). The duration of REM sleep and REM latency, as well as REM density, may also be affected by FLU (Nicholson and Pascoe 1988; von Bardeleben et al. 1989; Nicholson et al. 1989; Bakalian and Fernstrom 1990; Hanzel et al. 1991; Saletu et al. 1991). These effects likely depend upon both the dose and duration of FLU treatment.

Changes in polysomnogram (PSG) measures associated with chronic FLU treatment in depressed subjects have been incompletely studied (Schenck et al. 1992). Relationships among PSG measures and serum concentrations of FLU and its active metabolite norfluoxetine (NFLU) have not been previously reported in depressed patients. This pilot study evaluated the effect of FLU and NFLU on PSG measures in a group of medication-responsive depressed outpatients.

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Received April 12, 1993; revised October 29, 1993; accepted November 5, 1993.

Published by Elsevier Science, Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/94/$7.00

METHODS

Subjects

Subjects were selected from a pool of self-referred patients (n = 5) and symptomatically depressed volunteers (n = 4) who were recruited by local advertisements. Following a screening visit, potential subjects had full clinical evaluations, which included administration of the Structured Clinical Interview for DSM-III-R (Spitzer et al. 1986). Evidence of general medical, sleep, or neurologic disorders was exclusionary. Only nonsteroidal, antiinflammatory agents were permitted during the 2-week period preceding PSG evaluations. Depressive symptom severity was measured by the 17-item Hamilton Rating Scale for Depression (HDRS-D) (Hamilton 1960) and the 30-item Inventory of Depressive Symptomatology, Clinician-Related Version (IDS-C) (Rush et al. 1986).

At the time of the study, diagnosis for all patients was nonseasonal, nonpsychotic, major depression, single or recurrent type, with moderate to severe symptoms, as evidenced by a 17-item HDRS-D score greater than 16. Patients with a history of any other psychiatric disorder, including psychoactive substance abuse, were dropped from consideration for the study. No subject had ever received prior treatment with FLU. Table 1 describes the sample.

Table 1. Sample Characteristics

	Full Sample (n = 9)
Demographics	
Age	37.3 ± 10.6
Female	44.4%
Major depression[a]	100.0%
Number of episodes	2.7 ± 1.5
Current episode length (months)	19.3 ± 21.4
Age at onset (yrs)	28.6 ± 11.6
Pretreatment symptom severity	
HDRS-D score	21.9 ± 4.7
IDS-C score	38.9 ± 9.2
Posttreatment symptom severity	
HDRS-D score	7.8 ± 2.5
IDS-C score	14.3 ± 9.1
Prior course of illness	
Single episode	22.2%
Recurrent	67.7%
Measures of fluoxetine exposure	
T_2 dose (mg/day)	36.7 ± 10.0
T_2 cumulative dose (total mg)	2884.4 ± 1345.5
T_2 FLU concentration (ng/ml)	342.3 ± 152.5
AUC FLU concentration	21951.7 ± 11200.1
T_2 NFLU concentration (ng/ml)	404.4 ± 160.6
AUC NFLU concentration	25634.3 ± 13288.8
T_2 FLU + NFLU (ng/ml)	746.8 ± 301.5
AUC FLU + NFLU concentration	47586.1 ± 23939.6

[a] Includes eight patients with major depression and one with bipolar II, depressed phase disorder.

Patients received FLU in an open-label fashion and were managed under standard clinical guidelines. Weekly evaluations included completion of the 17-item HDRS-D and the 30-item IDS-C. Fluoxetine was initiated at a dose of 20 mg/day (AM administration). The dose was increased initially to 40 mg/day if remission did not occur within 6 weeks. Treatment compliance was monitored by patient self-report.

Procedures

Each subject's requirement for and adequacy of nocturnal sleep had been identified and firmly established in advance of both PSG assessments. During the week preceding these recordings, patients maintained a 5-day sleep diary to document regularity of bed and rise times, nightly net sleep, and sleep quality. Napping was proscribed. Each patient retired and rose at individualized clock times. These were established following consultation with the patient and examination of the information recorded in the patient's sleep diary.

Prior to treatment with FLU, baseline PSG assessments were conducted during 2 consecutive nights in the Department of Psychiatry Sleep Study Unit of the University of Texas Southwestern Medical Center. All patients were drug free for at least 2 weeks prior to the initial night of PSG recording.

The electroencephalogram (EEG) was recorded from central sites referenced to contralateral ear lobes (C3–A2, C4–A1) on a polygraph (GRASS model 78; Quincy, MA) equipped with 7P-511 AC amplifiers set at a sensitivity of 5. The half-amp low- and high-frequency bandpass filters were set at 0.3 and 30 Hz, respectively (24 dB/octave). A 60-Hz notch filter attenuated electrical noise. Electrodes and transducers were also affixed during the first night of baseline sleep assessment to identify respiratory disturbances and periodic limb movement disorder.

A second series of 2-night PSG evaluations was conducted "on drug" after 7 to 29 weeks (median 11.9 weeks) of treatment (T_2). At T_2, the individualized doses ranged from 10 to 50 mg/day (36.7 ± 10.0), prescribed in once-a-day or alternating daily regimens. At T_2, seven of nine patients had achieved remission, which occurred between the 3rd and 14th week (median 8.0 weeks) of treatment with FLU. Remission was defined as an HDRS-D score less than or equal to 9 and an IDS-C score less than or equal to 14 for at least 2 consecutive weeks. The remaining two subjects responded significantly (T_2 HDRS-D score = 11.0 ± 1.4). Table 2 shows the PSG parameters at baseline (T_1) and after the acute treatment phase (T_2).

Visual sleep-stage scoring was performed according to standardized criteria (Rechtschaffen and Kales 1968) by personnel trained to better than 90% agreement. Polysomnogram parameters that were computed

Table 2. Polysomnographic Variables at T_1 and T_2 for Nine Subjects

Variables Analyzed as T_1–T_2 Differences	Pretreatment (Drug Free) (T_1)	Posttreatment (On Drug) (T_2)
TIB (min)	477.0 ± 24.3	481.3 ± 32.2
TSP (min)	423.1 ± 43.2	406.7 ± 40.7
TST (min)	379.9 ± 53.9	355.6 ± 62.0
REM Latency (min)[a]	86.3 ± 26.7	147.4 ± 69.5*
% Stage REM in TSP	14.7 ± 5.3	11.4 ± 4.2*
REM Density	2.1 ± 0.5	2.6 ± 0.7*
AMT in TSP (min)	43.8 ± 31.1	51.6 ± 32.5
AMT in first 1/3 TIB (min)	70.8 ± 29.2	74.8 ± 40.3
AMT in second 1/3 TIB (min)	35.9 ± 33.5	51.8 ± 43.6
AMT in third 1/3 TIB (min)	60.9 ± 50.8	51.6 ± 44.1
Stage 1 min in TSP	73.6 ± 21.1	125.6 ± 40.4*
Stage 2 min in TSP	228.9 ± 29.2	179.8 ± 59.7
Stages 3 and 4 min in TSP	13.6 ± 16.9	3.1 ± 4.9
% Sleep efficiency[b]	79.6 ± 10.0	74.3 ± 14.1
% Sleep efficiency minus stage 1[c]	73.1 ± 7.5	62.9 ± 20.0
Sleep latency (min)	35.8 ± 12.3	42.0 ± 23.0

[a] Includes AMT.
[b] (TST ÷ TIB).
[c] (TST − Stage 1 ÷ TIB).
* $p < .05$ based on paired t-test uncorrected for number of comparisons.

at T_1 and T_2 included 1) total time in bed (TIB)—time in minutes from "lights out" to "lights on"; 2) onset of total sleep period (TSP)[1]—the time of appearance of the half-minute epoch that initiates the first 10-minute period of recording that includes at least 8 minutes of any stage of non-REM sleep or the first epoch of REM sleep, whichever is sooner; 3) sleep latency—time from "lights-out" to onset of TSP; 4) wake-up time (WUT)—the first epoch of wake following the last 10-minute period of sleep that contains at least 8 minutes of any stage of sleep; 5) total sleep time (TST)—net minutes of sleep within TSP; 6) awake and movement time (AMT)—total minutes of AMT in the TSP and also in the first, second, and third one-thirds of the night; 7) stage 3 plus stage 4 sleep—total minutes of stage 3 combined with stage 4; 8) sleep efficiency—percentage of TST in total TIB; 9) sleep efficiency minus non-REM stage 1 sleep—percentage of TST minus non-REM stage 1 in total TIB; and 10) REM latency—time from onset of TSP to the first half-minute epoch of REM sleep. REM density was scored on a 0 to 4-point scale for each minute of REM sleep. Polysomnogram variables were averaged across nights for each subject at each measurement occasion (T_1 and T_2). Additional details relevant to scoring criteria are presented by Emslie et al. (1990).

Weekly serum samples were obtained in the morning approximately 24 hours after the last medication dose, before ingestion of medication for that day. Blood was drawn for analysis at 8 AM (range 8 to 10 AM) following the second night of PSG recording at T_2.

[1] Total sleep period is often referred to as the period of persistent sleep.

Fluoxetine and NFLU were isolated from serum by liquid–liquid extraction. They were then separated and quantified by reverse-phase, high-performance liquid chromatography (HPLC) with ultraviolet detection. Units reported are ng/ml. Within-run precision was determined, yielding a coefficient of variation between 0.0% and 5.1% for FLU and 1.3% and 7.7% for NFLU. The between-run coefficient of variation was 4.1% to 6.8% for FLU and 6.2% to 8.8% for NFLU (Orsulak et al. 1988).

Statistical Analyses

The statistical analyses were divided into three parts. First, to test for changes in PSG between T_1 and T_2, we conducted paired t-tests. Second, to measure the relationship between the FLU exposure and changes in PSG, correlations between these measures were conducted. Third, we estimated sample sizes needed to replicate the finding based on the regression results with power set at .80 and alpha at .05. All statistical analyses were computed using a commercially available software program (SAS Institute Inc. 1988).

Contemporaneous FLU measures used in the analyses included 1) current FLU dose; 2) FLU serum concentration; 3) NFLU serum concentration, and 4) total (FLU plus NFLU) serum concentration. Additional parameters designed as measures of cumulative effects of FLU treatment were cumulative oral dose at T_2 and total area under the serum concentration curve (AUC) for FLU and NFLU (i.e., the serum concentration analogs of cumulative oral dose). Cumulative FLU dose and AUC encompass the entire treatment period. The AUC was estimated by a straight-line fit. A polygon was con-

Table 3. Posttreatment (T_2) Correlation of Independent Measures, Dose, and Blood Levels[a]

	Cumulative Dose	FLU AUC	NFLU AUC	Total AUC	T_2 Dose	T_2 FLU Concentration	T_2 NFLU Concentration	T_2 Total Concentration
T_2 dose	0.62	0.65	0.57	0.62	1.00	0.82	0.82	0.85
T_2 FLU concentration	0.37	0.54	0.43	0.49	0.82	1.00	0.85	0.96
T_2 NFLU concentration	0.54	0.68	0.58	0.64	0.82	0.85	1.00	0.96
T_2 total concentration	0.47	0.64	0.53	0.59	0.85	0.96	0.96	1.00
Cumulative dose	1.00	0.94	0.95	0.97	0.62	0.37	0.54	0.47
FLU AUC	0.94	1.00	0.91	0.97	0.65	0.54	0.68	0.64
NFLU AUC	0.95	0.91	1.00	0.98	0.57	0.43	0.58	0.53
Total AUC	0.97	0.97	0.98	1.00	0.62	0.49	0.64	0.59

[a] Pearson product-moment correlation coefficient ($n = 9$).

structed using the weekly serum concentrations as its height and the days of treatment as its width. The area of the polygons estimated the AUCs for both FLU and NFLU. Inasmuch as contemporaneous and cumulative measures were mathematically related, correlations among them are shown in Table 3.

Table 3 suggests that the four measures of contemporaneous FLU exposure and the four measures of cumulative exposure have considerable overlap within each group of measures. The correlations between the contemporaneous and cumulative measures are lower, suggesting that the current and cumulative measures are less interdependent.

As a caution to the reader, the analyses reported in this paper are exploratory and designed to serve as a guide for future research. Both the *t*-test of PSG T_1 to T_2 difference scores and the correlations between the exposure to FLU measures and PSG T_1 to T_2 difference scores are considered potentially confounded by the alleviation of depression. Although multivariate statistical analyses can be designed to test and separate the influences of multiple effects, in this study with only a few subjects, it is either impossible to perform such analyses or the results may be misleading because they were conducted on a very small sample. In addition, no attempt was made to statistically correct for the number of tests being used and the probability reported should only be used as a guide to measures that would be useful in future research.

RESULTS

Overall Changes in the Polysomnogram

Results of the *t*-test of the differences between T_1 and T_2 measures revealed an increase in stage 1 sleep, REM latency and REM density between T_1 and T_2 (Table 2).

Polysomnogram Changes in Relation to Medication Dose and Serum Concentrations

The correlations presented in Table 4 between FLU measures suggest the following relationships: 1) Ease of falling asleep (sleep latency) was affected most by the cumulative dosage and cumulative serum concentration (AUC) of FLU rather than by its contemporaneous dose or concentration at T_2; 2) Intervening wakefulness (AMT) (overall and in the first one-third of the night) were most strongly correlated with contemporaneous FLU dose at T_2; the cumulative exposure measures correlated with AMT in the first one-third of the night, and the cumulative measures of NFLU AUC and total AUC correlated with AMT in the last one-third of the night; 3) sleep efficiency was affected by both the cumulative dosage and serum AUC for FLU as well as current dose.

Findings in the seven treatment remitters were equivalent to those of the group as a whole ($n = 9$), except for a correlation between FLU AUC and AMT in the third one-third of the night ($r = .784$) in the remitters, which was not found for the complete sample.

Because these data were collected as a pilot study, we estimated the sample sizes needed to detect a relationship between FLU dose and serum concentrations and changes in PSG measures between T_1 to T_2. Based on these data, a wide range of sample sizes would be needed. For example, samples with 5 to 37 subjects would be sufficient to find significant changes in total AMT in the first and third one-thirds of the night in relation to FLU AUC. In contrast, to find a significant relationship between FLU AUC and minutes of stage 1 sleep would require a sample in the thousands.

DISCUSSION

In this sample of nine depressed patients who underwent sleep studies before and during the course of treatment with FLU, the drug appeared to alter both sleep continuity and sleep-stage architecture. Sleep changes observed between drug-free (pretreatment) and on-medication (posttreatment) conditions were increases in REM latency, stage 1 sleep and REM density, and decreases in percent REM sleep. It appears that sleep shifted from deeper (non-REM stages 2, 3, and 4) to

Table 4. Correlations Between PSG Changes, Dose, and Blood Levels[a]

Variables Analyzed as T_1–T_2 Differences	Cumulative Dose	FLU AUC	NFLU AUC	Total AUC	T_2 Dose	T_2 FLU Concentration	T_2 NFLU Concentration	T_2 Total Concentration
REM latency (min)	−0.14	−0.09	−0.01	−0.05	−0.01	0.31	0.05	0.18
% Stage REM in TSP	0.08	0.06	0.12	0.09	0.56	0.43	0.40	0.43
REM density	−0.31	−0.22	−0.31	−0.27	0.18	0.32	0.37	0.36
AMT in TSP (min)	−0.41	−0.43	−0.35	−0.39	**−0.72**	−0.38	−0.47	−0.44
AMT in first 1/3 TIB (min)	**−0.80**[b]	**−0.86**	**−0.68**	**−0.78**	**−0.81**	−0.57	−0.63	−0.62
AMT in second 1/3 TIB (min)	−0.50	−0.47	−0.32	−0.40	−0.55	−0.16	−0.22	−0.20
AMT in third 1/3 TIB (min)	−0.66	−0.55	**−0.76**	**−0.68**	−0.37	−0.07	−0.30	−0.19
Stage 1 min in TSP	0.17	−0.05	−0.03	−0.04	−0.24	−0.51	−0.62	−0.59
Stage 2 min in TSP	0.63	−0.65	0.54	0.61	**0.68**	0.34	0.57	0.45
Stages 3 and 4 min in TSP	−0.15	−0.33	−0.04	−0.17	−0.09	−0.33	−0.23	−0.29
% Sleep efficiency minus stage 1	−0.08	0.20	0.10	0.15	0.24	0.56	0.64	0.62
% Sleep efficiency	0.74	**0.72**	0.62	**0.68**	**0.68**	0.27	0.44	0.37
Sleep latency (min)	**−0.75**	**−0.86**	−0.59	**−0.73**	−0.60	−0.46	−0.56	−0.53

[a] Pearson product-moment correlation coefficients (n = 9).
[b] Correlation coefficients in boldface are less than p = .05.

lighter stages with more wakefulness, although changes in the deeper sleep measures did not reach statistical significance in this small sample.

Cumulative treatment exposure particularly affected ease of falling asleep, conventional sleep efficiency, and wakefulness in the first and last one-thirds of the night. The relationship of NFLU to wakefulness during sleep appeared to be greatest in the latter part of the night. The NFLU AUC correlated strongly with the decline in AMT in the last one-third of the night (reduction in "terminal" insomnia) and may be a marker of the antidepressant effects of FLU. The meager amount of deep non-REM sleep and the great interindividual variability evident at T_1 may explain the poor correlation between the decrements in deep non-REM sleep and FLU treatment (see Table 4). Overall, the cumulative measures appear to be somewhat more sensitive to sleep changes than contemporaneous measures.

The PSG changes that related to FLU and NFLU were in a direction opposite to changes that have been reported when there is a reduction in depressive symptoms. Increased REM latency and REM density and decreased percent REM, which were unrelated to FLU and NFLU measures, have been found with a reduction in depressive symptoms.

Other investigators have found that treatment with FLU affects the sleep of depressed patients (Kerkhofs et al. 1990; Keck et al. 1991). However, Keck et al. (1991) reported baseline PSG data for only one patient in their sample (n = 7). Sleep continuity was disturbed, as exemplified by increases in the number of arousals and sleep-stage shifts. Consistent with our data, the proportion of stage 1 sleep seemed to increase, whereas deep non-REM sleep and sleep efficiency declined.

Suppression of REM sleep has been noted in patients treated with either FLU or amitriptyline (Kerkhofs et al. 1990). Our findings are similar to those of Kerkhofs et al. (1990), but provide an analysis of serum concentrations of FLU and NFLU as well.

Although we also found a lengthening of REM latency, an increase in REM density, and a reduction in overall REM percent, they did not correlate with the amount or duration of FLU treatment in this sample of patients. Such findings suggest that increased REM latency and decreased REM sleep, although occurring following exposure to many types of antidepressant drugs, are not uniquely related to specific characteristics of drug dose and serum concentrations. However, because of the high interindividual variability of the T_2 REM latency in our subjects, a larger sample is needed to support this contention.

Single doses of FLU (20 to 80 mg) also affect the sleep of nondepressed, healthy adults (Nicholson and Pascoe 1988; Nicholson et al. 1989; von Bardeleben et al. 1989; Saletu et al. 1991). Sleep was found to be of poorer quality following a dose of FLU, with a rise in the number of arousals and in stage 1 sleep. Percentage of REM sleep was reduced and REM latency was lengthened, a finding common to many antidepressant medications. However, results from single-dose studies have only a restricted application in the management of major depressive episodes during which antidepressant agents are usually prescribed for weeks or months.

The pharmacodynamic properties of FLU and NFLU probably influence their effects on sleep. Following an oral dose of FLU, peak serum concentrations are reached within 6 to 8 hours. Fluoxetine is extensively metabolized to equipotent NFLU. The long elimination half-life of FLU (2 to 3 days) and NFLU (5 to 9 days) assures a large accumulation of both substances. After multiple doses of FLU, serum concentrations and ratios of FLU to NFLU are unpredictable (Lemberger et

al. 1985; Stark et al. 1985; Benfield et al. 1986; Orsulak et al. 1988; Keck and McElroy 1992). Accumulation of FLU and NFLU in the brain may contribute to both therapeutic and toxic effects (Renshaw et al. 1992).

Chronic alterations in sleep can cause excessive daytime sleepiness. Patients who report this condition may metabolize FLU differently, resulting in an accumulation of NFLU, which in turn, may exacerbate excessive daytime sleepiness. Keck and McElroy (1992) reported plasma FLU/NFLU ratios less than 1.0 in eight patients who reported excessive daytime sleepiness and ratios greater than 1.0 in those who did not report this phenomenon. However, it is also possible that the symptom of excessive daytime sleepiness follows upon the light and disrupted sleep secondary to FLU treatment. Normal subjects have reported drowsiness on the day following a single dose of FLU. They also evidence reduced coding ability and prolonged reaction times (Saletu and Grunberger 1985; Nicholson and Pascoe 1988).

The cumulative effects of FLU may be important in elderly patients who are generally subject to more disturbed sleep and reduced daytime wakefulness than are younger adults (Czeisler et al. 1992; Bliwise 1993). The elderly are sensitive to cumulative effects of drugs, particularly when multiple drugs are administered for concomitant systemic illnesses.

This preliminary study suggests that some of the cumulative effects of FLU and NFLU on sleep (i.e., sleep efficiency, sleep latency) may be different. In addition, the size of sleep changes may depend upon the duration and strength of exposure to one or the other substance. Certain PSG parameters, such as changes in REM latency or deep non-REM sleep, do not appear to correlate specifically with either FLU or NFLU parameters. This interpretation is consistent with the REM sleep differences reported after single doses and after chronic exposures of 30 days or longer, as noted above. A more definitive study is needed to fully evaluate the relative effects on the PSG of cumulative versus contemporaneous measures of FLU treatment.

Finally, several investigators have noted an increase in non-REM eye movements with FLU (Keck et al. 1990; Schenck et al. 1992). Keck et al. (1990) have also shown that FLU-induced eye movements occur most often in stage 1 sleep. These eye movements can potentially compromise sleep-stage discrimination, perhaps resulting in the misclassification of sleep stages. It is possible that the FLU-induced eye movements resulted in an increase in scorable stage 1 sleep, accompanied by a decrease in the identification of stage 2 sleep. This potential sleep-stage misclassification could have resulted in the decrease in stage 2 sleep observed upon treatment in this study. Upon reviewing the PSG records, FLU-induced eye movements create the largest uncertainty in differentiating stage 1 from wakefulness and from REM sleep, which suggests that the decreased stage 2 sleep observed in this pilot study is unlikely to have resulted from sleep-stage misclassification. However, to further clarify this issue, a systematic, quantitative study of the distribution of FLU-induced eye movements across sleep is currently underway, including an assessment of interrater disagreement on sleep-stage classification.

The influence of FLU on sleep does not appear to hinder its efficacy in the acute treatment phase of major depression. Lower doses (e.g., 10 mg/day) than those usually used in the acute treatment phase may produce or sustain a remission of symptoms without the excessive daytime sleepiness found with high serum concentrations of NFLU. Our findings, if replicated, would be consistent with the strategy of lowering the dose of medication in subjects who have responded clinically to FLU, but who subsequently develop an impairment in falling asleep or in maintaining sleep (Cain 1992).

ACKNOWLEDGMENTS

The authors wish to express their appreciation to Mary DeLira, R.N. and Terry Cook, L.V.N. for technical assistance, to the technical staff of the Sleep Studies Unit under the supervision of Darwynn D. Cole, B.A., to David Savage for secretarial assistance, and to Kenneth Z. Altshuler, M.D., Stanton Sharp Professor and Chairman, for his administrative support.

This study was supported in part by grants from the National Institute of Mental Health to A. J. Rush (MH-35370) and to the Department of Psychiatry, University of Texas Southwestern Medical Center at Dallas (MH-41115), by the Department of Veterans Affairs Medical Center, Dallas, Texas, and by a Veterans Administration Research Training Grant to W. A. Hendrickse.

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Journal of Abnormal Child Psychology, Vol. 10, No. 3, 1982, pp. 307-324

Development of a Structured Psychiatric Interview for Children: Agreement Between Child and Parent on Individual Symptoms[1]

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To test the reliability of children's reporting as compared with that of their mothers, a highly structured psychiatric diagnostic interview was used with 307 subjects, ages 6 through 16. Another interviewer gave each mother a similar interview about the child. Responses of each mother-child pair to 168 questions were compared using the kappa statistic. Highest agreement was found on questions concerning symptoms that are concrete, observable, severe, and unambiguous. Mothers tended to report significantly more behavioral symptoms, and children more subjective symptoms. Reasons for low kappas and asymmetrical reporting of symptoms are discussed.

There has recently been an increased interest in obtaining information about children by using a structured interview with the child (Berg & Fielding, 1979; Langner, Gersten, McCarthy, Eisenberg, Greene, Herson, & Jameson, 1976; Rutter & Graham, 1968). A structured interview is highly desirable, since lay interviewers, in addition to qualified researchers and clinical diagnosticians, can be trained to use it. Much less time is required than with the more traditional indirect methods of eliciting

Manuscript received in final form September 3, 1981.
[1]The authors wish to thank Robert Cloninger, M.D., John Rice, Ph.D., and Irving I. Gottesman, Ph.D. for their assistance in the statistical analysis and critical review of the manuscript.
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0091-0627/82/0900-0307$03.00/0

information from children. Finally, a highly structured instrument permits the maximizing of reliability. In addition to parents' and teachers' reports about children, the children themselves now provide an additional source of information through the use of the interview.

In previous studies of the interview schedule described here, Herjanic, Herjanic, Brown, and Wheatt (1975) showed that children ages 6 through 16 can provide reliable information as judged by concordance with information given by their mothers, and Herjanic and Campbell (1977) showed that this interview can distinguish disturbed from nondisturbed children.

Herjanic et al. (1975) compared information from mothers' interviews with information obtained from interviews with their children, since mothers are the most frequently used source of information about their children. Such information has traditionally been regarded as important and reliable, and for this reason they assumed that good agreement between mothers and children would indicate a reasonable degree of reliability on the part of the children.

The aims of the present study were to further test mother-child agreement, to delineate areas in which mothers and children had either good or poor agreement, and to hypothesize reasons for good or poor agreement.

Additionally, individual questions were analyzed to determine the characteristics of questions that produced good or poor agreement, as a study of this process can teach us how to phrase questions to elicit both the most reliable and the most valid responses.

Most studies of reliability are test-retest studies; that is, the subject is interviewed twice. In our study different people (mothers and their children) were interviewed by different interviewers. The kind of agreement that we found between mothers and children would not have been possible if the instruments for both mothers and children were not reliable to a significant extent. While Carey and Gottesman (1978) have pointed out that a high reliability does not ensure validity, in this case it seems apparent that establishing reliability is a first step in the development of an instrument that will be both reliable and valid.

METHOD

Subjects

A total of 307 children ranging in age from 6 through 16 were given a structured diagnostic interview. There were 110 girls and 197 boys. Of

these, 208 were white and 99 were black; 114 children were aged 12 to 16, 84 were aged 10 to 11, and 109 were aged 6 to 9 years. Using the Duncan occupational scale (Reiss, Duncan, Hatt, & North, 1961), 51% of the subjects were in families that rated 0-33, 30% rated 34-66, and 19% rated 67 or above. The lower numbers included the unemployed, those on welfare, and those with low-paying jobs, and the higher numbers included high-income and professional families. Also, 222 were children who came for evaluation to a psychiatric service in a general children's hospital, 35 were pediatric inpatients seen by a psychiatrist in consultation, and 50 were children selected at random from a pediatric outpatient clinic. The only selection criteria were age, sufficient intelligence and language facility to participate in an interview, and willingness to take part in research.

Interview Procedure

Each child and mother was interviewed simultaneously in separate rooms by different interviewers. The data were collected over a 3-year period, with approximately 15 different interviewers who ranged in experience from undergraduate psychology and premedical students to child psychiatrists. Training consisted of observation of the interview being given at least once, detailed verbal instructions about the administration, and then a review in detail of each completed interview with a child psychiatrist. None of the interviewers or reviewers had any information about the child subject prior to the interview. There was no exchange of information between the interviewers of the child and the mother prior to the described procedures. Informed written consent for the interviews was obtained from each mother, and verbal assent from each child.

The Interview

The interview itself was a highly structured questionnaire covering information about the children's relationships at home, at school, and with peers; school progress; social behavior in the community; a review of somatic symptoms; and questions covering a range of psychiatric symptoms from depression and anxiety to psychosis. Most of the questions could be answered by "yes" or "no," a "yes" meaning that the symptom was present. The areas covered and kinds of questions asked are given in Table 1. The interview questions compared in this study were exactly the same for the mother and child except for wording, which directed the question to either one: "Do you . . . ?" or "Does your child . . .?" Only the mothers were asked about early development, paranatal history, family history, and

socioeconomic status. This information did not enter into the present comparison of child-mother reporting.

Two interrater reliability studies using a videotaped interview of the child were done. Each time, 10 interviewers watched one of the two taped child interviews and independently scored it. The participants included research assistants, medical students, residents, and staff physicians. Overall agreement on responses to each question on the child interview was 84% and 85% on the two occasions. Probes for severity and functional impairment were not used. Therefore, ambiguous answers such as "sometimes" could be coded either "yes" or "no," according to the interviewer's judgment.

One intrarater reliability study was done with five psychiatrists rescoring the same taped interview after a 2- to 3-month interval. The range of agreement on individual symptoms was 80% to 95%, with a mean rate of agreement of 89%.

Analysis

The mother-child interviews were compared using the kappa statistic to measure the extent to which agreement between them exceeds chance expectations. The advantage of this method is that it takes into account the high rate of agreement one almost invariably finds between two people when symptoms are absent or rare. It is usually easy to obtain agreement on the absence of any problem, producing a high "percent agreement" by chance alone. The kappa statistic (see Cohen, 1960; Fleiss, 1971) varies from negative values for less than chance agreement, through 0 for chance agreement, to 1.0 for perfect agreement. Depending upon what is being compared, each investigator determines what is an acceptable level of kappa. In general, a kappa of .5 or higher is considered to show reliable agreement (Helzer, Clayton, Pambakian, Reich, Woodruff, & Reveley, 1977).

The kappas for 185 symptoms ranged from .00 to .87. We divided them into three groups: high, middle, and low. The high group, kappas of .50 and over, were taken to indicate good agreement and have been called "reliable." The low group, .29 and below, indicated poor agreement and have been called "unreliable." The middle range of kappas, .30 to .49, are referred to as "middle kappas." Since one purpose of the study was to determine what kinds of questions produce the most reliable information, the middle group was analyzed for characteristics that distinguish them from both the lower and higher groups.

The choice of .30 as the cutoff point between "unreliable" and "middle" kappas is arbitrary because there is no precedent for determining

the degree of reliability of a kappa in comparing answers from a child and his mother to questions about the child. However, as shown in a study of diagnoses, a kappa of .30 for diagnoses made from mother and child interviews compares favorably with kappas of diagnoses obtained from interviews with adults and their first-degree relatives (Reich, Herjanic, Welner, & Gandhy, 1982).

Symptoms that were reported significantly more frequently by either the mother or the child were designated as "asymmetrically reported." Significance was determined by the McNemar chi-square test (Bishop, Fienberg, & Holland, 1975). If there were sufficient positive responses by both mother and child to a particular symptom, the result could show middle or high agreement, yielding a kappa above .30, but could still be called "asymmetrical," because either parent or child reported significantly more positive responses than the other. All symptoms on which there were fewer than 10 responses have been omitted, even though agreement was high, because the kappa statistic is not useful for very low frequencies and responses.

RESULTS

High and Middle Kappas

The headings for each group of symptoms (see Table I) correspond to the order used in the interview, but under each heading the symptom order has been arranged according to the magnitude of kappa. For easier reference, each question used for illustration in the text is preceded by the number assigned to it in Table I.

Several characteristics of the high kappas are noteworthy. First, the highest kappas (.70 +) were for objective, concrete questions, such as: 29. Were you ever suspended or expelled from school? (.75); 58. Have you ever stayed overnight or longer in the hospital? (.70); 91. Do you take pills or other medicine regularly? (.70); and for girls, 134. Do you have monthly periods? (.78). These questions are based on simple, irrefutable facts, which could not be easily ignored by either child or parent.

Second, factual questions concerning behavior reflecting a degree of seriousness that could not be overlooked tended to have high kappas, such as: 30. Have you ever repeated a grade? (.68); 31. Have you ever played hookey from school? (.50); or 48. Have you ever been in trouble with the police or a juvenile officer? (.64). These were frequently characterized by the fact that an outside person, such as the police or the teacher,

Table 1. Comparison of 307 Child-Mother Responses to 168 Questions on a Diagnostic Interview About the Child

Symptom	Kappa	Symptoms Scored Positive on Interviews: Both mother and child	Mother only	Child only	Chi square
Relationships at home					
1. Sasses parents	.36	79	64[a]	31	11.45
2. Tells lies to parents	.29	100	61	47	
3. Doesn't do chores	.27	117	72[a]	38	10.50
4. Fights a lot at home	.26	68	61	47	
5. Takes things from home	.25	40	50	43	
6. Doesn't come in on time	.21	59	48	66	
7. Doesn't listen when spoken to	.20	118	68	51	
8. Goes out without telling parents	.19	50	44	68[a]	5.14
9. Loses temper easily	.18	115	63	59	
10. Throws, breaks things when mad	.18	37	62[a]	41	4.28
11. Anything upset him lately	.18	35	71[a]	24	23.25
12. Thinks he's blamed a lot	.14	137	66	53	
13. Punished more than most	.14	23	42	48	
14. Doesn't mind very well	.12	119	68	62	
15. Hurts other children	.12	23	37	59[a]	5.04
Relationships with peers					
16. Fights a lot	.27	35	46	37	
17. Pesters, picks on others	.16	27	76[a]	23	28.37
18. Prefers to be alone	.16	23	50	35	
19. Trouble keeping friends	.15	31	61[a]	40	4.85
20. Too shy	.12	20	48	42	
21. Loses temper easily	.08	57	83[a]	52	7.11
22. Has trouble making friends	.08	18	48	44	
23. Restricted more than friends	.06	30	50	68	
24. Gets mad easily/quits	.04	41	95[a]	43	19.59
25. Feelings easily hurt	.04	74	106[a]	44	25.62
Homicidal thoughts					
26. Tried to kill someone	.18	3	16[a]	6	4.54
27. Threatened to kill someone	.17	16	37	30	
28. Had thoughts killing/hurting	.07	28	39	77[a]	12.44
Adjustment at school					
29. Suspended or expelled	.75	40	4	17[a]	8.04
30. Repeated a grade	.68	63	21	16	
31. Played hookey	.50	26	21	17	
32. In trouble/bad behavior	.38	119	58[a]	36	5.10
33. Sasses adults (teachers)	.38	34	35	28	
34. Has trouble with math	.38	74	39	48	
35. Breaks school rules	.36	29	47[a]	16	15.25
36. Didn't finish work	.34	98	82[a]	20	37.68
37. Has trouble with reading	.34	54	57[a]	30	8.38

Table 1. Continued

Symptom	Kappa	Symptoms scored positive on interviews: Both mother and child	Mother only	Child only	Chi square
38. Won't stay in seat	.30	68	65[a]	37	7.68
39. Has trouble with spelling	.27	39	40	46	
40. Has problems learning	.27	77	50	55	
41. Doesn't turn in assignments	.26	72	76[a]	32	17.92
42. Pretended sick to stay home	.25	27	47	30	
43. Doesn't do homework	.22	43	65[a]	31	12.04
44. Pesters other children	.21	40	83[a]	23	33.96
45. Fights too much	.21	25	33	47	
46. Talks when not supposed to	.19	120	73[a]	46	6.12
47. Doesn't understand instructions	.14	59	56	66	
Social adjustment					
48. In trouble with police	.64	28	4	21[a]	11.56
49. Appeared in juvenile court	.62	7	2	6	
50. Ran away from home	.54	18	14	11	
51. Caught stealing	.39	16	23	14	
52. Drank beer/other alcohol	.35	9	4	24[a]	14.28
53. Pulled knife/gun on someone	.35	9	10	17	
54. Set fires	.33	13	25	14	
55. Hurt someone badly in fight	.27	8	6	28[a]	14.23
56. In trouble for sexual behavior	.24	2	5	6	
57. Injured/killed animal for fun	.19	4	8	18[a]	3.84
Medical history					
58. Has been in hospital	.70	164	34[a]	9	14.53
59. Went to emergency room	.54	132	39	30	
60. Reason to see doctor often	.46	52	41	25	
61. Ever seen psychiatrist	.42	50	56[a]	16	22.22
62. Ever knocked unconscious	.34	17	23	22	
Phobias					
63. Fears interfere with sleep	.19	23	23	62[a]	17.89
64. Fears unusual for age	.07	17	43	50	
65. Fears interfere with schoolwork	.03	0	6	22[a]	9.14
66. Afraid, can't go out with friends	.00	1	12	22	
Obsessions					
67. Worries a lot	.14	75	75	53	
68. Worried about parents	.13	19	27	60[a]	12.51

Table I. Continued

Symptom	Kappa	Symptoms scored positive on interviews: Both mother and child	Mother only	Child only	Chi square
69. Stayed home because worried	.12	9	40"	21	5.91
70. Can't forget bad dreams	.07	14	19	63"	23.60
71. Hears voice inside head	.07	5	11	38"	14.87
72. Has thoughts/can't get rid of	.01	22	48	68	
Compulsions					
73. Spells of hand washing	.18	2	6	9	
74. Upset over changes in in routine	.08	15	40	45	
75. Special habit/touching things	.08	6	31	22	
76. Takes long time/ dress/wash	.04	7	59"	12	31.11
Depression					
77. Lost weight	.38	8	2	21"	15.69
78. Crying spells/no apparent reason	.32	16	24	22	
79. Trouble sleeping	.30	16	23	26	
80. Bad thoughts, feelings, depressed	.24	34	53"	34	4.14
81. Stopped activities	.23	9	14	27"	4.12
82. Can't concentrate	.17	13	27	35	
83. Lost appetite	.15	7	14	32"	7.36
84. Appetite going up and down	.10	5	19	22	
85. Depressive symptoms in past	.09	5	25	17	
Suicidal thoughts					
86. Attempted suicide	.49	8	3	12"	5.40
87. Wished self dead, guilty	.33	45	44	39	
88. Thought about suicide	.33	21	22	28	
89. Threatened suicide	.24	13	24	26	
90. Would repeat suicide attempt	.02	1	17	9	
Somatic concerns					
91. Takes pills, other medicine	.70	93	21	21	
92. Allergic to anything	.51	57	23	36	
93. Missed school due to illness	.45	56	36	33	
94. Sees doctor often	.44	64	23	36	
95. Trouble with nerves	.18	54	103"	22	52.48
96. Has poor health	.16	10	25	29	
97. Aches and pains	.15	57	73"	51	3.90
Anxiety symptoms					
98. Pains in chest	.36	16	14	24	
99. Trouble breathing	.30	20	37	20	

Table I. Continued

Symptom	Kappa	Symptoms scored positive on interviews: Both mother and child	Mother only	Child only	Chi square
100. Gets short of breath	.24	8	17	18	
101. Light-headedness	.14	12	20	46[a]	10.24
102. Heart pounds when sitting still	.13	7	21	28	
103. Worries about heart	.08	5	16	33[a]	5.89
Unusual symptoms					
104. Unable to feel (numb)	.35	7	1	22[a]	19.17
105. Band squeezing head or chest	.19	5	7	25[a]	10.12
106. Couldn't move part of body	.17	5	13	21	
107. Lump in throat/can't swallow	.12	6	8	42[a]	23.12
108. Lost voice	.02	0	4	17[a]	8.04
Nervous system					
109. Had fit or seizure	.57	18	21[a]	2	15.69
110. Fainted/passed out	.39	12	14	16	
111. Blurring, difficulty seeing	.27	29	34	40	
112. Wakes at night/pains in legs	.25	18	22	36	
113. Seeing double	.19	8	13	31[a]	7.36
114. Buzzing/ringing in ears	.15	15	6	84[a]	67.60
115. Has headaches	.10	101	49	88[a]	11.10
116. Amnesia	.09	3	5	33[a]	20.63
117. Dizzy/room spinning	.07	18	31	68[a]	13.82
118. Thought he was going blind	.05	1	4	20[a]	10.66
119. Afraid he was going deaf	.01	0	4	7	
Gastrointestinal system					
120. Needs laxative/ suppository	.34	15	22	19	
121. Throws up often	.29	11	15	24	
122. Pains in stomach	.25	41	44	48	
123. Gets sick to stomach easily	.22	36	28	68[a]	16.66
124. Pain with bowel movement	.20	7	15	22	
125. Certain foods make him sick	.16	22	20	72[a]	29.36
126. Loose bowels often	.12	4	13	22	
Encopresis					
127. Bowel movement in pants or bed	.15	7	28	18	
Enuresis					
128. Wets bed at night	.54	40	30	15	
129. Still wets in first grade	.53	45	22	19	

Table 1. Continued

Symptom	Kappa	Symptoms scored positive on interviews: Both mother and child	Mother only	Child only	Chi square
Genitourinary system					
130. Kidney trouble	.42	11	11	14	
131. Trouble urinating	.21	4	11	12	
132. Backache not related to injury	.19	9	13	34[a]	9.38
133. Seen doctor for trouble urinating	.17	2	6	9	
Menstruation					
134. Has monthly periods (N = 60)	.78	36	4	2	
135. Missed school/cramps	.53	5	3	3	
136. Has cramps (N = 41)	.26	15	8	7	
Sexual experience					
137. Had sexual relations (N = 75)	.58	5	2	4	
138. Dress up/boy's (girl's) clothes	.33	7	9	13	
139. Sexual activity with adult	.11	1	11[a]	2	6.23
140. Wished was boy (girl)	.10	2	6	16[a]	4.54
141. Masturbates often	.09	1	4	6	
142. Sexual play with peers	.04	1	30[a]	13	6.72
143. Scolded for masturbating	.02	1	16	8	
Self-concept					
144. Harder time in school than peers	.29	54	67[a]	19	26.79
145. People can't trust him	.25	21	31	28	
146. Into more trouble than others	.24	26	47[a]	22	9.05
147. Gives up easily	.19	45	91[a]	12	60.59
148. Different from others	.14	53	80[a]	25	28.80
149. Someone makes him do wrong things	.02	7	39	24	
150. Thinks something odd about him	.01	3	46[a]	13	18.45
Ideas of reference					
151. People talking behind back	.03	32	59	67	
152. Person tried to hurt him	.03	3	20	25	
153. Thinks people laughing at him	.02	11	59[a]	32	8.01
Depersonalization					
154. Strange feelings in body	.02	0	5	13	
155. Body changed, strange way	.02	0	5	12	

Table I. Continued

Symptom	Kappa	Symptoms scored positive on interviews: Both Mother and child	Mother only	Child only	Chi square
Derealization					
156. Feels world changed, unreal	.05	1	4	20[a]	10.66
157. Felt in different place	.02	0	5	23[a]	11.57*
Passivity and control					
158. Can read another's mind	.02	0	4	13[a]	7.11
159. Person could use him like robot	.01	0	3	14[a]	7.11
160. Heard his thoughts spoken out	.00	0	1	17[a]	14.22
161. Person could read his mind	.03	0	7	19[a]	5.53
Hallucinations					
162. Heard voices, nobody there	.05	3	5	49[a]	35.85
163. Peculiar taste in mouth	.03	1	2	34[a]	28.44
164. Felt creepy things on skin	.02	1	3	35[a]	26.94
165. Saw things others couldn't	.01	1	12	32[a]	9.09
166. Smelled strange things	.00	0	0	22[a]	22.00
Delusions					
167. Felt had special power	.03	0	7	14	
168. Had false beliefs	.01	1	26	14	

[a]Either mother or child reporting significantly more frequently than the other.

would be likely to report the behavior to the parent and make its seriousness clear to the child.

A third characteristic of questions with high kappas was that they tended to ask about problems or events that would not likely be misunderstood or misinterpreted by children; for example: 59. Have you ever had an accident so that you went to the hospital emergency room to get stitches or a cast? (.54) or 128. Do you wet the bed at night? (.54).

Fourth, the high kappas described symptoms that by their very nature would likely be known to the mothers, such as: 50. Have you ever run away from home overnight or longer? (.54) or 109. Have you ever had a fit or a seizure? (.57). The question concerning seizures, while showing high agreement, also had significantly more positive responses from mothers than from children. The question was not limited to the memory span

of the child, and mothers responded "yes" to seizures occurring in infancy or in the preschool years.

Of the 16 questions producing high kappas (.50 or over), the only one that did not fit the above set of characteristics was 137. Have you had sexual relations? (.58). Although this was a concrete question, we expected a low kappa, because we thought many children might try to keep this information from their mothers.

Out of 10 antisocial symptoms responded to positively by at least 10 subjects, 7 had kappas in the high to middle range. Reliable reporting of antisocial behavior may be due in part to the fact that older children who engaged in this type of behavior agreed more with their mothers with respect to symptom reporting than those below 12 years of age. It is also true, however, that the antisocial symptoms with high kappas have the same characteristics as other symptoms with high kappas; namely, they refer to observable, unambiguous behaviors that were so severe that they would likely be brought to the mother's attention and not be misunderstood by the children.

The questions producing middle kappas (.30 to .49) were for the most part objective and also elicited reports of behavior rather than subjective feelings. However, this group of questions was characterized by a certain amount of disagreement, or possible different interpretations. For example: 34. Do you have trouble with math? (.38); 37. Do you have trouble with reading? (.34); or 38. Do you get into trouble in school because you won't stay in your seat? (.30) are questions that, even if the problem were severe, could be judged differently by the mother and the child. These differences depend to a large extent upon variation in the way the teacher describes the problem to the mother or handles it with the child.

In all, 30 questions fell within the middle kappa range. However, in 10 of the 30 items the numbers of positive responses in both the "mother only" and "child only" columns exceeded the number of "yes" responses to the same question by both mother and child. All 10 of these had kappas below 40. In addition there were 6 items in which the number of "mother only" responses was greater than "both," 3 of these significantly so. There were also 6 items in which "child only" responses were greater than "both," 4 of these significantly so. Only 3 questions in the 40-to-49 kappa range showed a higher number of responses in either the "mother only" column (#61) or the "child only" column (#86 and #130) than the "both mother and child" column. These data suggest that a kappa of 40 or above is a more reliable cutoff point than 30.

Low Kappas

Out of the 168 questions, 122 (73%) had kappas below 30. Of these, 58 showed neither significant agreement nor preponderance of reporting

by either mother or child and are designated as the most unreliable. It is important to note, however, that both mothers and children reported the presence of these symptoms. In fact, in many cases, the number of reports was quite high. The mothers and children, however, were not agreeing with one another. There is no way of knowing who was reporting accurately, or if both were reporting incorrectly, either because the question was misunderstood or for some other reason.

Two factors characterize the unreliable symptoms. First, the questions required judgment as to the presence or absence of a symptom, or as to the severity of a symptom. Questions such as: 16. Do you get into trouble for fighting a lot? (.27) or 67. Do you worry a lot? (.14) require both mothers and children to make the same decision as to what is considered a lot of fighting or a lot of worrying. In the case of worrying or other symptoms of anxiety, part of the reason for the low kappa may be that the child is feeling either better or worse at the time of the interview (Wing, Birley, Cooper, Graham, & Isaacs, 1967).

Second, the questions could easily be misunderstood or misinterpreted, such as: 23. Do you have problems with your friends, because you aren't allowed to do what they like to do? (.06); 82. Has your mind been bothering you lately so that you can't concentrate? (.17); 84. Has your appetite been going up and down a lot lately? (.10); or 145. Do people have a hard time trusting you? (.25). Not only do these questions seek subjective information, but also they are vaguely worded and subject to misinterpretation.

The area in which there was the least agreement was that of relationships at home. Of the 15 symptoms in that area, only number 1, sasses parents, had a moderate kappa (.36). In all, 6 symptoms were asymmetrically reported, 4 by the mothers and 2 by the children, and 9 were unreliable, i.e., they had low kappas and no asymmetrical reporting. The area of home relationships in this interview, therefore, was one in which little reliable information was gained. Although mothers do report more deviant behavior than their children, the number of unreliable symptoms indicates that children are reporting this behavior, but they are not agreeing with their parents about which behavioral symptoms are important. This area received the highest rate of positive answers of any section of the interview, showing that most of the 15 symptoms are fairly common among children. It is not surprising, therefore, to find that mothers and children are in disagreement as to whether or not a particular symptom is a problem.

Children's Asymmetrical Reporting

There were four kinds of symptoms that children reported significantly more frequently than their mothers. These are marked with a

superscript in column four of Table I. Of these 44 symptoms, 38 had kappas below .30, 4 were in the middle range, and 2 were high.

The first were symptoms of a very subjective nature, including those of various neurotic disorders and depression. Symptoms that indicate worried, anxious, or depressed feelings are subjective, and one would expect that people experiencing them would more likely be aware of them and report them. This finding is important because of the implication that there are some areas in which children may be the best and, in some cases, the only source of information about a problem. Examples of such symptoms are: 65. Are you so afraid of some things that you can't do your schoolwork? and 68. Are you worried that something bad might happen to someone like your mother or your father?

The symptom under "suicidal thoughts" that was reported asymmetrically by the children (86. Have you ever tried to kill yourself?) also fell into the middle range of kappas (.49), showing a fairly high agreement between mother and child. This asymmetrical reporting on the part of the children is, in fact, surprising in that attempted suicide is the kind of behavior that would seem likely to be brought to the attention of the parents. It is possible that some children have a different understanding about what is meant by a suicide attempt. For example, one child considered running into the bathroom, slamming the door, and screaming that she wouldn't come out until she starved to death a suicide attempt. Some children responded "yes" and described an incident that they considered a suicide attempt, but said they had never told their parents about it.

Along with symptoms of anxiety and depression, children reported significantly more somatic symptoms than their mothers. Fifteen out of 33 somatic complaints (items 98-126, 130-133 in Table I) were reported asymmetrically by the children. In this interview, somatic complaints with a medical basis were not distinguished from those with no medical explanation. It is possible that children were responding "yes" to complaints that their mothers considered to be irrelevant because medically explained, or insignificant and therefore negative. Children were also undoubtedly responding to temporary complaints that they had not reported to their parents that day.

The third type of symptom that was reported asymmetrically by the child was antisocial behavior, sometimes quite severe in nature. As noted above, responses to several antisocial symptoms received high kappas. It is interesting to learn that two out of seven symptoms with high kappas and two with low kappas were reported asymmetrically by the children, none by the mothers. The asymmetrical reporting of antisocial behavior may simply mean that mothers were not aware of the extent to which the

child was engaging in a particular behavior. The two symptoms with low kappas that were reported asymmetrically by the children included: 55. Hurting someone badly in a fight and 57. Injuring or killing a small animal just for fun, both behaviors that might escape the mother's attention.

The fourth kind of symptom reported significantly more frequently by the children was in the area of psychotic symptoms (items 151-168 in Table I), of which 11 out of 18 were reported asymmetrically. Because of the lack of an adequate structured probing mechanism in the interviews, there is doubt as to whether or not positive answers to these questions indicate the presence of a real psychotic symptom, or whether the child is describing some subjective experience that may have happened only once or may resemble the symptom about which the interviewer is asking. For some symptoms there might be a simple physical explanation. The answers to these questions indicate, however, that children are able and willing to report unusual subjective information when directly asked.

Mothers' Asymmetrical Reporting

Out of 35 symptoms reported significantly more frequently by mothers, 26 fell in the low kappa range, 7 in the middle range, and 2 in the high. Many of the symptoms thus reported involved aspects of the child's behavior that might be troublesome to the mother, or described personality characteristics of the children that perhaps were more obvious to the mothers than to the children themselves. Examples are: 24. Gets mad easily and quits; 25. Gets his feelings hurt easily; plus 5 out of 7 symptoms, 144 through 150, under the heading Self-concept.

Out of the 10 school behavior problems, 5 were reported asymmetrically by the mothers. Three of these: 32. In trouble for bad behavior, 35. Breaking school rules, and 38. Won't stay in seat, had middle kappas. The only school behavior symptoms that had low kappas and no asymmetry of reporting were 42. Pretended sick to stay home and 45. Fights too much, which require the kind of judgment that we have already characterized as unreliable.

The school behavior problems had the highest percentage of asymmetrical reporting by mothers among the behavior problems. This may be due to the fact that mothers are reporting information originally brought to their attention by the teacher. This would minimize the amount of judgment about the child's behavior on the part of the mother. In fact, the question on the mother's interview starts: "Has his teacher ever reported to you that . . . ?"

The asymmetrical reporting of school behavior problems by the mothers may also be due in part to the fact that these kinds of school problems are often denied, particularly by preadolescent boys. That denial is not the only explanation, however, is shown by the fact that 6 out of 10 school behavioral symptoms had middle to high kappas. This seems to indicate that children do agree with their parents on some deviant behavior at school even though mothers report it more frequently.

Whether children are not reporting as much as the mothers because they do not understand the implications of their own behavior, whether the teacher makes the problem more clear to the parent than to the child, whether we are not asking the right questions, or not asking them in the right way, or whether some other factors are involved are the subjects for further research.

Low agreement between mothers and children also occurs in the area of peer relationships. Out of 10 symptoms concerning peer relationships, mothers reported 5 asymmetrically, and 5 were unreliable. All of the peer relationship symptoms had low kappas. The 5 that were reported asymmetrically by the mothers tended to involve behavior that could be observed by the mothers, such as: 19. trouble keeping friends and 24. gets mad easily and quits. Those that were unreliable involved more judgment, such as: 16. fights a lot or 20. is too shy.

Mothers reported some subjective symptoms asymmetrically, including: 80. Does he have bad thoughts or feelings making him depressed? and 95. Does he have trouble with his nerves? In light of the tendency of children to report subjective feelings of this nature, it seems likely that these questions were confusing to the children, and that the mothers were giving positive responses more frequently on the basis of behavior resulting from the children's depressed or nervous feelings.

DISCUSSION

These data indicate that when given similar structured interviews, children and mothers agree most often about the child's problems when the questions concern symptoms that are concrete, observable, severe, and unambiguous. There is the least amount of agreement when mothers and children must each make a judgment as to the severity of the problem, when there is some question as to whether or not the behavior really is a problem, and when the question is phrased in such a way that it could easily be misunderstood. This indicates the importance of careful phrasing of the questions used in a structured interview, in order to obtain the maximum amount of reliable information.

Low kappa values also occurred when either mothers or children gave positive responses significantly more frequently to a question. Occasionally,

however, if the total number of "yes" responses to a question was quite high, asymmetrical reporting was found along with a high level of agreement. An example was question number 29. being suspended or expelled from school, with a total of 61 "yes" responses, 40 with mother-child agreement giving a kappa of .75, plus 17 positive responses by the child only, compared to 4 by the mothers only, a significant difference ($p = < .01$).

On the whole, mother "yes" and child "no" disagreements were related to milder and fairly common types of behaviors that mothers observe and report as meaningful but children either deny or do not consider to be a "problem." Child "yes" and mother "no" disagreements were related mainly to subjective symptoms that reflect inner feelings, either psychological or somatic. The data demonstrate clearly that children do not hesitate to report subjective symptoms or experiences usually considered to be unusual or strange, if they are directly questioned about them. The results suggest that children may, in fact, be the best source of information for research requiring the answers to very personal questions relative to themselves.

One shortcoming of research that depends solely on the reports of parents and teachers about children is that no account is taken of possible psychiatric or personality disturbance on the part of the parent (Marks, 1961) or teacher informant. If the child is given an opportunity to be an informant on his own behalf, areas of serious disagreement can alert the researcher to the need for further probing into the parent's or teacher's accuracy of reporting. At the present state of the science of interviewing, one cannot assume that, because of age, the adult's reports are necessarily more accurate than the child's.

It seems clear that a great deal can be done to improve the reliability of information obtained from mothers and their children. Such an improved set of questions about symptoms would make clinical diagnosis less prone to error, and assessment of the course of psychological disorders in children more accurate. The observation that certain clusters of symptoms are significantly more often reported by mothers or children may lead to the evolution of different interviews for each. The integration of reliability and validity studies where the relative prognostic performance of each variable can be assessed is needed.

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Psychiatric Disorders in a Community Sample of Adolescents

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The prevalence of psychiatric disorders diagnosed according to DSM-III in adolescents in the general population is not known. The authors address this issue in a community sample of 150 adolescents 14–16 years of age. Structured interviews as well as other instruments were used to collect data. Twenty-eight (18.7%) of the 150 adolescents were identified as having a psychiatric disorder. These 28 adolescents viewed their parents as less caring, had lower self-esteem, and resolved their conflicts through verbal aggression and physical violence more often than did the adolescents who did not have a psychiatric disorder. The authors make recommendations regarding the use of structured interviews in future research.

(Am J Psychiatry 1987; 144:584–589)

Only a limited number of studies have addressed the prevalence of psychiatric disorders in community samples of adolescents (1). In Australia, Krupinski et al. (2) and Henderson et al. (3) used medical students to interview all families in a small town to determine the prevalence of all forms of medical disability. They reported some type of psychiatric disorder in about 10% of the children and 16% of the adolescents. Unfortunately, the criteria for disorders were not specifically defined. Leslie (4) made a psychiatric assessment of 141 adolescents 13 and 14 years old in Blackburn, an industrial town in northern England. The diagnoses, however, were globally categorized into neurotic, conduct, and mixed disorders; the total prevalence rates for boys and girls were reported to be 21% and 14%, respectively. Lavik (5) compared adolescents who resided in a suburb of Oslo with another group from a rural area in southwest Norway and reported that suburban adolescents had significantly more psychiatric disorders.

In the Isle of Wight study (1, 6, 7), it was reported that psychiatric disorders at age 14 were similar in many respects to those reported at age 10, with the exception of depression, which was much more common in the adolescent sample. Overall, psychiatric disorders were slightly more common in adolescence than in middle childhood. Considering various sources of data collection, the authors estimated that the 1-year period prevalence of psychiatric disorders in adolescents was 21%.

It is noteworthy that all of these studies were conducted outside the United States. Furthermore, most of them used a very global system of diagnostic classification (e.g., neurotic, conduct, and mixed disorders). In addition, all of these studies were conducted before the development of *DSM-III*.

In the United States, Myers et al. (8) found that the 6-month prevalence rate of adult psychiatric disorders in three communities was substantially higher for people under the age of 45. Rates were about two times higher for individuals younger than 45 years of age than for those 45 years of age and older. Further comparisons revealed that in all three communities the prevalence of *DSM-III* disorders was higher in subjects between the ages of 18 and 24 years. This is an interesting finding, since it identifies younger adults and some teen-agers (18- and 19-year-olds) as a group with the highest prevalence of psychiatric disorders. Because this study did not include subjects under age 18, the prevalence of psychiatric disorders in the younger age group remains unknown.

The present study was designed to determine 1) the prevalence of psychiatric disorders in an adolescent population and the coexistence of various *DSM-III* diagnoses, 2) correlations between psychiatric disorders and sex, age, and other demographic characteristics, such as having lived in a broken home, 3) conflict resolution in the group with psychiatric disorders and the association between physical abuse and psychopathology, 4) the relationship between self-concept and psychiatric disorders, 5) how adolescents with psychiatric disorders view their parents, and 6) some general issues relevant to the mental health of adolescents, such as sexual relations and smoking.

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METHOD

Subjects in this study were 150 adolescents 14–16 years of age; they represented 7% of all adolescents in this age group attending public schools in Columbia, Mo. Subjects' names were initially drawn in a systematic manner to obtain equal numbers in each age group (50 in each) and an equal number of boys and girls (75 of each). The sample size was essentially determined by budgeting limitations. There were 142 Caucasian, six black, and two Oriental adolescents in the sample. According to Hollingshead and Redlich's social class criteria (9), 16 (10.7%) were in class I, 47 (31.3%) were in class II, 44 (29.3%) were in class III, 41 (27.3%) were in class IV, and two (1.3%) were in class V.

Procedure

Subjects' participation was solicited by phone. Data on each subject were obtained during a home interview and by means of mail-in questionnaires. During the home visit, the adolescent and one parent were each given a structured psychiatric interview, including the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents–Parent Version (10, 11). Each parent also completed the Child Behavior Profile (12, 13) and gave information regarding socioeconomic and marital status during the home visit. Likewise, each adolescent completed a set of questionnaires, including the Parental Bonding Instrument (14), the Conflict Resolution Scale (15), and the Piers-Harris Children's Self-Concept Scale (16).

Three clinicians with master's degrees who were doctoral candidates in psychology (C.F., C.M.C., and J.A.M.) served as data collectors. Their training followed the general format used in several of our past studies at the University of Missouri. To describe the method briefly, all interviewers first underwent a training program in administration of the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents–Parent Version. As part of this training, each clinician-interviewer conducted several interviews while being videotaped. These videotapes were then observed by the other two clinicians, as well as the senior investigators (J.H.K. and N.C.B.). Interrater reliability training was accomplished by having the interviewers fill out Diagnostic Interview for Children and Adolescents and Diagnostic Interview for Children and Adolescents–Parent Version forms while observing the videotaped interviews. This was followed by a series of group meetings during which correspondence between ratings as well as disparate scores were reviewed in detail. Actual study interviews did not take place until each interviewer pair had achieved an interrater agreement rating of at least 95%. For the first 20 subjects, each interviewing clinician was observed by one of the other two clinicians, who also recorded the subject's responses. Subsequently, ongoing supervision of recorded responses was conducted and regular retraining exercises were held every 30–50 interviews to minimize rater drift (17).

Every effort was made to keep the refusal rate low. Of 214 individuals solicited by phone, 115 (72.4%) agreed to participate. Information with which to calculate socioeconomic status scores was obtained for 41. The mean socioeconomic status level for these 41 adolescents was 2.98; for the 150 participants it was 2.77. The difference between groups was not significant (Mann-Whitney U test).

We developed a 4-point scale to rate generalized dysfunction and the need for treatment of adolescents: 1=healthy—no need for treatment, 2=mildly impaired—might benefit from treatment, 3=moderately impaired—definite need for treatment, and 4=severely impaired—serious need for treatment. The rating was made and recorded by the clinician at the end of the interview, along with her clinical impression regarding the subject's diagnosis. Only those individuals with ratings of 3 or 4 were considered as needing treatment; subjects with ratings of 1 or 2 were categorized as not needing treatment.

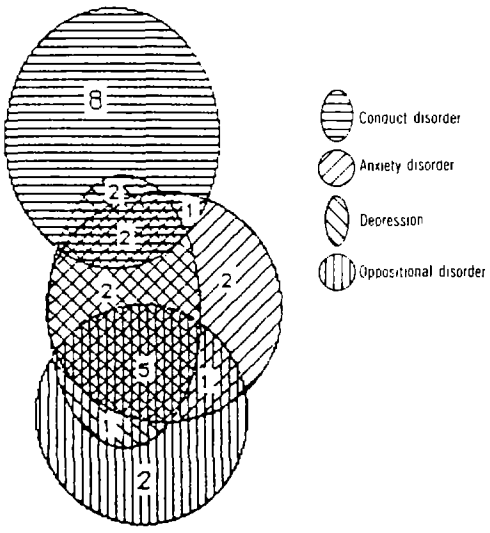
Definition of "Caseness"

Since "caseness" in the general population is neither assumed nor implied, a precise definition of "caseness" was among our most important tasks (18; unpublished 1969 paper of Dohrenwend et al.). However, due to the lack of observable or measurable physical representation of psychiatric disorders, "caseness" inevitably derives from psychiatric opinion and clinical experience (19).

Since meeting the criteria for a disorder does not necessarily imply a concomitant need for treatment, we decided to accept as "cases" only those individuals who not only met *DSM-III* criteria for a disorder but also were rated as needing treatment. Taking into account that the need for treatment is dependent on the clinician's opinion, we decided to accept as valid only those "cases" where two independent judges agreed that an individual needed intervention.

In the present study, at the conclusion of each interview the clinician used her clinical judgment to determine probable diagnoses and the need for treatment for that particular subject. In addition, a child psychiatrist (J.H.K.) reviewed all of the child and parent responses on the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents–Parent Version. However, he was unaware of the results of other measures. On the basis of this information and his clinical judgment, the psychiatrist made a recommendation as to whether the subject needed treatment. Although a decision as to "caseness" was made after the information from the parents was also obtained, the final diagnosis was based on the Diagnostic Interview for Children and Adolescents. This approach is in line with recent work

FIGURE 1. Overlap of Four Most Common Diagnoses Among 28 Adolescents With Psychiatric Disorders[a]



[a]Conduct disorder and oppositional disorder do not overlap because *DSM-III* states that subjects meeting criteria for conduct disorder should not be diagnosed as having oppositional disorder.

by Edelbrock et al. (20), who found that the reliability of the child increased sharply with age and, conversely, that the reliability of the parent's report decreased with the age of the child.

Two-way contingency tables were analyzed by chi-square or by Fisher's exact tests if the number of observations was small. Tests for location were Wilcoxon-Mann-Whitney U tests. Confidence intervals for proportions were determined by approximating a binomial distribution rather than by adding and subtracting a constant times the standard error from the proportion.

RESULTS

Sixty-two (41.3%) of the 150 adolescents were found to have at least one *DSM-III* diagnosis based on the Diagnostic Interview for Children and Adolescents without the criteria of impaired functioning and the need for treatment. When these additional criteria were used (as agreed on by at least two independent clinicians, the interviewer, and the child psychiatrist), 28 adolescents (12 boys and 16 girls) were identified as having a psychiatric disorder, yielding a current point prevalence rate of 18.7%. A total of 67 diagnoses were made: seven of the adolescents had only one disorder, 10 had two, four had three, and seven had four; the mean number of diagnoses was 2.4. Figure 1 illustrates interrelationships among the four most common diagnoses, anxiety disorder, conduct disorder, depression, and oppositional disorder. The only diagnoses for which there were significantly different intersex prevalence rates were depression and anxiety disorders. Table 1 shows the diagnoses made in the order of their prevalence. The three most common diagnoses were conduct disorder, anxiety disorder, and depression.

A number of variables that were collected showed no relation with psychiatric disorder in adolescents. For example, the association between adolescents with psychiatric disorder and sex was not significant. Sixteen (57%) of the 28 adolescents with a psychiatric disorder were girls; 59 (48%) of the 122 adolescents without disorder were girls ($\chi^2=0.70$, df=1, n.s.). Likewise, the socioeconomic status of the family and race failed to distinguish adolescents with psychiatric disorder. The mean socioeconomic status level of the adolescents with disorders was 2.9, compared with 2.7 for the rest of the sample. Divorce or parental separation did not significantly distinguish the two groups either. Eight (29%) of the 28 diagnosed adolescents and 29 (24%) of the remaining 122 adolescents reported such a history ($\chi^2=0.28$, df=1, n.s.). A history of behavior disorder dating back to preschool years (obtained from the Diagnostic Interview for Children and Adolescents–Parent Version) was reported by the parents of diagnosed adolescents more frequently than by those of the rest of the sample. However, the difference was not statistically significant: 11 (39.3%) of the adolescents with psychiatric disorder and 31 (25.4%) of those without reported such a history ($\chi^2=2.19$, df=1, n.s.).

Other variables, however, did correlate positively with psychiatric disorder. Physical abuse significantly distinguished the two groups: 12 (43%) of the adolescents with but only six (5%) of those without reported severe beating that left marks and bruises (Fisher's exact test, $p<.0001$). An association also emerged between psychiatric disorder and sexual relationships. Fifteen (54%) of the adolescents with disorders but only 21 (17%) of the remaining sample reported having had sexual relations with at least one partner by the time of this study ($\chi^2=16.5$, df=1, $p<.0001$). The same held true for cigarette smoking. Thirteen (46%) of the diagnosed adolescents reported smoking daily for at least 1 or more months, versus only five (4%) of the remaining sample (Fisher's exact test, $p<.0001$).

Adolescents with psychiatric disorders differed from those without in their methods of conflict resolution (15). The diagnosed adolescents reported resolving their conflicts significantly more frequently through verbal aggression and physical violence than did the rest of the sample (table 2). In regard to self-concept, adolescents with disorders had significantly lower self-concepts according to the Piers-Harris Scale (19) (table 2). The Parental Bonding Instrument, which attempts to assess parental styles of child rearing, also served to distinguish adolescents with psychiatric disorders from those without. The mean±SD care factor score of the

TABLE 1. Prevalence of Psychiatric Disorders in 150 Adolescents

DSM-III Diagnosis	Boys (N=75) N	%	Girls (N=75) N	%	Total (N=150) N	%	95% Confidence Intervals Lower	Upper
Anxiety disorder	3	4.0	10[a]	13.3	13	8.7	4.9	14.7
Conduct disorder	7	9.3	6	8.0	13	8.7	4.9	14.7
Depression (major depression and dysthymic disorder)	2	2.7	10[b]	13.3	12	8.0	4.4	13.9
Oppositional disorder	3	4.0	6	8.0	9	6.0	3.0	11.4
Both alcohol and drug abuse or dependence	5	6.7	4	5.3	9	6.0	3.0	11.4
Drug abuse or dependence	4	5.3	4	5.3	8	5.3	2.5	10.5
Alcohol abuse or dependence	3	4.0	2	2.7	5	3.3	1.2	8.0
Attention deficit disorder	1	1.3	2	2.7	3	2.0	0.5	6.2
Somatization disorder	1	1.3	1	1.3	2	1.3	0.2	5.2
Mania	0	0.0	1	1.3	1	0.7	0.0	4.3
Enuresis	0	0.0	1	1.3	1	0.7	0.0	4.3
Anorexia or bulimia	0	0.0	0	0.0	0	0.0	0.0	0.0

[a]Significantly more girls than boys had this diagnosis (Fisher exact p=.03).
[b]Significantly more girls than boys had this diagnosis (Fisher exact p=.02).

TABLE 2. Conflict Resolution and Self-Concept Scores of Adolescents With (N=28) and Without (N=122) Psychiatric Disorders

Measure	Score: Adolescents With Psychiatric Diagnoses Mean	SD	Adolescents Without Psychiatric Diagnoses Mean	SD	p[a]
Conflict Resolution Scale[b]					
Reasoning subscale (range=0–18)	11.1	4.1	11.7	3.2	n.s.
Verbal aggression subscale (range=0–36)	20.6	7.5	14.4	5.7	.0001
Physical violence subscale (range=0–48)	16.4	9.6	10.1	4.7	.0001
Piers-Harris Children's Self-Concept Scale[c]					
Behavior (range=0–18)	10.8	3.4	15.3	3.3	.0001
Intellect (range=0–18)	10.9	4.0	14.1	3.3	.0001
Physical appearance (range=0–12)	7.5	3.0	8.7	2.8	.05
Anxiety (range=0–12)	6.7	2.4	8.7	2.6	.0001
Popularity (range=0–12)	8.2	3.0	9.5	2.5	.03
Happiness, satisfaction (range=0–9)	5.5	2.6	7.0	2.0	.003
Total raw score (range=0–80)	48.6	13.5	61.5	12.2	.0001

[a]Mann-Whitney U test.
[b]A higher score on any subscale indicates a greater use of the item listed.
[c]Greater self-concept is indicated by a lower score on the anxiety item and higher scores on the other items.

former was 22.8±7.8, while it was 28.4±6.8 for the latter (p<.0003, Mann-Whitney U test).

Finally, the parental report data from the Child Behavior Profile (12, 13) indicated that the boys with psychiatric disorder were given higher "externalizer" ratings (62.5±12.3) than boys without disorder (52.0±8.8) (p<.002, Mann-Whitney U test). They were also more aggressive, hyperactive, and hostile or withdrawn than the boys without disorder. Alternatively, girls with psychiatric disorder were reported to have more somatic complaints (66.4±6.6) than girls without disorder (62.3±7.4) (p<.03, Mann-Whitney U test).

DISCUSSION

This study described strategies and methods crucial to conducting epidemiological studies in the general population. These include the definition of "caseness," problems of using structured interviews, training the interviewers, the importance of rating the severity of adolescent dysfunction, and the need for psychiatric intervention. The major findings of this study may be summarized as follows:

1. Twenty-eight (18.7%) of 150 adolescents from a nonreferred sample were found to have at least one *DSM-III* diagnosis, were functionally impaired, and were judged to need treatment. The three most common diagnoses were anxiety disorder, conduct disorder, and depression.

2. A history of physical abuse distinguished the group of adolescents with psychiatric disorders from those without psychiatric disorders. At the same time, the adolescents with disorders reported a tendency to resort more frequently to verbal aggression and physical violence to resolve conflicts.

3. A history of initiating sexual relations and smok-

ing by age 14–16 was seen more often in adolescents with than in those without psychiatric disorder.

4. In addition to having a low self-concept, boys with psychiatric disorders were frequently described by their parents as externalizers, while somatic complaints were reported more frequently among girls with disorders.

5. The parents of adolescents with psychiatric disorders were described as significantly less caring than were the parents of adolescents without psychiatric disorders.

Several of this study's limitations need to be acknowledged. Due to the small sample size this study should be considered a pilot and preliminary attempt to answer the questions raised. Although structured interviews have improved data collection and reliability in child and adolescent psychiatric investigations, several recent studies have suggested that structured interviews designed for clinical samples might lead to overestimation of the reported prevalence in the general population (21; Patricia Cohen, 1986 personal communication). Lerner et al. (22) used the Diagnostic Interview for Children and Adolescents in a follow-up study of 88 children and stated that "using *DSM-III* (or instruments based on DSM-III criteria) for general population screening may overestimate the true prevalence of psychiatric disorder." To circumvent this bias, in this study we not only used a scale for severity but also considered impairment of functioning and the need for treatment.

Because our sample did not include mentally retarded or institutionalized adolescents, the findings cannot be generalized to these groups. Additionally, the measures used did not tap organic dysfunction and intellectual level. We also recognize that mild cases of some conditions were not included in the prevalence data—for example, anxiety disorders (with a severity rating of 2). However, at this preliminary stage, data concerning the frequency of *DSM-III* psychiatric disorders in adolescents from the community are sparse, and we preferred to be conservative rather than overinclusive. Regarding the prevalence of psychiatric disorders in adolescents, to our knowledge there are no similar published studies of adolescents using a structured interview based on *DSM-III* criteria, although Offer's estimate (23) that 20% of the adolescents in our culture are considered disturbed approximates our findings. The only study with which we could attempt comparison was an adult NIMH-supported study by Myers et al. (8) However, several important differences distinguish our study from theirs. Perhaps most important, a *DSM-III* diagnosis was necessary but not sufficient for "caseness" in our study. Further, we relied on trained mental health professionals rather than lay personnel to interview our subjects, and agreement of at least two mental health professionals was required for both a diagnosis and the presence of "caseness." Myers et al. found phobia, alcohol abuse, and depression to be the three most prevalent psychiatric disorders; in our study, the three most common diagnoses were anxiety disorder, conduct disorder, and depression.

We found significantly different intersex prevalence rates for only two diagnoses, anxiety disorder and depression, both of which were higher in girls. *DSM-III* considers anxiety, panic attacks, and phobias as associated features of major depression. In this study we found that depression and anxiety disorder coexisted (figure 1). However, it was not possible to distinguish primary from associated conditions.

The significant relationship between "caseness" and exposure to physical violence is of interest. The adolescents with psychiatric disorders used verbal aggression and physical violence to resolve conflicts. Their previous victimization by violence may have been adopted as a model by which they resolved future conflicts with others.

The Parental Bonding Instrument, which measures qualitative aspects of the parent-child relationship and parental styles, supported the diagnosed adolescents' perception that they were not wanted. The care factor, which assesses the degree of affection, emotional warmth, empathy, and closeness at one pole, and emotional coldness, indifference, rejection, and neglect at the other, significantly distinguished adolescents with and without psychiatric disorders. According to the diagnosed adolescents, their parents seldom smiled at, talked with, or praised them. They also reported that their parents failed to console them when they were upset, recognize their needs, make them feel wanted, show understanding, or extend a helping hand. Therefore, the data provide further evidence for the importance of parental care and its relationship to the existence or absence of psychiatric disorders.

It is also interesting to note that not only were the total raw scores on the Piers-Harris Children's Self-Concept Scale significantly lower among the adolescents with psychiatric diagnoses, but also all of this instrument's subscales (factors) exposed significant differences between the two groups. Factors 1 and 2 indicated that the diagnosed adolescents perceived their behavior and intellectual ability as lower than those of other children their age. Factors 3 and 4 suggested that they did not see themselves as having substantial status among peers and that they were anxious, while factors 5 and 6 indicated that they did not feel they were wanted by others and were not satisfied with life. Such findings have clinical implications for the treatment of disturbed adolescents—treatment methods need to be directed at improving adolescents' self-concept.

In terms of future research, we suggest that severity ratings as well as ratings of impaired functioning and/or the need for treatment be made by trained professionals. These should be considered and incorporated into the basic design of studies that use structured interviews based on *DSM-III* to examine a larger number of children and adolescents from general populations.

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Depression, Depressive Symptoms, and Depressed Mood Among a Community Sample of Adolescents

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Using a structured interview, the authors found that the prevalence of major depression and dysthymic disorder was 4.7% and 3.3%, respectively, in a community sample of 150 adolescents. All of the adolescents who met the criteria for major depression and dysthymic disorder had other psychiatric disorders as well; anxiety was the most frequent accompanying DSM-III *diagnosis.*
(Am J Psychiatry 1987; 144:931–934)

The latest edition of the *Comprehensive Textbook of Psychiatry* acknowledges a lack of empirical data on affective disorders in adolescents in nonclinic populations (1), and several researchers have expressed concern over this issue (2–4). Prevalence estimates of affective disorders in adults have been previously reported by Weissman and Myers (5) and more recently by Myers et al. in a multicenter, NIMH-supported study; Myers et al. reported a 6-month prevalence rate ranging from 4.6% to 6.5% for all affective disorders in adults (6). In a study of a preadolescent group, Kashani et al. reported a prevalence of 1.8% for major depression (7). Thus, data are available for other age groups; however, extrapolation of these data from one age group to another is clearly untenable. For instance, in Rutter et al.'s Isle of Wight study, the 9- and 10-year-old children, re-examined 4 years later, demonstrated a threefold increase in the depression rate from preadolescence to adolescence (8). Rutter et al. also reported that more than 40% of the adolescents expressed feelings of depression and misery during the interview. Interestingly, self-rating revealed feelings of depression much more frequently in the adolescents than in their parents, again underscoring the specificity of affective symptoms with regard to age (8).

Although empirical data for estimating the prevalence of depressive disorder have been lacking, data on the frequency of depressive symptoms exist. For instance, Kandel and Davies administered a six-item self-report inventory to adolescents (13–19 years) and their parents, with female adolescents reporting significantly more depressive symptoms than their male counterparts. They also found that the adolescents reported more symptoms than their parents, and that among the parents, mothers had more depressive symptoms than the fathers (9). Kaplan et al. have also reported on the prevalence of depressive symptoms in adolescents, using the Beck Depression Inventory (10). Cognizant of the limitations of their study, Kaplan et al. stated that "validating the prevalence of major depressive disorder in adolescents with a structured psychiatric interview in a general adolescent population merits further investigation."

The purpose of the present study is to fill in some of these gaps, namely 1) to determine the existence of depressive disorder in a nonclinic sample, and given its existence, to determine prevalence rates and identify subtypes; 2) to study adolescents who manifest depressive symptoms but who do not meet the full criteria for depressive disorder, in order to explore the entire spectrum of depression (11), ranging from the mildest forms to full-blown syndromal depression as defined by *DSM-III;* and 3) to specify the coexistence of other psychiatric disorders with depression.

METHOD

We studied 150 subjects age 14, 15, and 16 years in the ninth, 10th, and 11th grades, representing 7% of all adolescents attending public schools in Columbia, Mo. They were systematically solicited from an initial pool of 1,700 to form a total group comprising 50 of each age and 75 of each sex. In order to keep the homogeneity of the group, only those 14, 15, and 16 years old who did not change age during the data collection period (5 months) were selected. The majority (about 95%) were Caucasian, and the rest were

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black or Oriental. Their socioeconomic status, based on Hollingshead and Redlich's two-factor social class index, was as follows: class I, 10.7%; class II, 31.3%; class III, 29.3%; class IV, 27.3%; and class V, 1.4%. Subject participation was solicited by telephone, and during the phone interview the study was introduced. Every effort was made to keep the acceptance rate high. This included conducting an interview at the homes of participants and offering a $20 fee as compensation for their time. These efforts led to an overall acceptance rate of 72.4%. During the telephone interview, socioeconomic status data were all that we could obtain from the families who refused to participate. The mean socioeconomic status for the refusal subjects was 2.9 and for the 150 participants, 2.7 (Mann-Whitney U test, p=n.s.).

Subjects who agreed to participate were scheduled for a home interview. Both parents (if available) and the adolescents were asked to sign a consent form as required by the institutional review board of the University of Missouri—Columbia. The adolescent and the parents were reassured about the confidentiality of the data obtained. During the home visit, the adolescent was interviewed with the Diagnostic Interview for Children and Adolescents and the parents with the Diagnostic Interview for Children and Adolescents: Parent Version (12, 13). Since these instruments do not include dysthymic disorder, we modified them, adding questions from *DSM-III* criteria for dysthymic disorder (Z. Welner, personal communication, 1985).

Interviews were conducted by three clinicians with M.A. degrees who were Ph.D. candidates in psychology. Interrater agreement of at least 95% was obtained, and ongoing supervision of the recording of subjects' responses was continued throughout the study. For the first 20 subjects, each interviewer was observed by one of the other two, who also recorded the subjects' responses on the interview measure and parents' responses on the parent version. Retraining exercises were also conducted after every 30–50 interviews in order to minimize rater drift (14).

At the end of each interview, the interviewer made a clinical judgment as to whether any diagnosis based on *DSM-III* existed and, if so, whether treatment was necessary. A "case" was defined as an individual who met the criteria for any *DSM-III* diagnosis and who, in the clinician's judgment, was dysfunctional and needed treatment. A child psychiatrist (J.H.K.) reviewed the interview data from the adolescents and the parents; his agreement with the interviewers on the diagnosis and need for treatment was required. Another child psychiatrist (G.A.C.) independently reviewed the information from the adolescents and their parents, and full agreement between the two child psychiatrists (J.H.K. and G.A.C.) also was required for diagnosing depression cases in this sample. Therefore, any subject who had depressive symptoms but for whatever reason was not diagnosed as depressed by any of the three sources (the clinician or either of the two child psychiatrists) was included in another group labeled "with depressive symptomatology." This group included subjects whose interviews indicated the presence of symptoms requisite for major depression or dysthymic disorder but with 1) insufficient duration of symptoms, 2) a clinician's judgment that treatment was not necessary, or 3) the adolescent's statements during the interview that his or her depression did not interfere with his or her work (i.e., depressive symptoms resulted in minimal dysfunction).

RESULTS

Of the 150 adolescents, 7 (4.7%) were found to have major depression. However, all of these subjects met the criteria for dysthymic disorder as well. Therefore, major depression and dysthymia coexisted in these individuals (double depression) (15). Five other adolescents (3.3%) were also found to meet the criteria for dysthymic disorder. Hence, 12 adolescents (two boys and 10 girls), or 8% of the total sample, met the criteria for some type of depressive disorder on the basis of *DSM-III*.

In addition, 33 other adolescents (11 boys and 22 girls) reported depressive symptoms but did not meet the requirement for caseness; namely, their depressive symptoms did not result in their being dysfunctional, nor were they rated as needing treatment. They did, however, meet the symptom counts for major depression or dysthymic disorder. In this study, this group will be referred to as "with depressive symptoms."

Finally, 28 adolescents reported dysphoric mood for either 2 weeks (N=20) or 1 year (N=8). The remaining 77 adolescents did not report any type of dysphoric mood.

A comparison of the 12 depressed individuals with the 33 who had depressive symptoms failed to show significant differences in sociodemographic variables such as age, sex, race, socioeconomic status, parents' marital status, and so forth. However, the two groups differed in several ways. For instance, every individual in the depressed group had another *DSM-III* diagnosis, whereas only 61% of the group with depressive symptoms had an accompanying *DSM-III* diagnosis. In addition, the diagnosis of anxiety disorder was significantly more frequent in the depressed group than in the group with depressive symptoms (nine of 12 [75%] versus seven of 33 [21%]; Fisher's exact test, p<.002).

With regard to the coexistence of a *DSM-III* diagnosis in the four groups of adolescents, all of the 12 depressed adolescents had additional diagnoses: 75% (N=9) had anxiety disorder, 50% (N=6) had oppositional disorder, 33% (N=4) had conduct disorder, 25% (N=3) had alcohol abuse, and 25% (N=3) had drug abuse; there were also single cases of mania, attention deficit disorder, and enuresis. In the group with depressive symptoms (N=33), 61% had a *DSM-III* diagnosis; the three most common were anxiety

disorder (21%, N=7), oppositional disorder (18%, N=6), and drug abuse (15%, N=5). Of the 28 individuals with dysphoric mood, 36% had a *DSM-III* diagnosis; the two most common were anxiety disorder (21%, N=6) and oppositional disorder (18%, N=5). Finally, 26% of the remaining 77 subjects were found to have a *DSM-III* diagnosis (i.e., oppositional disorder, 10%, N=8; conduct disorder, 9%, N=7; and anxiety disorder, 5%, N=4). A comparison of the above four groups of adolescents (N=12, 33, 28, and 77) for additional diagnoses considering ordered categories indicated the existence of a significant trend (100% versus 61% versus 36% versus 26%; χ^2= 29.92, df=3, p<.005) (16, 17).

DISCUSSION

Data regarding epidemiology of psychiatric disorders among adolescents remain scanty, despite burgeoning interest in adolescent mental health (4). The present study provides information on the prevalence of adolescent depression in a community sample of adolescents between the ages of 14 and 16, with a reported prevalence of 4.7% for major depression and 3.3% for dysthymic disorder. The reported prevalence among adolescents in this study is higher than that previously reported for preschoolers (18) and more than twice the reported prevalence in school-age children (7). This is in agreement with Rutter, who found that depression increased threefold from preadolescence to adolescence (19). In addition, Rutter et al. (8) reported that nearly half of adolescents from a general population sample admitted during direct interviews to appreciable misery or depression, a finding similar to our own (N=73, 48%). However, the prevalence of depressive disorders in this study is comparable to that found in Myers et al.'s adult study, documenting prevalence ranges of 2.2%–3.5% and 2.1%–3.8% for major depression and dysthymic disorder, respectively, among a group of 18–24-year-olds (6).

It is interesting to note that all the adolescents who met criteria for depression had other psychiatric disorders as well. This may be a result of our selection process, which required evidence of impairment of functioning as well as the need for treatment for each case. In each of the three groups of adolescents (those with depression, depressive symptoms, or dysphoric mood), anxiety disorder was the most frequent accompanying *DSM-III* diagnosis.

Although *DSM-III* describes associated features of depression in boys (e.g., grouchiness, negativism, antisocial behaviors, alcohol and drug abuse), corresponding associated features in girls are not addressed. Since the present study found more girls both in the depressed group and in the group with depressive symptoms and because anxiety was found to be the most common disorder and affect associated with depression, this study provides information that is lacking in *DSM-III*.

In the present study, additional *DSM-III* disorders correlated positively with increasing severity of depression. The reason for this increase in accompanying *DSM-III* disorders is unknown. However, a recent study reported by Boyd et al. (20) found that disorders which are related to each other according to *DSM-III* were more strongly associated than unrelated conditions. In general, the tendency toward a co-occurrence was such that the presence of any psychiatric disorder increased the odds of having any other *DSM-III* disorder.

Follow-up of adolescents with depressive symptoms is not only of interest but also necessary. Akiskal et al. (21) reported that an atypical case of neurotic depression, which they consider the most frequent type in adolescents, is a precursor to a later clear-cut affective disorder. Further study will be necessary to determine how many teenagers with depressive symptoms not currently impairing their function will later suffer more pervasively from their symptoms.

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Amitriptyline in Children with Major Depressive Disorder: A Double-Blind Crossover Pilot Study

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This study reports the effect of amitriptyline and placebo in nine prepubertal depressed children in a double-blind crossover design. The children were assigned randomly to placebo or amitriptyline for 4 weeks and then were switched to the other. Results indicate that amitriptyline may have a place in the treatment of childhood depression.

Journal of the American Academy of Child Psychiatry, 23, 3:348–351, 1984.

The heterogeneity of adult depressive disorders has long been recognized. The biochemical and pharmacological evidence suggests that depression may be divided into at least two subtypes (Hollister et al., 1980). The first subtype is characterized by subnormal urinary excretion of 3 methoxy-4-hydroxyphenylglycol (MHPG), the main metabolite of CNS norepinephrine, and a favorable response to imipramine (Beckman and Goodwin, 1975; Maas et al., 1972); the second is characterized by excess urinary excretion of MHPG and a favorable response to amitriptyline (Beckman and Goodwin, 1975; Schildkraut, 1973, 1982).

The above evidence is supported by the in vitro pharmacologic profile of imipramine and amitriptyline. Imipramine and amitriptyline are tertiary amine tricyclics that are relatively more potent in their inhibition of serotonin re-uptake than desipramine (a metabolite of imipramine), nortriptyline (a metabolite of amitriptyline) (secondary amine tricyclics) which are more potent in their inhibition of norepinephrine re-uptake (Hollister et al., 1980). Preliminary studies suggest that, in patients receiving long-term imipramine, levels of desipramine exceed plasma imipramine levels. In fact, in a recent study (Preskorn et al., 1982) comparing plasma imipramine levels and clinical response in a group of depressed children, no apparent relationship could be demonstrated between clinical response and plasma concentration of imipramine alone. Instead there appeared to be a relationship between total plasma drug concentration (imipramine + desipramine) and response, and the relationship was seemingly determined primarily by the concentration of desipramine. On the other hand, in patients receiving long-term treatment of amitriptyline, plasma amitriptyline levels exceed plasma nortriptyline levels (Hollister et al., 1980). Therefore, it is thought that patients taking imipramine should have more effective blockade of norepinephrine because of higher desipramine concentrations while those taking amitriptyline should have more effective blockade of serotonin.

Although imipramine and amitriptyline are widely used in the treatment of adult affective disorders, imipramine is the only tricyclic recommended by the FDA for use in children under the age of 12. Accordingly, it has been used in a variety of childhood psychiatric disorders including enuresis, hyperactivity, school refusal and depression. More recently, a few investigators have employed imipramine in controlled studies directed toward childhood depression (Puig-Antich, 1980; Weller et al., 1982). Amitriptyline, on the other hand, which is not recommended by the FDA for use in children under the age of 12, is rarely used in children and to our knowledge there are no published controlled studies on the use of amitriptyline in childhood depression using DSM-III criteria for major depressive disorder. One earlier study by Lucas and associates (1965), however, did use amitriptyline in depressed children, but the present diagnostic criteria for depression were not available at that time; moreover, subjects included preadolescents and adolescents as well as some schizophrenic children. The latter should be excluded from the major depressive group when using DSM-III diagnostic criteria.

The purpose of this pilot study was to compare in a fixed dose double-blind crossover design the effects of amitriptyline and placebo in depressed children diagnosed according to DSM-III criteria and the Bellevue Index of Depression (BID), (Petti, 1978).

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The authors wish to thank the Merck Sharp & Dohme for providing amitriptyline, placebo, and the random assignment schedule.

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Method

Nine prepubertal children who were admitted to an inpatient child psychiatry service participated in the study. There were eight boys and one girl with a mean age of 10.8 years (range 9–12). All were Caucasian with socioeconomic status (SES) of 4.1 based on Hollinghead and Redlich's (1958) classification. The diagnosis of major depressive disorder was given independently by two child psychiatrists following extensive evaluation of both children and parents, and comprehensive data collection from the clinical staff's observations in the inpatient setting. Each child in this protocol fulfilled the criteria for major depressive disorder of DSM-III and the BID. The BID comprises 40 symptoms relevant to childhood depression. The severity of these symptoms is scaled from 0 to 3. Such a graded scale has the potential to monitor remissions and exacerbations in depressed children. The BID requires a total score of at least 20 to designate a child as depressed. The instrument is completed by interviewing the child and parents, as well as obtaining information from other sources (Kazdin and Petti, 1982). Agreement between BID and the clinician's diagnostic judgment of depression has been shown to be high (83%), but the validity remains to be demonstrated. Since aggressive behavior is not part of the core symptom of major depressive disorder, in this study aggressive items in the BID were not taken into account.

After obtaining consent from both children and parents, and a 3–4-week baseline evaluation in the hospital, the children received a 4-week trial of amitriptyline or placebo in Phase I of the study, using a random-order crossover design. In Phase II, the subjects received the alternate treatment and the differences in BID scores after Phase I and after Phase II were completed for each of the two groups. Baseline evaluation included a complete physical workup, including blood and urine laboratory tests, and EEG, and an ECG. Repeat ECGs were obtained after each 4-week treatment period of either amitriptyline or placebo to assess any changes associated with amitriptyline administration. The DSM-III and BID were administered at baseline and again during the amitriptyline/placebo periods.

Approval was obtained from the FDA for utilizing amitriptyline in children in this age group. Amitriptyline, placebo, and the random assignment schedule of both were supplied by the drug company. A fixed dosage protocol started with amitriptyline (or placebo) at 1 mg/kg per day in three divided doses and increased after 3 days to 1.5 mg/kg per day. This dosage was then maintained throughout the remainder of the 4 weeks. The same protocol was followed during the next crossover 4-week time period for alternate treatment.

Results

Overall clinical evaluation of the children revealed a favorable response to amitriptyline in six children, in whom dysphoric mood either disappeared or was dramatically improved. Furthermore, a substantial increase in their overall level of interest was reported. BID scores dropped below the cutoff of 20 in all six children. In one subject (Case 3) there was no significant response to either amitriptyline or placebo and in two other cases (Cases 6 and 8) the patients responded to placebo.

The dependent variable was the decrease in BID score from the baseline (administered before the experiment) to the start of the changeover, or from the start of the changeover to the end of the experiment. The overall plan of analysis involved essentially two steps, with the outcome of the previous step (significant or nonsignificant) determining the model to be used in the subsequent step. The initial step was to determine if residual effects existed in the model, for example, if patients initially on the drug condition had some carryover to the placebo condition. The testing of this hypothesis requires strict random assignment of patients to conditions, which was satisfied in this study.

Residual effects might have occurred from the ceasing of one sequence to the commencement of the second sequence. If residual effects were not significant, then the second step would take this form: the residual term would be dropped from the model, and treatment effects (drug vs. placebo) could be tested using information from both groups.

Following Grizzle (1965) and using a modification of a proposal by Aitchison et al. (1983), an analysis of variance was run to test for residual effects and direct effects. Regarding patients as a random factor, the analysis of variance to test for residual effects was $F = 1.4$, $p = 0.28$, which was not significant. After dropping residual effects term from the model, an analysis of variance to test for drug effects produced $F = 3.96$, $p = 0.087$, which is not far from the classical significance level of <0.05.

If a concern were to be raised about normality, the data could be analyzed using nonparametric techniques (Koch, 1972). The results from nonparametric analyses were similar to the above results in that residual effects were not significant, neither were drug effects assuming residual effects were not in the model, but that the test for drug effects assuming the equality of both residual and period effects (which was the case) produced $p = 0.09$ (exact binomial probability

TABLE 1

A Comparison of BID Scores in Depressed Children before and after the Administration of Amitriptyline and Placebo[a]

Patient No.	Age	Sex	IQ	BID Score at Baseline	Phase I	BID Score	Phase II	BID Score
1	11	M	86	(27)	A	(16)	P	(12)
2	12	M	81	(32)	P	(30)	A	(17)
3	9	M	95	(24)	A	(22)	P	(22)
4	12	F	143	(27)	P	(26)	A	(14)
5	12	M	75	(29)	A	(16)	P	(14)
6	12	M	86	(30)	P	(17)	A	(12)
7	11	M	107	(22)	P	(22)	A	(12)
8	9	M	101	(23)	A	(22)	P	(16)
9	9	M	101	(25)	A	(16)	P	(13)

[a] A = amitriptyline, P = placebo.

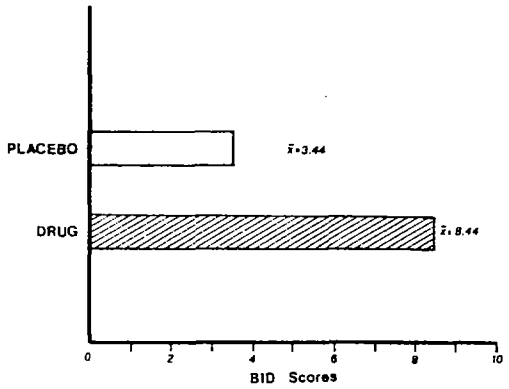

FIG. 1. Decrease in BID scores after placebo ($\bar{X}$ = 3.44) and drug ($\bar{X}$ = 8.44).

from a sign test), about the same p-level as the analysis of variance results described above.

Table 1 shows that mean BID scores decreased under both drug and placebo conditions, but that a greater decrease (8.25 vs. 4.64, $p = 0.09$; see also Figure 1) obtained for the nine patients when they were under the drug condition.

A careful observation of all children failed, except in one instance, to show any significant clinical side effects. The only exception was that of an 11-year-old boy who developed an hypomanic reaction while on the protocol. This child has a mother with a bipolar depressive disorder and an alcoholic father. The details of this hypomanic reaction to amitriptyline are reported elsewhere (Kashani et al., 1980). Monitoring the ECGs and blood pressure of the nine children failed to document any changes attributable to the use of the amitriptyline with the specified dose.

Discussion

Both groups, placebo and drug, had decreases in the BID scores. It is not unusual for placebo groups also to improve. The study design did not permit an estimation of a milieu effect separate from the placebo effect. To control for milieu effect, it would have been necessary to have an additional group with neither placebo nor drug. However, all children were admitted to the same inpatient setting, and the assumption was made that milieu was constant across groups. Another possible influence is the carryover effect. There was a random assignment of patients to treatment, but some residual drug or placebo effect may have been present at the commencement of the second phase. However, any residual effects were not significant, as noted before.

The drug effect in this study was the difference between the decrease in the placebo group's BID scores and the decrease in the drug group's BID scores (Table 2). As noticed, the drug group had a greater decrease ($p < 0.09$) in BID scores over the same time period. Although statistically it just failed to reach significance, two-thirds of the patients improved and the results are encouraging. This provides some evidence that amitriptyline may be an effective and safe treatment of childhood depression and would, therefore, justify trials of amitriptyline in a larger number of depressed children. The daily dosage in this study ranged from 45 mg to 110 mg/day. Such a regimen proved free of any clinical side effects or significant ECG changes. The one child who developed an hypomanic reaction improved dramatically after dosage reduction and was subsequently discharged symptom-free. The response to amitriptyline in this study was evidenced by an improvement in children's mood and an increase in their level of interest (i.e., increasing involvement with other children and playful activities). The evidence to date from several previous studies on the use of imipramine in depressed children (Petti and Law, 1982; Puig-Antich et al., 1979), and the data from this study demonstrate possible efficacy of tricyclic antidepressant in the treatment of depressed children. Despite this, the clinician should be

TABLE 2

Mean Decreases in BID Scores (N = 9)[a]

Drug Condition	Placebo Condition
$\bar{X} = 8.44, s = 4.64$	$\bar{X} = 3.44, s = 4.07$

[a] F for mean differences = 3.96, $p = 0.087$.

cognizant of the fact that tricyclics have additional effects such as stimulant-like action and cholinergic blocking properties, as well as antidepressant effect (Rapoport and Mikkelsen, 1978).

Two drawbacks of this study include the fixed dosage regimen and the relatively low dosage of amitriptyline utilized. Nevertheless, the children improved clinically on this dosage regimen. We suggest that amitriptyline may have a place in the treatment of depressed children. We further suggest a replication of this double-blind crossover study in a larger number of subjects. As already pointed out, there are important differences in plasma levels and components between different antidepressants which may add to our knowledge about their action and the nature of childhood depression. Therefore, future studies may employ a variable medication dosage titrated upward to a maximal clinical benefit, while closely monitoring plasma amitriptyline levels.

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Pergamon

J psychiat Res., Vol. 28, No. 3, pp. 319–329, 1994

0022-3956/94 $7.00 + .00

0022-3956(94)E0011-E

SECULAR TRENDS IN AGE AT ONSET OF MAJOR DEPRESSIVE DISORDER IN A CLINICAL SAMPLE OF CHILDREN

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(*Received for publication* 24 *February* 1994)

Summary—Using a psychiatrically referred, depressed, school-age sample, we sought to cross-validate the clinically pertinent epidemiologic finding that the distribution of age at onset of first episode of major depressive disorder (MDD) is subject to birth-cohort and period effects. Demographic and historical variables also were considered in attempting to explain the variability in age-at-onset. The results indicated a birth-cohort effect, but no discernable period effect on age at onset of MDD; successive birth cohorts were younger when they first developed MDD even after stringent analyses were conducted that corrected for structural sampling biases in the sample. In view of the relatively small size and clinical nature of the sample and the restricted birth-year span that characterizes children, the results are presented to stimulate further discussion of this topical area.

ACCORDING to recent studies, individuals born in the later decades of the 1900s report progressively younger ages as the time of onset of their first episode of major depression (Klerman & Weissman, 1989). Such secular trends have been identified among adult relatives of affectively ill probands (Gershon et al., 1987; Lavori et al., 1987; Klerman et al., 1985), participants in a multisite epidemiologic study of psychiatric disorders (Burke et al., 1991; Wickramaratne et al., 1989), and nonselected or "at-risk" community residents (Hagnell et al., 1982; Joyce et al., 1990; Lewinsohn et al., 1993). A birth-cohort effect on first-onset depression also was detected in a large community sample of 14–18 year old students (Lewinsohn et al., 1993). Although these findings have important implications for the management of clinically referred individuals, they have not been cross-validated in samples of depressed patients.

In the present study, we therefore examined whether the distribution of age at onset of major depression in a clinically referred depressed sample of school-age children was subject to secular trends. There were several considerations that prompted us to cross-validate in a group of depressed youngsters a clinically pertinent epidemiologic finding. First, given that juvenile-onset and later-life depressions are continuous in some patients (Akiskal et al., 1985) and that the phenomenology of these disorders among children and adults is similar (Kovacs et al., 1984a, b, in press; Keller et al., 1982a, b; Ryan et al., 1987; Strober et al., in press), studying the impact of a particular variable at different ages may facilitate the understanding of affective illness across the life-span. Second, because earlier age at

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onset of major depression in childhood appears to be associated with more protracted episodes (Kovacs et al., 1984a, submitted), it is imperative to elucidate the factors that may influence onset. Third, if there are indications of a downward trend in age at onset among depressed, clinic-referred youths, there may be a need for special efforts at treatment development targeted at younger ages. Additionally, among school-age children, the time between the onset of a disorder and study participation cannot exceed more than a few years, thereby minimizing memory biases and faulty dating of episodes that constrain the study of adults (Klerman & Weissman, 1989; Hasin & Link, 1988).

In studying secular or temporal trends, three effects must be considered, namely those attributable to birth cohort, chronologic age, and historical period. Birth-cohort effects reflect events that had a uniform and permanent impact on individuals born around the same time; age-effects refer to the influence of events that are associated with a particular chronologic age; period-effects mirror the influence of the historical period in which the disorder became manifest or was ascertained. Although some statistical methods to disentangle these three effects have been proposed (Lavori et al., 1987; Wickramaratne et al., 1989; Holford, 1983), the effects cannot be estimated separately. For example, the birth-year and age at onset of a person's first depression define the period of onset of the disorder.

Mindful of the foregoing consideration, we used data from our longitudinal study of childhood-onset affective disorders to examine whether age at onset of major depression among juveniles is affected by birth year. When we commenced patient recruitment in the late 1970s, depression among children was receiving increased research attention. Because increased awareness of a disorder may produce secular changes in its characteristics, we also examined the effects of period of ascertainment (year of study entry) on the age-at-onset distribution. Furthermore, we considered gender, race, and socioeconomic status as potentially influencing disorder-onset. Finally, because children are dependent on the resources of the family, we examined two variables that might be surrogates for reduced social–familial resources and thereby affect disorder-onset, namely, having been born out of wedlock and living in a non-intact family at study entry.

It must be emphasized that the present study and investigations of secular trends in populations differ from one another in several regards, in addition to the age range of the subjects. Most importantly, because all of our cases *have* the disorder in question, our focus is on the age-at-onset distribution of depressed children. In contrast, epidemiologic studies yield estimates of the risk of depression at particular ages among people, only some of whom have the disorder. Compared to community- or population-based studies of adults in which the birth-years spanned several decades, we had a narrow band of birth-years (1965–1976). Thus, given the clinical nature, characteristics, and size of our cohort, the results are presented to stimulate further study of this topical area.

Subjects and Methods

Design

Subjects for the larger, nosologically-oriented longitudinal investigation of childhood-onset depressive disorders were recruited in two phases, primarily through the child psychiatry outpatient service of the University of Pittsburgh (PA) and the general medical

clinic of the Children's Hospital of Pittsburgh (PA). A few were recruited through other avenues, as described in detail elsewhere (Kovacs et al., 1984a). Our research staff systematically screened consecutive cases who were referred to these sites for a variety of reasons. Study participation was based on whether or not the child met our inclusionary criteria; it was *not* based on referral reason to the clinic or the service provider's diagnosis.

To be considered for the study, each child had to meet the following demographic criteria: 8–13 years old, not mentally retarded, no major systemic medical illness, ambulatory psychiatric or medical status, and living with parent(s) or legal guardian(s) within commuting distance of Greater Pittsburgh. Signed consents were obtained from parent(s) and children, and families received a monetary reimbursement at each assessment. The protocol specified a maximum of four evaluations in the first year of study participation and semiannual assessments in subsequent years.

Psychiatric evaluation and diagnosis

At study entry and at each evaluation thereafter, research clinicians completed standardized sociodemographic data forms based on an interview with the parent. Also at each assessment, the parent first was interviewed alone about the symptoms and adjustment of the child, and then the child was interviewed separately by the same clinician. The psychiatric evaluations were conducted with the semistructured Interview Schedule for Children (ISC) and its Addenda. The interviewers were mental-health professionals (M.A., M.S.W. or Ph.D. level) with prior experience in psychiatric settings, who were further trained in psychiatric assessment and diagnosis for this project.

Diagnoses were based at each assessment on the interviewing clinician's final ratings of each ISC and pertinent Addenda symptoms, according to the reports of both parent and child, as well as additional information, as needed. The reliability of the ISC ratings has been reported (Kovacs, 1985). Only symptom ratings meeting operational criteria for clinical severity were used to assign a diagnosis (Kovacs et al., 1984a, b). All diagnoses conformed to DSM-III criteria (APA, 1980) and were assigned by *consensus* among the research clinicians.

Dating the onset of a disorder

For history and onset dates of disorders, we relied primarily on parental report. The onset of a disorder was dated to the time when, according to all indicators, the child had the full syndrome in question. To assist recall, informants were usually asked to draw a "life-line," place marker events (e.g. holidays, birthdays, start of school year) on the line in the proper sequence, and locate the period of the child's disturbance in relationship to the marker events. All available information was utilized to assure precision in the dating of disorders. If an onset date could not be readily determined, a calendar interval was delimited during which the problems emerged (e.g. "between Christmas and Easter"). The date in question was then set at the midpoint of that interval. Onset dates also were consensually assigned by the research clinicians.

Cohort

Study cases were recruited between April 1978 and March 1987 and were grouped according to their *index depression* (determined at study entry or during the following 6 months of diagnostic verification). The index depressions were: major depressive disorder (MDD), dysthymic disorder (DD), both major depressive and dysthymic disorders (MDD/DD), and adjustment disorder with depressed mood (ADDM). The present analyses are based on the 92 patients who had an index diagnosis of *major depressive disorder* (60 with an index diagnosis of MDD and 32 with an index diagnosis of MDD/DD). The index MDD was the first episode for 84 children (91%) and the second episode for five (5%); for the latter cases the first episode of MDD was used in the analyses. The episode number of the index MDD could not be determined for three cases because of changes in caretakers, however, they were operationally treated as first episodes. The ages at entry and birth-years of the 92 children by study recruitment year are presented in Table 1.

There were 41 boys and 51 girls; mean age was 11.4 years (range: 8.3–13.9 years); 64% was white and 36% was black or biracial. Altogether, 29% were living in intact families of origin at study entry and 37% had been born out of wedlock. By Hollingshead's Two Factor Index of Social Position (unpublished copyrighted manuscript, 1957), socioeconomic status was as follows: 3% in category I (highest); 7% in category II; 23% in category III; 39% in category IV; and 28% in category V (lowest).

Variables

The dependent variable was age at the onset of the first episode of MDD. The main independent variable was the subject's year of birth (birth-cohort). The other independent variable was the subject's study entry year, or the "period" of case ascertainment. Youths entered the study in close proximity to the onset of their major depression. For example, the elapsed time between onset of the index MDD and study entry was 6 months or less for 72% of the "truncated" sample of MDD cases (see below) and 12 months or less for 87% of them. Therefore, the period of ascertainment in the present study also reflects the period of illness-onset.

Five covariates were considered for their effects on the distribution of age at onset of MDD. The demographic variables were gender, race (dichotomized as white vs not white), and socioeconomic status (SES) determined by Hollingshead's Index (already noted) but

Table 1
Characteristics of the Study Cohort by Year of Study Entry (N = 92)

Variables	Year of study entry				
	1978–1979	1980–1981	1982–1983	1984–1985	1986–1987
Number of cases	5	19	27	28	13
Age at intake (mean years)†	11.19	11.35	11.48	11.20	11.70
Birth years of cases	1965–1969	1966–1972	1969–1974	1970–1976	1972–1976

†Age at study entry was restricted by the protocol to 8–13 years.

dichotomized for the analyses as higher (categories I, II, III) vs lower SES (categories IV, V). The other variables were whether the subject was born out of wedlock (no vs yes) and living in an intact family of origin at study entry (no vs yes).

Statistical methods

The relationship of birth cohort and period of ascertainment to age at onset of first MDD was analyzed in a number of ways. For most analyses, birth years, study entry years, and ages-at-onset were grouped into 2-year intervals. Cross-classified categorical data were examined by means of chi-square tests and log-linear models. Nonparametric analysis of variance (Kruskal–Wallis test) was also employed to compare age at onset across birth cohorts. We used the Kaplan–Meier method to estimate the age-specific probability of the onset of the first MDD, and Cox regression analyses (Kalbfleisch & Prentice, 1980) to model the effects of covariates on the probability of the first episode of a MDD onsetting at particular chronologic ages. In the Cox regression analyses, we employed a step-wise procedure, with "birth cohort" entered as the first covariate. Each of the remaining covariates was then entered, one at a time, and was retained in the model only if $p < .05$ for the difference in chi-square. The analyses were implemented using BMDP software (Dixon et al., 1990) or StatExact (Mehta & Patel, 1991).

Results

Computation of the mean age at onset of first MDD by birth cohort (grouped by 2-year intervals) suggested that children born in later periods had progressively earlier onsets of major depression, as compared to those in prior birth cohorts. For example, young patients born in 1965–1966 were aged 12.7 years on average at the onset of their MDD, those born in 1971–1972 were aged 11.0 years, on average, whereas the 1975–1976 birth cohort had a mean age of 9.2 years at MDD-onset. Computation of the mean age at onset of MDD by study entry year (grouped into 2-year intervals) revealed no evident effect for period of ascertainment (range: 10.6–11.2 years).

However, the foregoing computations had not been corrected for possible sampling artifacts. In particular, there exist structural sampling biases in the birth cohorts at both the left and right ends of the curves (that is, prior to 1969 and after 1975) due to the age limits imposed by the study design (age at entry 8–13). For example, because study recruitment started in 1978 and included an age cut-off, only 13-year-olds from the 1965 birth cohort could have been enrolled. *Therefore, we truncated the sample for further analysis and included only children born between* 1969 *and* 1975.

Within the truncated sample, we conducted a further test in order to rule out the possibility that older children (earlier birth cohorts) may have been inadvertently over-represented among earlier study recruits, whereas younger children (later birth cohorts) may have been over-represented towards the end of the recruitment period. Such a sampling bias could have yielded the age-at-onset by birth-cohort distribution noted above. A contingency table analysis revealed no association (Fisher's exact test $p = .28$) between age at entry (categorized in three groups: 8–9, 10–11, 12–13) and year of entry (also grouped into three intervals: 1978–1980, 1981–1983, 1984–1987).

Birth cohort effect

The subjects in the truncated sample (n = 79) were grouped into three birth-cohorts (1969–1970, 1971–1972, 1973–1975). Then, three approaches were used to test further for an association between birth cohort and age at onset of depression. Computing the mean age at onset of MDD for each of the three birth cohorts revealed that children in the first (earliest) birth cohort (1969–1970) were the oldest, on average (11.62 years), when they had their first MDD (see Table 2). Successive birth cohorts were successively younger at the onset of their depression (Kruskal–Wallis test $\chi^2 = 17.95$, $df = 2$, $p = .0001$). The existence of a downward trend in age at onset of MDD was further supported by a three-by-three contingency table analysis (see Table 2) of birth cohort vs age at onset (the latter categorized as $\leqslant 9$, 10–11, $\geqslant 12$ years). The model of independence was rejected for this table ($\chi^2 = 17.87$, $df = 4$, $p = .001$).

Finally, the age-specific probability of the onset of the first-episode of MDD was computed separately for each of the three birth cohorts, via the Kaplan–Meier estimator (Kalbfleisch & Prentice, 1980). The three survival curves, depicted in Figure 1, were significantly different [Generalized Savage (Mantel–Cox) $\chi^2 = 15.87$, $df = 2$, $p = .0004$], with later birth cohorts being progressively younger at the time of onset of first MDD.

The effects of the covariates (gender, SES, race, intact family at study entry, born out of wedlock) on the distribution of age at onset of depression (in the presence of birth cohort) was examined via Cox regression analysis. With each covariate having been entered one at a time, only "born out of wedlock" made a marginally significant contribution (with $.05 < p < .10$) to the model that included birth cohort. Thus, irrespective of birth cohort, children born out of wedlock were somewhat younger at MDD-onset than the rest of the

Table 2
Characteristics and Distribution of Age at Onset of First Episode of Major Depressive Disorder For Three Birth Cohorts (Truncated Sample, N = 79)

Variable	Age at depression onset, years				
	N	Median	Mean	(*S.E.*)	Range
Birth cohort 1 (1969, 1970)	23	11.51	11.62	(.26)	8.27–13.40
Birth cohort 2 (1971, 1972)	25	11.21	10.98	(.30)	7.75–13.57
Birth cohort 3 (1973, 1974, 1975)	31	9.97	9.90	(.25)	7.75–12.99
	N	≤9 years	10–11 years		≥12 years
Birth cohort 1 (1969, 1970)	23	2	10		11
Birth cohort 2 (1971, 1972)	25	5	13		7
Birth cohort 3 (1973, 1974, 1975)	31	16	12		3

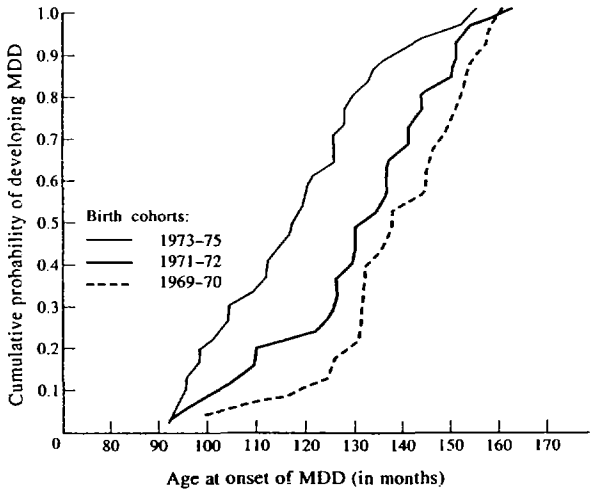

Figure 1. Cumulative probability of developing MDD as a function of age for the three birth cohorts (truncated sample).

cases. A contingency table analysis of birth status by birth cohort reconfirmed that the proportion of children born out of wedlock was stable across the three birth cohorts ($\chi^2 = 0.80$, $df = 2$, $p = .67$).

Period of ascertainment effect

The most informative assessment of a potential period-effect would be a loglinear analysis, using a three-way table of birth cohort by age-at-onset by intake period, in the manner suggested by Holford (1983). However, the small sample size precluded this approach. Instead, we examined the bivariate relation between age at onset (three-way grouping) and study-entry year (also a three-way grouping), but did not detect an association (Fisher's exact test, $p = .36$). Therefore, the model of independence of age at MDD onset and period of ascertainment could not be rejected.

Comment

In the present investigation of a child psychiatric sample, we sought to cross-validate a clinically pertinent epidemiologic finding regarding secular trends in age at onset of major depression. More specifically, we examined whether age at onset of major depressive disorder among clinically referred school-age children was subject to birth-cohort and period effects. Demographic and historical variables also were considered as possible predictors of age-at-onset of major depression. It is important to reemphasize at the start that our investigation focused on the age-at-onset patterns among referred children, all of whom *had* the disorder in question. Therefore, the findings do not allow inferences about the risk of MDD developing among children in the general population.

We found that age at onset of the first episode of major depression declined across successive birth cohorts in our clinical sample. Children born in 1969–1970, for example, were 11.6 years old, on average, when they had their first MDD, as compared to children born in 1973–1975, who were 9.9 years old, on average, when they first became depressed. None of the sociodemographic variables that was examined appeared to explain the variability in age-at-onset of depression. Although children who had been born out of wedlock tended to have somewhat earlier onsets of MDD than the rest of the youths, this marginally significant effect was independent of the birth-cohort effect.

The above-noted secular trend could have been obtained if, as a consequence of increased societal attention to juvenile-onset psychiatric disorders, children were getting referred to clinics at younger ages. However, the distribution of age at onset of MDD did not change appreciably as a function of year of study entry (period of ascertainment). As a further check on a possible period-effect, we also examined (post-hoc) the age distributions of all treatment referrals to our child psychiatry clinic during the study recruitment years. Usable clinical census data were available starting with the year of 1982. We found that the average age of referred children was consistently between 10 and 11 years for each year from 1982 through 1987 (when study recruitment was closed).

Although the present findings should be considered as preliminary because of the characteristics of the sample, our data, together with trends detected in a community-based study (Lewinsohn et al., 1993), do suggest that age at onset of major depression among the very young also may be declining with successive birth cohorts. This tentative conclusion is further supported by the results of a study of 86 siblings (mean age of 13.2 years) of prepubertal depressed children and 77 siblings (mean age of 11.6 years) of normal prepubertal probands (Ryan et al., 1992). In both groups, the risk of depression developing was affected by birth cohort. The accumulating evidence of a declining age-at-onset of major depression across successive birth cohorts of children has potentially important clinical ramifications. For example, in treatment studies, a child's birth cohort will have to be taken into account because of its relationship to age-at-onset which, in turn, appears to be inversely related to length of MDD episode (Kovacs et al., 1984a, submitted). Additionally, efforts to develop psychosocial treatments for depression will have to address the special needs of younger children.

Purely genetic explanations of the birth-cohort effect have been considered as unlikely (Gershon et al., 1987; Klerman et al., 1985; Wickramaratne et al., 1989). Purely social-environmental explanations have been viewed as unsatisfactory (e.g. Gershon et al., 1987) in light of evidence that depressive disorders have a high familial aggregation and that earlier age-at-onset is related to increased morbid risk among first-degree relatives (Gershon et al., 1976; Mendlewicz & Baron, 1981; Weissman et al., 1988; Orvaschel, 1990). Instead, many authors have favored an explanation involving some "gene–environment interaction," mindful of the fact that a birth-cohort effect can refer to any factor *related* to (but occurring later than) the year of birth, not only the birth-year itself (Holford, 1991). According to Gershon and associates (1987), for example, "an inherited vulnerability is more likely to be expressed in recently born cohorts," possibly owing to the stresses of rapid social changes. Klerman and associates (1985) have argued that the cohort effect may be a "proxy" for a period-effect reflecting urbanization, changes in population demo-

graphics and the structure of the family, and shifts in occupational and employment patterns.

The foregoing arguments appear to suggest that successive birth cohorts may have been exposed to more of the 'causal,' presumably negative social processes, or were exposed to the negative psychosocial factors at earlier or more vulnerable ages. It is unlikely, however, that birth-cohort effects directly mirror changes in the social milieu. These trends may instead reflect losses in protective factors, such as coping resources and coping responses/behaviors (Pearlin & Schooler, 1978) that, in turn, render cohorts less resistant to stressors. For example, as a byproduct of cultural changes, children and young adults may have fewer social and interpersonal resources upon which they can draw in the face of persistent life-strains that, coupled with inherited vulnerability (Gershon et al., 1987), could result in earlier psychopathology.

One factor that prompted the present study was that accurate dating of onsets of psychiatric disorders is probably somewhat better in younger age groups than in adults (Lewinsohn et al., 1993; Aneshensel et al., 1987; Bromet et al., 1986) because the time-frame is much narrower. However, the narrow age at onset span that characterizes the study of childhood disorders also imposes methodologic constraints. Our investigation also was constrained by the small sample size, and the fact that only patients with birth years from 1965 to 1976 were sampled. Given that we addressed several major scenarios that may have produced spurious results in the present data set, it is remarkable that there exists evidence for a birth-cohort effect over such a short time interval. Therefore, there is a need for replication on larger clinical samples of more recent birth cohorts that also are diagnostically more heterogenous. Such studies may shed further light on whether there exists a general downward trend in age-at-onset of MDD among depressed children.

Acknowledgements—This research has been supported by Grant Number MH33990 from the Health and Human Service Administration and by a grant from the W. T. Grant Foundation. Appreciation is expressed to Lydia Voti, M.S. who conducted the statistical analyses and Lucy P. Parrone, M.S. who was responsible for programming tasks. We also thank Evelyn J. Bromet, Ph.D. and David Goldston, Ph.D. for their comments on a previous version of this article.

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VOL. 21, NO. 4, 1985

*The Children's Depression, Inventory (CDI)[1,2]

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Self-rated depressive symptom inventories have long played a role in clinical research on adults. These tools are economical, easy to administer, and readily analyzable. Because they quantify the severity of the depressive syndrome, they have been used for descriptive purposes, to assess treatment outcome, test research hypotheses, and select research subjects.

However, in contrast to the availability of self-rated symptom scales for adults, there were no corresponding instruments for youngsters. The Children's Depression Inventory (CDI) was developed in response to this need. The present article describes its development, psychometric properties, and research uses.

Description of the CDI

The CDI is a 27-item, self-report, symptom-oriented scale that was designed for school-aged children and adolescents. Its "readability" is at the first-grade level (Kazdin & Petti, 1982). The instrument quantifies a range of depressive symptoms including disturbed mood, hedonic capacity, vegetative functions, self-evaluation, and interpersonal behaviors. Several items concern the consequences of depression in contexts that are specifically relevant to children (e.g., school).

Each CDI item consists of three choices, keyed from 0 to 2 in the direction of increasing severity. Thus, the total score can range from 0 to 54. About 50% of the items start with the choice that reflects the greatest symptom severity; for the rest, the sequence of choices is reversed. A scoring template is available.

The respondent is instructed to select the one sentence for each item that *best* describes him or her for the *past 2 weeks*. Next to each item, there is room for the child to mark his or her response.

Scale Construction

The 21-item, self-rated Beck Depression Inventory (BDI) for adults (Beck, 1967) was the starting point for the children's scale. Samples of 10- to 15-year-old "normal" youths, as well as inpatient and partially hospitalized youngsters, assisted in rewording the items for children. Consequently, the item on libido was replaced and five appendix items were added concerning school and peer functioning, which were adopted from another study (Albert & Beck, 1975).

Further testing, as well as semantic and conceptual analyses, yielded a new version which was administered to 39 consecutively admitted 8- to 13-year-old patients in a child guidance center; 20 age-matched "normal" controls; and 127 children, aged 10 to 13, in the Toronto public schools (Friedman & Butler, 1979). The data were subjected to standard psychometric analyses. Consequently, four items were replaced by ones with better face validity and all

[1]This study and preparation of this manuscript were supported by Grant No. MH-33990 from the National Institute of Mental Health and Grant No. AM-25568 from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases.

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*PLEASE NOTE: All references in this paper are presented in a single reference section to be found on pages

the items were recast into a three-choice format.

This version of the CDI (dated 5/77) was again piloted; the comprehensibility of the items was further improved; a cover page was added with a sample item; and critiques were solicited. The final CDI (dated 7/77) underwent one minor format change; namely, the score values from the inventory were eliminated (dated 8/79), and a scoring template was constructed.

Administration of the CDI

The CDI was designed for individual administration in clinical research settings using standard principles of testing. Instructions for its administration are available. The respondent is handed a copy of the scale. An administrator reads aloud the CDI, while the subject reads along silently on his or her own copy *and* marks the answers. The purpose of this procedure is to assist the child with a reading or attention problem; it may be dispensed with after a few items, particularly with older subjects.

In a number of studies (e.g., Friedman & Butler, 1979) the CDI was *group*-administered in the schools as a researcher or teacher read aloud the items. Because no difficulties were reported, the instrument appears to be usable in a group format.

The Reliability of the CDI

Two samples were used to establish the reliability of the instrument. One group consisted of 75 youths consecutively referred to a child guidance center who were recruited into a descriptive clinical research project. Ss had to be 8- to 13-years-old; without evidence of mental retardation or major systemic illness; and had to be living with parents/guardians. The medical pediatric sample consisted of 80 children with recently diagnosed insulin-dependent diabetes mellitus (IDDM) who were consecutive admissions to a pediatric metabolic unit; were also recruited into a descriptive research study; and met the same criteria as the psychiatric group (except, of course, for the presence of IDDM). For both samples, the results of the first CDI administration were analyzed; for the psychiatric group, this was several weeks after the clinic referral; for the IDDM group, this was 2 to 3 weeks after the medical illness was diagnosed.

The internal consistency of the CDI was analyzed by means of coefficient alpha. In the diagnostically heterogeneous, psychiatric sample, the coefficient was .86. The scale's internal consistency in the pediatric-medical outpatient group was .76. The latter group's CDIs were re-examined to assess if time-of-testing was salient. Using data gathered 1 year after the IDDM was diagnosed (n = 61), the internal consistency of the CDI was indeed higher with α = .82.

Item total-score correlations were the most acceptable in the psychiatrically referred sample. With the exception of items 5, 15, and 18, which barely contributed to the total score (rs = .13 to .25), the coefficients for the rest of the items ranged from .29 to .62. On the other hand, in the IDDM sample, the item-total-score correlations at initial testing were not impressive, with a low of r = .10 and a high of r = .47. However, analysis of the diabetic children's scores 1-year postdiagnosis yielded improved item-total-score correlation coefficients, with a range from .08 to .63.

Thus, the construct which is quantified by the CDI does not have the same "reality" to different respondent groups. The diabetic subjects' initial test response pattern was clearly unusual. And yet, with the passage of time, their endorsement pattern began to approximate the clustering of symptoms that characterizes this syndrome in children.

One month test-retest data were available for 29 recently diagnosed juvenile diabetics. The resultant coefficient of r = .43 ($p < .01$) revealed acceptable stability. When two obvious outliers were removed (n = 27), the test-retest correlation coefficient was found to be higher, namely, .82 ($p < .0001$).

The Validity of the CDI

The concurrent validity of the CDI was determined against two self-rated scales which quantify related constructs, namely, the Revised Children's Manifest Anxiety Scale (Reynolds & Richman, 1978) and the Coopersmith Self-Esteem Inventory (Coopersmith, 1967). In the psychiatrically referred sample, the results of these concurrently administered scales

were correlated. The association between the depression and the anxiety scales was highly significant ($r = .65$, $p < .0001$, $n = 55$); self-rated depressive symptomatology and low self-esteem were also correlated ($r = -.59$ $p < .0001$, $n = 51$).

CDI data were provided to the author on a large sample of children, tested in the Toronto public schools (Miezitis et al., 1978). Subjects ($n = 860$) were 8- to 14-year-olds, in grades 4 through 8, with a slight majority of boys. These data were factor analyzed using Varimax rotation. The procedure yielded one principal factor with an eigenvalue of 5.95 that accounted for 63.7% of the variance. Although the second factor accounted for an additional 10.7% of the variance, its eigenvalue was just short of unity. Therefore, in large samples of "normals," the CDI may act as a unidimensional scale.

The discriminant validity of the CDI has been problematic. For example, the diagnostically heterogeneous psychiatric sample ($n = 75$) had the following score characteristics: mean = 9.7, S.D. = 7.3, range = 0-37. For youths with IDDM ($n = 79$), at initial testing the scores were: mean = 5.6, S.D. = 4.1, range = 0-20. And in the Canadian student sample ($n = 860$) the following characteristics were obtained: mean = 9.3, S.D. = 7.3, range = 0-51. Thus, the CDI cannot differentiate "normals" and a heterogeneous child psychiatric sample. It is notable, therefore, that the CDI score characteristics and distribution in the Canadian sample (inverted J-curve) were practically identical to the results reported for normative samples in the U.S.A. (Finch et al., 1985; Smucker et al., in press).

CDI scores were examined for sex- and age-effects. Among the psychiatric outpatients ($n = 75$), age and CDI scores were not significantly correlated ($r = -.10$); neither did the scores of boys and girls differ ($t = -.34$). Data from the Toronto public schools sample and from the diabetic cohort yielded similar results; no significant age-CDI associations ($r = -.02$; $r = -.08$, respectively) and no significant sex effects ($t = 1.73$; $t = 1.40$, respectively).

The next logical question was whether the CDI discriminates psychiatrically diagnosed school-aged depressed children and cases whose disorders are not in the depressive domain. Therefore, scores of five groups of ambulatory subjects from the author's naturalistic study (Kovacs et al., 1984a) were compared. Psychiatric diagnoses were reached via the Interview Schedule for Children, described elsewhere in the present volume, and were independent of the CDI administration. The diagnostic groups (at the time of the corresponding CDI assessment) were as follows: major depressive disorder ($n = 53$); dysthymic disorder ($n = 24$); major depression in partial remission ($n = 13$); adjustment disorder with depressed mood ($n = 22$); and a conduct-oppositional sample of pathologic controls ($n = 24$).

The findings suggest that the CDI can discriminate certain diagnostic groups, as operationalized in the DSM-III (American Psychiatric Association, 1980), and is sensitive to the extent of the depressive syndrome. One-way analysis of variance on the five groups' CDI scores was significant [$F(4,131) = 3.24$, $p < .02$]. The score characteristics were as follows:

DIAGNOSTIC GROUP	CDI MEAN	S.D.	S.E.	RANGE
Major depressive disorder (MDD)	12.8	6.3	.87	4-31
Dysthymic disorder (DD)	11.7	6.7	1.37	1-25
MDD in partial remission	8.5	5.6	1.55	2-19
Adjustment disorder with depressed mood	3.6	6.1	1.30	0-21
Conduct/Oppositional disorder	8.6	6.7	1.36	0-30

The scores of the following diagnostic groups were significantly different: MDD vs. MDD in partial remission ($t = -2.17$, $p < .04$); MDD vs. adjustment disorder ($t = -2.61$, $p < .01$); and MDD vs. pathologic controls ($t = -2.70$, $p < .01$).

Because major depressive and dysthymic disorders are phenomenologically similar, the lack of a between-group CDI difference was not entirely surprising. However, the CDI was sensitive to the severity of depressive illness, as reflected by score differences across patients with "full-blown" major depression, partially remitted MDD, adjustment disorder with depressed mood, and disorders *not* in the depressive domain. Therefore, these data lend some support to the *diagnostic validity* of the CDI.

It should be noted, however, that the actual score differences across these *outpatient* groups were not that substantive. And even for cases

with MDD, the mean CDI was considerably lower than figures reported for juvenile *inpatients* with depressive illness (Preskorn et al., 1982). Therefore, at least in ambulatory samples, it would not be wise to use the inventory on its own for *patient* selection. Instead, the CDI should initially serve as an adjunct to diagnostic screen.

Conclusion

The CDI was developed because there was a need for standardized assessment tools in the study of the depressive disorders among juveniles. Because the CDI is a self-rating scale, it is economical to use and easy to administer. Among school-aged "normal" and clinic-referred children, the scores are not related to the respondent's age and sex.

Data on the CDI's validity are equivocal. Its factorial structure may differ depending on the population being studied. The relationship between the distribution parameters of the CDI in normal and psychiatrically referred samples needs further scrutiny. However, *within* psychiatric outpatient groups, the data do suggest that CDI scores and diagnoses are related, in the expected fashion. The magnitude of between-group score differences nonetheless suggests that the inventory alone should *not* be used to select research patients. But, it can serve as an index of the severity of depression and, probably, as a measure of change. Because the instrument was designed as a *severity* rating scale and not as a diagnostic tool, the foregoing uses would be the most appropriate. For example, in one study of severely depressed, hospitalized children, CDI scores were found to be related both to clinical status and blood levels of tricyclic antidepressants; and the CDI was also a good index of change (Preskorn et al., 1982). Therefore, the CDI has clear promise as an assessment tool in treatment-outcome studies.

Clinical Effects of Amitriptyline in Adolescent Depression

A Pilot Study

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Abstract. To determine the effects of antidepressant medication on adolescent depression, we compared the efficacy of amitriptyline (200 mg daily) with placebo in a double-blind experimental design. Diagnosis of adolescent depression (n = 20) was achieved using the psychiatric interview, psychiatric rating scales, and psychometric instruments. No significant differences were reported between the amitriptyline and placebo groups on the Psychiatric Rating Scale or the Minnesota Multiphasic Personality Inventory. There were differences between groups at week 6 on the Depression Adjective Check List. Within group significance occurred from onset of treatment to conclusion on all instruments. The results suggest that prescription of amitriptyline for treatment of adolescent depression may be no more efficacious than the use of placebo.

Journal of the American Academy of Child Psychiatry, 20:636–44, 1981.

This paper reports on a study of the effectiveness of amitriptyline in adolescent depression. Previous studies on antidepressant medication usage in adolescents and children have been done on variably defined groups. In two studies (Weinberg et al., 1973; Brumback et al., 1977), dysphoric mood was considered to be primary in the diagnosis which led to treatment, regardless of other presenting symptomatology. The drugs tested in these two studies were mainly tricyclics with dosages ranging from 25 mg/day to 125 mg/day. One study (Lucas et al., 1965) with a primarily adolescent

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The research was supported in part by the University of Connecticut School of Medicine, Reference Number 345-75, and the Merck, Sharp, and Dohme Research Laboratories.

The authors gratefully acknowledge the assistance of Alexandre B. Todorov, M.D., Howard Pressman, M.D., and the clinical and nursing staff of the Child and Adolescent Psychiatric Service, Mount Sinai Hospital, Hartford, Connecticut, where the study was conducted.

0002-7138/81/2003-0636 $00.88

population used an optimum dose of 50 mg/day of amitriptyline. However, none of their subjects had a primary diagnosis of depression. Frommer (1967, 1968) used tricyclics and monoamine oxidase inhibitors. The symptomatology for diagnosis was nonspecific. All studies stated that the children improved whether on tricyclics or MAO inhibitors, as compared to placebo or no drugs. None indicated the parameters that were used to measure improvement; none of the studies used a double-blind analysis.

Method

Subjects

Each patient referred to the Mount Sinai Hospital Child and Adolescent Psychiatric Service (CAPS) was initially interviewed by a psychiatric social worker. If the social worker saw symptoms such as suicidal ideation or attempts, sadness, insomnia, withdrawal, etc., and felt the patient to be dysphoric, the patient was considered for admission to the study. They and their parents were then asked to sign an informed consent form. There were, after final diagnostic evaluation (see below), 6 males and 4 females in the placebo group, and 1 male and 9 females in the amitriptyline group ($p = 0.05$). There was no statistically significant difference for any of the other demographic variables (table 1).

Diagnosis

Upon admission the patient was interviewed by the chief psychiatrist. The interview technique was structured and formal. Each patient was rated according to a global impression of dysphoric symptoms in addition to specific responses to a set of criteria listed in table 2. The numerical values assigned to each area are also given in table 2. If the patient scored a 7 or above on the Psychiatric Rating Scale (table 2) and the global impressions indicated a pathological state of depression without other underlying pathology of a primary nature, a series of psychological tests were administered to verify the diagnosis. They included the Minnesota Multiphasic Personality Inventory (form R) and the Depression Adjective Check List (form A). Both tests were administered two days after the interview for two reasons. First, the admission procedure, psychiatric interview, separation from family and/or previous living situation, and general adjustment to a psychiatric setting were deemed stressful enough without the two additional hours re-

Table 1

Demographic Distribution of Patients in Amitriptyline and Placebo Groups

Variable	Amitriptyline	Placebo
Sex		
Male	1	6
Female	9	4
Age		
Male (average)	15.1	15.1
Female (average)	14.0	15.0
Range	13.0–16.1	13.1–17.0
Age at Onset	12.1	12.1
Range (years prior to admission)	1–3	1–7
Race		
White	8	8
Black	2	0
Puerto Rican	0	2
School Grade		
Male	10.0	8.8
Female	8.7	9.5
Socioeconomic Level		
Welfare	4	1
Lower	0	3
Middle	5	4
Upper	1	2
Number of intact families	6	3
Number of single parent families	4	7
Number of depressed mothers	4	5
Number of depressed fathers	0	2
Average number of siblings	2.5	2.3
WISC		
Verbal	96.3	96.4
Performance	99.4	101.9
Full scale	97.6	98.5
WRAT		
Reading	7.8	7.8
Spelling	6.2	6.1
Math	6.9	5.4

quired for psychological testing. Second, the Depression Scale of the Minnesota Multiphasic Personality Inventory is often defined as a "mood" scale and is sensitive to transient emotional states. With this in mind, it was felt that patients adversely affected by the hospitalization process and not "clinically" depressed would be excluded after a 2-day adjustment period. Secondary diagnosis was allowed if it was not considered causative of the primary diagnosis

of depression. The depression must have been manifested for at least 6 months prior to admission and the subject must have been nonfunctional in relation to school. If, after the administration of the psychometric tests, the patient presented only a depressed profile as outlined by Marks et al. (1974), and no other primary pathology, he or she was admitted to the study.

Design

Utilizing a double-blind experimental design, 20 depressed adolescents were randomly assigned to either a placebo or active medica-

Table 2

Psychiatric Rating Scale: Subjects per Group during Six Week Experimentation Period

			Week 1		Week 6	
Variable	Category	Score	Amitriptyline	Placebo	Amitriptyline	Placebo
Sadness/Helplessness	Absent	0	–	–	4	0
(Present situation)	Feeling on Question	1	6	7	5	4
	Reports Spontaneously	2	4	3	1	6
Hopelessness/Worthlessness	Absent	0	–	–	5	2
	No Plans for Future	1	4	3	5	6
(Future orientation)	Future is Bleak	2	6	7	0	2
Guilt	Absent	0	2	5	4	7
	Bad Person/Responsible for Difficulties	1	6	2	4	3
	Ruminations about Feelings of Being Bad	2	2	3	2	–
Suicide	Absent	0	1	1	6	5
	Not Worth Living	1	1	2	1	3
	Death Wishes	2	1	4	2	1
	Suicidal Wishes	3	2	1	1	1
	Suicidal Attempt	4	5	2	–	–
Insomnia	Absent	0	2	2	6	9
	Difficulty Falling Asleep Occasionally	1	1	3	3	0
	Difficulty Falling Asleep Nightly	2	–	–	1	1
	Excessive Sleeping	2	7	5	1	1
Retardation	Absent	0	4	2	6	2
	Slight	1	5	3	3	2
	Obvious	2	1	5	1	6
Concentration difficulty	Absent	0	–	–	9	2
	Slight	1	8	3	1	8
	Obvious	2	2	7	–	–

tion group by using a random distribution table supplied by Merck, Sharp, and Dohme.

Medication

Amitriptyline was administered in the following manner: Initial doses of 25 mg, four times a day, followed by 25 mg increments until a maximum dose of 200 mg/day in divided doses was achieved. Placebo doses were supplied according to the same schedule. This dose was reached within 3 days of admission to the study and maintained without variation throughout the entire study. No other psychotropic drugs were administered during this time.

Evaluation of Ongoing Treatment

During the experimental period, each subject was interviewed two additional times by the same examiner during the third and sixth weeks. (For simplicity, only data on the first and sixth week evaluations are presented here.) The psychometric instruments were administered as follows: The Depression Adjective Check List (forms B, C, and D) was given the third, fifth, and sixth weeks, respectively. The Minnesota Multiphasic Personality Inventory was administered during the sixth week. All instruments were given according to the instructions as outlined by the respective tests. Interviews and psychological testing were administered on random days during those weeks stated.

Psychiatric Program

Each subject in the study followed a daily schedule identical to those patients not involved. This included school, work experiences within the hospital setting, group and individual therapy, and recreational activities. All subjects were considered a part of the psychiatric community and not identified to other patients as participants in a psychiatric investigation.

Statistical Methods

The data were analyzed using programs available in the Statistical Package for the Social Sciences (version 7.0, 1979) and the Biomedical Statistics Programs (1975 version). Analysis of variance (program ANOVA) and multivariate analysis of variance and covariance (program MBD12V) were performed. In addition, paired t-tests were run. To control for the multivariate nature of the data, and to adjust for the fact that several comparisons have

been made with the same set of data, the significance values were adjusted according to the Bonferroni multiple comparison technique.

Results

Analysis of all available data at the same time showed no difference between the active and placebo groups ($F_{3,39} = 0.89$). A breakdown by instrument and by group is summarized in table 3.

Psychiatric Rating Scale (PRS)

At the outset of the study there were no significant differences ($t_{18} = 0.92$, $p > 0.90$) reported between the amitriptyline and placebo groups (respective mean values 10.2 ± 0.6 and 10.3 ± 0.7). Each subject was considered severely depressed upon the initial interview with scores ranging from 7 to 14 on the psychiatric rating scale. Psychiatric ratings by categories and groups are presented in table 2.

Upon the final interview of each subject during week 6, there was marked improvement in both groups as compared with week 1 (active group $t_9 = 5.08$, $p = 0.008$; placebo group $t_9 = 6.5$, $p = 0.001$). However, no significant difference ($t_{18} = 0.88$, $p > 0.90$)

Table 3

Degree of Significance for Differences between the Amitriptyline (Active) and the Placebo Groups

Diagnostic Instrument	Active	Placebo	t value	df	p value
		Week 1			
Psychiatric Rating Scale	10.2 ± 0.6	10.3 ± 0.7	0.92	18	> 0.90
Depression Adjective Check List	16.2 ± 1.2	25.2 ± 0.8	2.30	18	> 0.40
Minnesota Multiphasic Personality Inventory	77.4 ± 1.8	80.7 ± 2.3	0.65	18	> 0.90
		Week 6			
Psychiatric Rating Scale	5.6 ± 0.8	3.9 ± 1.1	0.88	18	> 0.90
Depression Adjective Check List	10.3 ± 0.4	22.7 ± 0.7	24.65	18	< 0.001
Minnesota Multiphasic Personality Inventory	61.4 ± 3.6	67.1 ± 3.8	2.23	18	> 0.46

was reported between the active and placebo groups on overall score (respective mean values 5.6 ± 0.8 and 3.9 ± 1.1).

Depression Adjective Check List (DACL)

There was no initial difference between the two groups at week 1 (t_{18} = 2.30, p = 0.40). There was improvement in both groups at week 6 (active group t_9 = 20.05, p < 0.001; placebo group t_9 = 6.63, p < 0.001). However, the amitriptyline group improved more, and there was a statistically significant difference between the active and placebo groups (t_{18} = 24.65, p < 0.001). It should be pointed out that this result could be biased because the placebo group started higher and ended higher (mean values 25.2 ± 0.8 and 16.2 ± 1.2) as compared with the "active" group (mean values 22.7 ± 0.7 and 10.3 ± 0.4).

The Minnesota Multiphasic Personality Inventory (MMPI)

The active and the placebo groups showed no difference (t_{18} = 0.65, p > 0.90) on the D scale of the MMPI at the outset of the study (mean values 77.4 ± 1.8 and 80.7 ± 2.3). In terms of overall profiles, both groups presented depressed profiles. When an analysis of the MMPI was undertaken after 6 weeks, significantly lower scores (active group t_9 = 5.37, p = 0.005; placebo group t_9 = 6.17, p = 0.002) on the D scale were reported within the active and placebo groups (mean values 61.4 ± 3.6 and 67.1 ± 3.8). The between-group analysis showed no significant statistical difference (t_{18} = 2.23, p = 0.46).

Discussion

The present study indicates improvement in depressive symptomatology in all of our patients to a significant statistical level on all measures (PRS, DACL, and MMPI). Overall there was no statistically significant difference between the active and placebo groups, which is to be expected as both groups improved over time. A breakdown by instrument shows differences between active and placebo groups on the DACL list. Both groups improved over time, but there was greater improvement in the amitriptyline group. This may mean that the DACL is a better measure of depression than our other scales or an unreliable measure. If it is a more sensitive measure of depression, then amitriptyline would be effective in adolescent depression.

The percentage drop over time on the Psychiatric Rating Scale (table 4) seems to indicate a greater proportion of patients in the

Table 4

Psychiatric Rating Scale: Percentage Change in Scores Over Six Week Period[a]

		Amitriptyline	Placebo
Minimal improvement	0–33%	2	4
Moderate improvement	34–66%	3	5
Maximum improvement	67%	5	1

[a] Based on total score of Psychiatric Scale Between Weeks One and Six within subjects χ^2 is not statistically significant.

amitriptyline group improved as compared with placebo. There was no statistically significant difference shown.

The Psychiatric Rating Scale and the MMPI show no significant difference in week 1 and week 6. This means that amitriptyline was not more effective than placebo in treating depression. This would point to hospitalization, with its attendant therapeutic modalities, as the main factor in improvement. Depression among adolescents would seem, in the present study, to be amenable to therapies other than medication, i.e., individual, family, and group. It is possible that if one controlled for these therapeutic modalities, then removal from a noxious home situation or living environment might alone be enough for alleviation of depression.

There are other problems inherent in the study which should be considered. The most obvious is that 6 males fall into the placebo group and only 1 in the amitriptyline group. However, sex as a predictor of response does not seem crucial (Bielski and Friedel, 1976).

In retrospect, the final diagnosis of 3 subjects in the placebo group would have excluded them from the study. This, however, does not alter the results in terms of within-group or between-group significance. The dosages used may have given inadequate plasma levels (Kupfer et al., 1977) or an excess plasma level (Zeigler et al., 1976). Further studies utilizing plasma levels seem warranted, particularly since even smaller doses have been administered in previous studies.

To prove the efficacy of antidepressants in adolescent depression a larger sample is needed, particularly in view of the difficulty of establishing the diagnosis of primary depression in this age group. If it is found that antidepressants do work, then perhaps the subgroup that contains the best responders can be extracted. If antidepressants do not work, then further study of the etiology, course, and biochemistry of depression in the younger age group, as opposed to depression in adults, is indicated.

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Major Depression in Community Adolescents: Age at Onset, Episode Duration, and Time to Recurrence

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ABSTRACT

Objective: This paper presents retrospective and prospective data regarding time course parameters of major depressive disorder (MDD) in community adolescents (14 to 18 years old): time to onset and recovery and, among those who recovered, time to recurrence. **Method:** Diagnostic interviews were conducted with 1,508 randomly selected high school students. Three hundred sixty-two had experienced at least one past or current episode of MDD. **Results:** Mean age at onset of first episode was 14.9 (SD = 2.8). Early MDD onset was associated with female gender and suicidal ideation. MDD episode duration ranged from 2 to 520 weeks, with a mean of 26.4 weeks (SE = 3.3) and a median of 8.0 weeks. Longer episodes were observed in those whose depression occurred early (at or before age 15), whose depression had been accompanied by suicidal ideation, and for whom treatment was sought. Of the adolescents who recovered, 5% relapsed within 6 months, 12% within 1 year, and approximately 33% within 4 years. Shorter time to recurrence was associated with prior suicidal ideation and attempt and with later first onset. **Conclusions:** Risk of MDD is low in childhood, increasing substantially with adolescence. The majority of episodes in community adolescents are relatively brief, although the risk of recurrence is substantial. Suicidal behaviors are important mediators of episode duration and of recurrence. *J. Am. Acad. Child Adolesc. Psychiatry*, 1994, 33, 6:809–818. **Key Words:** adolescent, depression, onset, duration, relapse.

Age at onset, episode duration, and the probability for recurrence as a function of time since recovery are major parameters of psychiatric disorders. A time course for major depressive disorder (MDD) which can be clearly distinguished from that of other psychiatric disorders lends empirical support to the validity of this diagnostic category (Keller et al., 1983). The importance of time course is affirmed by the *DSM-III-R* (American Psychiatric Association, 1987), which provides information about these characteristics for all disorders. The *DSM-III-R* states, "The average age at onset is in the late 20s, but a Major Depressive Episode may begin at any age, including infancy," and that duration is "also variable. . . . Untreated, the episodes typically last six months or longer. Usually there is a complete remission of symptoms and general functioning returns to the premorbid level; but in a large proportion of cases, some symptoms of the episode persist for as long as two years. . . . " (pp. 220–221). Unfortunately, this description is based almost entirely on empirical data from adult clinical populations. With few exceptions (e.g., Keller et al., 1988; Strober et al., 1993), few comparable data are available for adolescents.

In addition to providing information relevant to nosological issues, time course studies provide normative data for researchers and clinicians as a baseline against which to compare their samples. Knowledge regarding onset age and time course should influence efforts to develop effective treatment strategies and guide public health personnel in planning for the allocation of treatment resources. Finally, prognostic factors and theoretical hypotheses can be addressed by data that identify the personal and the environmental variables related to episode time course.

Accepted February 7, 1994.

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This research was supported in part by NIMH awards MH40501 and MH50522.

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Previous Studies of Onset Age, Duration, and Recurrence. Over the past decade there has been increasing interest in the natural history of affective disorders in adults, with studies examining onset age, recovery from depressive episodes, and the probability of recurrence after recovery. Three large community adult epidemiology studies have been conducted (Burke et al., 1990; Kessler et al., 1994; Lewinsohn et al., 1986a). All three used life table methods and the results are remarkably consistent, with the retrospectively reported prevalence of depression extremely low up to age 9 and rising sharply from ages 9 to 19, especially in females.

Episode duration studies of depressed adults (e.g., Keller et al., 1982a; Lewinsohn et al., 1986b) indicate that up to 50% recover within 6 months, and approximately 80% are recovered by 2 years. However, the recovery rate slows substantially for individuals who are still depressed at 6 months. Data from the community-based Epidemiological Catchment Area study over a 1-year follow-up period (Sargeant et al., 1990) suggest that the rates of recovery for community-residing cases of MDD are somewhat higher than those for treated samples.

Recurrence appears to occur at high rates after recovery: Belsher and Costello (1988) conclude that within 2 years after treatment for depression approximately 50% of adult patients recurrence at least once. The risk of recurrence seems to diminish after longer periods of well-time (Keller et al., 1982b, 1983). This decline in risk of recurrence over time appears to be more pronounced for community-residing men than women (Lewinsohn et al., 1989), with recurrence risk remaining essentially stable for women over a 10-year period, compared to a significant decrease for men over time.

The few studies of MDD time course in adolescents and children differ sufficiently in their design and methodology that only limited conclusions regarding youth MDD time course can be drawn. The reported MDD duration values for child and adolescent patients have included a median of 16 weeks (Keller et al., 1988) and means from 32 to 36 weeks (Kovacs et al., 1984a; McCauley et al., 1993; Strober et al., 1993). Regarding MDD recurrence in treated children and adolescents, Kovacs et al. (1984b) found that 26% of recovered patients relapsed within 1 year and that 40% had relapsed within 2 years.

Variables Impacting MDD Duration and Time to Recurrence. It is important to examine factors that may effect MDD duration and recurrence. Unfortunately, only a small number of prognostic factors have been examined, and then primarily with adult samples. Being female has been found to be associated with greater recurrence in some studies (Lewinsohn et al., 1989) but not in others (Keller et al., 1983), while gender has not been found to be associated with the duration of depressive episodes in adults (Billings and Moos, 1985; Keller and Shapiro, 1981; Shapiro and Keller, 1981; Keller et al., 1984; Lewinsohn et al., 1986b). With some exceptions (Shapiro and Keller, 1981; Keller and Shapiro, 1981), severity of depression episode has been found to be significantly associated with longer duration (Billings and Moos, 1985; Keller et al., 1984) and with greater likelihood of recurrence (Gonzales et al., 1985). The melancholic (endogenous) subtype of MDD was found to be associated with longer lasting episodes in adults, even after controlling for impairment (Lavori, P.W., Keller, M.B., Coryell, W., Maser, J.D., and Mueller, T.I., unpublished) but the impact of melancholia on recurrence has not been examined. Duration of the index MDD episode has not been predictive of recurrence (Gonzales et al., 1985). Suicidal behavior in depressed adults (Overholser et al., 1987) and adolescents (Brent et al., 1990) has been found to be associated with longer duration but has not been examined in relation to recurrence.

Most investigations have failed to find a significant relationship between age at onset and duration of MDD episodes in adults (Shapiro and Keller, 1981; Keller and Shapiro, 1981; Keller et al., 1984; Lewinsohn et al., 1986b). Lewinsohn et al. (1989) and Frank et al. (1989) found no relationship between age of onset and recurrence.

Utilization of mental health services may also be an important mediator of MDD time course, but to date it has not been systematically examined.

Another potential prognostic factor is comorbidity. A substantial proportion of depressed adults and adolescents have another coexisting psychiatric disorder, concurrently or over their lifetime (e.g., Rohde et al., 1991). Some studies have found comorbidity to be associated with longer episode durations in adults (e.g., Keller et al., 1984), whereas others have not (Rohde et al., 1991). The special case of MDD superimposed

onto a preexisting episode of dysthymia ("double depression") has been identified by Keller and Shapiro (1982) as a poor prognostic sign for recurrence in adults.

The Present Study. This is one of a series of papers from the Oregon Adolescent Depression Project (e.g., Lewinsohn et al., 1993a,b) reporting on a sample of 1,508 randomly selected high school students between the ages of 14 and 18 who participated in extensive diagnostic assessments (retrospective and current) at entry into the study and approximately 1 year later. The present investigation examines the distributions of the onset age of first MDD episodes, duration of these episodes, and the time from recovery to recurrence. We hypothesized that earlier onset, longer time to MDD recovery, and shorter time to recurrence would be associated with (1) being female; (2) lower parental socioeconomic status; (3) greater depression severity during the index episode; (4) greater functional impairment; (5) melancholic (endogenous) subtype; (6) a history of suicide attempt and/or suicidal ideation; (7) absence of treatment; and (8) presence of lifetime comorbidity with dysthymia or other mental disorders.

METHOD

Subjects and Procedure

Participants were randomly selected in three cohorts from nine senior high schools representative of urban and rural districts in western Oregon. A total of 1,710 adolescents completed the initial (T_1) assessments (interview and questionnaires) between 1987 and 1989, with an overall participation rate of 61%. Half of the T_1 sample (52.9%) was female, with an average age of 16.6 years (SD = 1.2). The representativeness of the T_1 sample was assessed using several approaches; differences between the sample and the larger population, and between participants and those who declined to participate, were very small (additional details provided in Lewinsohn et al., 1993a). Adolescents were paid for their participation, and written informed consent was obtained from both the participants and their legal guardians.

At the second assessment (T_2), 1,508 participants (88.1%) returned for a readministration of the interview and questionnaire (mean T_1–T_2 interval = 13.8 months, SD = 2.3). Biases that may have emerged due to attrition in the T_1–T_2 panel sample were infrequent and small in magnitude (described in Lewinsohn et al., 1993a). Most importantly, participants and dropouts did not differ on the number of episodes of most current and past mental disorders, including MDD.

Approximately half of the T_1–T_2 panel sample was female (53.7%), with an average T_1 age of 16.5 years (SD = 1.2). A total of 8.9% were nonwhite or Hispanic; 71.3% were living with two parents and 53% were living with two biological parents. The education levels of parents were assessed, with the following frequencies for the maximum level for mother or father: 1.9% had not completed high school, 16.1% had completed high school, 35.1% had a partial college education, and 46.9% had an bachelor's, advanced, or professional degree.

Occupations of the parents were classified using the Hollingshead (1975) index. The highest value for mother or father was selected, with the following distribution: 14.2% were semiskilled or unskilled workers; 20.2% were clerical, sales, or skilled workers; 15.7% were technicians or semiprofessionals; 25.0% were managers or minor professionals; 14.6% were administrators or owners of medium-sized businesses; and 10.3% were higher executives or major professionals.

Diagnostic Interview

Adolescents were interviewed at T_1 for past and current psychopathology with a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) that combined features of the Epidemiologic version (K-SADS-E) (Orvaschel et al., 1982) and the Present Episode version (K-SADS-P), and included additional items to derive diagnoses of psychiatric disorders as per *DSM-III-R* criteria. A total of 261 subjects reported a past episode of MDD; an additional 24 subjects were in an MDD episode at the time of T_1.

At T_2, subjects were interviewed regarding their psychiatric status between T_1 and T_2 using the Longitudinal Interval Follow-up Evaluation (Keller et al., 1987), which provides detailed information about the course of psychiatric symptoms and disorders since the initial K-SADS interview, with rigorous criteria for recovery from a disorder (i.e., symptom-free for 8 or more weeks). Seventy-seven subjects developed a first episode of MDD between the T_1 and T_2 assessments; this results in data regarding onset age, duration, and time to recurrence for a total of 362 (24.0%) participants who reported having experienced at least one episode of MDD before T_2.

For reliability purposes, a second interviewer reviewed audiotaped or videotaped recordings of a randomly selected 12% of the interviews. Interrater reliability was evaluated by the κ statistic (Cohen, 1960). With four exceptions (diagnoses for lifetime dysthymia, lifetime eating disorders, and current and lifetime anxiety disorders, κ values = .58, .66, .60, and .53, respectively), all T_1 κ values were equal to or greater than .80. At T_2, κ values for any disorder versus no disorder at T_2 and between T_1 and T_2 were .87 and .72, respectively.

Independent Variables

In addition to the adolescents' gender and parental education and occupation levels, the following 10 variables were created for use in the present study.

Lifetime Comorbidity with Dysthymia. The T_2 point and lifetime prevalence rates of dysthymia were 0.1% and 3.0%, respectively. A total of 7.1% of the subjects with MDD also had a comorbid dysthymia at some time in their life.

Lifetime Comorbidity with Anxiety Disorders. Anxiety disorders included panic disorder, agoraphobia, social phobia, simple phobia, obsessive-compulsive disorder, separation anxiety, and overanxious disorder. The T_2 point prevalence of anxiety disorders was 3.2%, and the lifetime prevalence was 5.6%. A total of 20.7% of the subjects with MDD also had a lifetime comorbid anxiety disorder.

Lifetime Comorbidity with Disruptive Behavior Disorders. Disruptive behavior disorders included attention-deficit hyperactivity disorder, conduct disorder, and oppositional disorder. The T_2 point prevalence of disruptive behavior disorders was 1.8%, and the

lifetime prevalence was 5.5%. A total of 10.8% of the subjects with MDD also had a lifetime comorbid disruptive behavior disorder.

Lifetime Comorbidity with Substance Use Disorders. Substance use disorders included substance abuse and dependence disorders. The T_2 point prevalence of substance use disorders was 2.3%, and the lifetime prevalence was 6.0%. A total of 22.9% of the subjects with MDD also had a lifetime substance use disorder.

Suicide Attempts. At both the T_1 and T_2 interviews, information was obtained regarding suicide attempts. A total of 7.6% of the T_2 sample reported having made a past suicide attempt. Of the adolescents with MDD, 28.5% had made a suicide attempt. The majority of these attempts were made either during (55%) or before (34%) the MDD episode.

The remaining five variables were obtained only for subjects who had experienced an episode of MDD.

Suicidal Ideation. Information was gathered at both the T_1 and T_2 interviews regarding suicidal ideation during an episode of MDD. Three items on the K-SADS assessed suicidal ideation (thoughts of death, wishes to be dead, thoughts of suicide). A continuous score was computed assessing the number of suicidal ideation items endorsed. The majority of adolescents with MDD had either none (51.7%) or one of the items (42.8%); 1.9% had two suicidal ideation symptoms, and 3.6% had all three items.

Depression Severity. Among the subjects meeting criteria for MDD, a continuous score was created consisting of the number of *DSM-III-R* criteria that had been met. Values included five symptoms (20.7%), six symptoms (23.8%), seven symptoms (24.6%), eight symptoms (19.1%), and nine symptoms (11.9%).

Endogeneity. Using the *DSM-III-R* criteria for melancholic subtype of MDD, a continuous score was created for each depressed subject. Data were available from the K-SADS for six of the nine symptoms listed in the *DSM-III-R*: loss of interest/pleasure, lack of reactivity, depression worse in the morning, early morning awakening, psychomotor retardation/agitation, and anorexia. Data for the remaining three criteria were either not assessed (i.e., personality disturbance before first MDD) or do not apply to a first episode of MDD (i.e., one or more previous MDD episodes followed by complete recovery, previous good response to somatic therapy). A total of 25.1% of the MDD subjects had zero or one of the endogenous symptoms; 33.4% had two endogenous symptoms, 26.5% had three endogenous symptoms, and 14.8% had four or more of the available endogenous symptoms.

Functional Impairment. Interviewers probed for the presence of impairment in three areas of functioning: socially (with peers), with family, and in school. Of the adolescents with MDD, 13.3% had no impairment, 30.7% had impairment in one area of functioning, 37.0% in two areas, and 19.1% in all three areas of functioning.

Mental Health Treatment Utilization. Treatment for depression was defined as receiving outpatient psychotherapy, antidepressant medications or lithium, being hospitalized, or receiving electroshock during an episode of MDD. A total of 20.7% of the subjects reported having received some form of treatment for their first episode of MDD.

RESULTS

Overview

Life table survival analyses (Singer and Willett, 1991) were used to examine the time to occurrence of the events under consideration (i.e., MDD onset, episode duration, and time to relapse). Survival analysis was used because it allows for the use of data from *all* subjects who are in the study, either to occurrence of the event or to the end of the observation period. Survival methods were used to compute hazard rates and the cumulative proportion of subjects experiencing the event. For example, the hazard rate for onset is the probability that an adolescent who has never been depressed at the beginning of a given time interval will develop an episode of MDD during the time interval. The cumulative proportion for onset indicates the number of adolescents who had developed an episode of depression by a certain age. One-year time intervals were used for MDD onset; the intervals for duration and recurrence were weeks and months, respectively.

Survival analysis also permits the assessment of the statistical significance of any differences in the survival experience among different subgroups. In this way we evaluated the effect of our independent variables on MDD onset, episode duration, and time to recurrence. In addition, the relation of selected characteristics of the MDD episode (i.e., presence of suicidal ideation, severity, endogeneity, impairment, treatment utilization) with onset age, episode duration, and time to recurrence was examined. All analyses in the present study were two-tailed.

Onset Age

The mean age at MDD onset of 14.92 years (SD = 2.8); median onset age was 15.5. Actuarial life table estimates of the annual hazard rates and Kaplan-Meier product-limit estimates of the cumulative proportion of subjects with MDD onset are shown in Table 1. As can be seen, the hazard rate increases substantially over the age span (i.e., the risk of developing depression increases with each year).

The impact of eight independent variables, available for the entire sample, on age of MDD onset was examined using univariate Cox proportional hazards models. As shown in the first column of Table 2, seven of the variables were significantly related to onset: female gender; lower parental education; comorbidity with dysthymia, anxiety disorders, disruptive behavior disorders, and substance use disorders; and history of suicide attempt. The seven variables with significant univariate associations were then entered into a multiple Cox proportional hazards model. As shown in the

TABLE 1
MDD Onset: Annual Hazard Rates and Cumulative Proportion of Subjects with MDD at the Beginning of Various Time Intervals

Age (yr)	Hazard Rate/Year (SE)	Cumulative Proportion with MDD at Beginning of Interval (SE)
5–6	.001 (.001)	.001 (.001)
6–7	.003 (.002)	.005 (.002)
7–8	.002 (.001)	.007 (.002)
8–9	.006 (.002)	.013 (.002)
9–10	.002 (.001)	.015 (.003)
10–11	.007 (.002)	.021 (.004)
11–12	.010 (.003)	.031 (.004)
12–13	.010 (.003)	.040 (.005)
13–14	.019 (.004)	.059 (.006)
14–15	.031 (.005)	.088 (.007)
15–16	.069 (.007)	.147 (.009)
16–17	.064 (.008)	.193 (.010)
17–18	.069 (.010)	.236 (.012)
18–19	.082 (.016)	.282 (.014)

Note: MDD = major depressive disorder.

second column of Table 2, all variables remained significant after controlling for the effects of the other measures.

To illustrate the magnitude of these effects, mean survival times were computed for subgroups dichotomized on each of the significant variables. The mean survival time values use extrapolation to estimate the average onset time for subjects in each of the two groups, assuming they had been assessed through the entire time period. Earlier MDD onset was associated with female gender (mean onset of 17.4 years for females versus 18.4 for males; SE = 0.09 and 0.07, respectively); lower parental education (17.7 versus 18.1 years; SE = 0.08 and 0.08); lifetime comorbid dysthymia (16.4 versus 17.9 years; SE = 0.45 and 0.06); lifetime comorbid anxiety (16.2 versus 18.0 years; SE = 0.27 and 0.06); lifetime comorbid disruptive behavior (16.9 versus 17.9 years; SE = 0.32 and 0.06); lifetime comorbid substance use (16.6 versus 18.0 years; SE = 0.23 and 0.06); and history of suicide attempt (15.8 versus 18.0 years; SE = 0.25 and 0.06).

It is possible that these seven variables were simply risk factors for the occurrence of MDD rather than predictive of an earlier age of MDD onset. That is, if a variable predicted the incidence of depression in the entire sample, it would be associated with onset age, since depressed adolescents obviously become depressed at an earlier age than those who do not become depressed. To clarify whether the independent variables were specifically predictive of *early* onset age, we restricted subsequent analyses to the 362 participants who had developed MDD either before or during the study period; *t* tests were used to compare subgroups dichotomized on the each of the independent variables. Only the effect of gender was significant in these subset analyses, with an earlier onset age for females; $t(233) = -2.27$, $p < .05$. Girls had their first episode at an earlier age (mean = 14.7 years) than did boys (mean = 15.4 years). The difference in onset age between those with and without a lifetime comorbid anxiety disorder approached significance; $t(119) = -1.86$, $p = .065$. The remaining five variables that had been significantly associated with onset age in the multivariate prediction analysis using the total sample were not associated with onset age in the 362 MDD cases.

Using the MDD sample, we also examined whether an episode occurring at an earlier age was more severe and debilitating than an episode occurring at a later age. Five characteristics of the MDD episode were examined using correlational analyses. Only one of these variables, suicidal ideation, was associated with onset age ($r = -.12$, $p < .05$); subjects with an earlier onset were more likely to report suicidal ideation.

Duration of MDD Episodes

Of the 362 subjects who had ever experienced an MDD episode, 336 recovered from the depression by T_2; the remaining 26 were still in the episode at the end of the data collection period and were therefore considered censored cases in the duration analyses. In an examination of whether censored subjects had especially long-lasting episodes, the mean duration value for these 26 subjects (20.0 months, SD = 36.8) was contrasted with that of the 336 remitted subjects (22.9 months, SD = 51.3). This difference did not attain statistical significance; $t(360) = 0.28$. Thus, although MDD duration values for the 26 censored cases were truncated, the censored cases did not appear to be an atypical subset with unusually long-lasting episodes.

The distribution of duration values was highly skewed, with a range of 2 to 520 weeks, a mean of 26.4 weeks (SE = 3.3), and a median of 8.0 weeks. The weekly hazard rates and the cumulative proportion of subjects still depressed for various time periods are shown in Table 3. In general, the likelihood of recovery

TABLE 2
Univariate and Multivariate Associations of Independent Variables with Age at MDD Onset, MDD Duration, and Time to MDD Relapse

	Age at Onset[a]		Duration[a]		Relapse	
Variable	Univariate Model z[b]	Multivariate Model z	Univariate Model z	Multivariate Model z	Univariate Model z	Multivariate Model z
Gender	7.25***	6.38***	NS	—	NS	—
Parental education	−3.42***	−2.53*	NS	—	NS	—
Parental occupation	NS	—	NS	—	NS	—
Comorbidity with						
Dysthymia	5.23***	2.29*	NS	—	NS	—
Anxiety	9.18***	6.18***	NS	—	NS	—
Disruptive	4.14***	2.71**	NS	—	NS	—
Substance	8.31***	5.84***	NS	—	NS	—
Suicide attempt	12.21***	8.06***	NS	—	4.17***	3.15**
Suicidal ideation[a]	N/A	—	−2.97**	−2.85**	3.66***	2.94**
Severity[a]	N/A	—	−2.06*	NS	2.60**	NS
Endogeneity[a]	N/A	—	NS	—	NS	—
Impairment[a]	N/A	—	NS	—	NS	—
Received treatment[a]	N/A	—	−2.21*	−2.69**	NS	—
Age at onset[a]	N/A	—	5.85***	6.21***	3.63***	3.00**
Duration[a]	N/A	—	N/A	—	−2.13*	NS

Note: MDD = major depressive disorder; NS = nonsignificant; N/A = not applicable.
[a] For the first MDD episode.
[b] Critical ratio z = coefficient/SE.
* $p < .05$; ** $p < .01$; *** $p < .001$.

(i.e., hazard rate) gradually decreases as the episode duration lengthens. Overall, the survival function projected that 25% of the subjects were recovered by 3 weeks, 50% by 8 weeks, and 75% by 24 weeks.

Univariate Cox proportional hazards model analyses were used to examine the effects of the 14 independent variables on MDD duration; the results are shown in the third column of Table 2. Longer MDD episodes were associated with an earlier first onset age, treatment utilization, suicidal ideation, and depression severity. To examine the combined influence of these variables, a multiple Cox proportional hazards model analysis was conducted. Because the severity variable included suicidal ideation as one of its items, severity was reconstructed without suicidal ideation for the multiple regression analysis. In the multivariate analysis, only earlier first onset age, treatment utilization, and suicidal ideation remained significant.

To illustrate the magnitude of the significant effects, mean MDD episode duration for subjects with early onset (defined as prior to 15.5 years of age) was 34.7 weeks (SE = 5.0) compared to 12.9 weeks (SE = 1.6) for subjects with later onset. Mean duration was 39.6 weeks (SE = 9.4) for subjects receiving treatment versus 23.2 weeks (SE = 3.3) for subjects not treated for their depression. MDD subjects with suicidal ideation had a mean duration of 33.4 weeks (SE = 5.5) compared with 19.4 weeks (SE = 3.5) for subjects who did not have suicidal ideation.

Time to MDD Relapse

Of the 336 subjects who recovered from an episode of MDD, 84 developed a second MDD episode before T_2. The monthly hazard rates and cumulative proportion of subjects relapsing at various time points are shown in Table 4. As can be seen, no temporal pattern emerges for the relationship between level of recurrence risk and passage of time since recovery. Cumulatively, 5% of the formerly depressed adolescents developed a second episode within 6 months of recovery, 12% developed a second episode within the first year, and approximately 33% were projected to have a recurrence within 4 years after recovery. The mean and median survival times between two MDD episodes were 73.8 months (SE = 123.0) and 73.0 months, respectively.

To identify factors related to MDD recurrence, the 15 variables were examined with univariate Cox

TABLE 3
MDD Duration: Weekly Hazard Rates and Cumulative Proportion of Subjects with MDD Who Were Still Depressed at the Beginning of Various Time Intervals

Weeks since MDD Onset	Hazard Rate/Week (SE)	Cumulative Proporation Depressed at Beginning of Interval (SE)
2–4	147 (.022)	1.000 (.000)
4–6	.099 (.018)	.745 (.023)
6–8	.034 (.009)	.611 (.026)
8–10	.083 (.020)	.571 (.026)
10–12	.025 (.012)	.483 (.027)
12–14	.129 (.030)	.460 (.027)
14–16	.022 (.013)	.355 (.026)
16–18	.077 (.024)	.340 (.026)
18–20	.011 (.011)	.291 (.025)
20–22	.045 (.022)	.285 (.024)
22–24	.018 (.010)	.261 (.024)
24–26	.058 (.026)	.252 (.024)
26–52	.026 (.014)	.224 (.023)
52–104	.015 (.009)	.114 (.018)
104–208	.005 (.003)	.053 (.013)
208–520	.007 (.006)	.013 (.010)

Note: MDD = major depressive disorder.

TABLE 4
MDD Recurrence: Monthly Hazard Rates and Cumulative Proportion of Subjects Who Had a Recurrence of MDD at the Beginning of Various Time Intervals

Months since First MDD	Hazard Rate/Month (SE)	Cumulative Proportion Relapsed by Beginning of Interval (SE)
2–4	.008 (.003)	.003 (.003)
4–6	.013 (.005)	.031 (.010)
6–8	.009 (.004)	.050 (.012)
8–10	.006 (.003)	.067 (.014)
10–12	.021 (.006)	.084 (.016)
12–18	.009 (.004)	.120 (.019)
18–24	.005 (.004)	.156 (.022)
24–36	.005 (.004)	.186 (.024)
36–48	.011 (.009)	.234 (.029)
48–60	.012 (.008)	.334 (.039)
60–72	.010 (.010)	.433 (.048)

Note: MDD = major depressive disorder.

proportional hazards model analyses; results are provided in the fifth column of Table 2. More rapid recurrence was associated with a history of suicide attempt, suicidal ideation during the first MDD episode, greater severity of first MDD episode, later age of first onset, and shorter first episode duration.

These five variables were entered into a multiple Cox proportional hazards model (again, severity was recomputed without the suicidal ideation items). As shown in the sixth column of Table 2, MDD severity and episode duration lost their significance after controlling for the influence of other variables. To illustrate the magnitude of the significant effects, mean survival times for subgroups of subjects dichotomized on each variable were computed. Mean survival time to MDD recurrence for subjects with a history of suicide attempt was 46.0 months (SE = 6.5), in comparison to 81.2 months (SE = 4.6) for those without a suicide attempt. Subjects with suicidal ideation during their first MDD had a mean survival time of 61.8 months (SE = 4.8), compared to 86.5 months (SE = 5.9) for those without ideation as a depression symptom. Finally, subjects with a later first onset of MDD (i.e., after 15.5 years of age) had a mean survival time of 31.7 months (SE = 1.2) to recurrence, versus 75.6 months (SE = 4.4) for subjects with an earlier first MDD onset.

Given that we previously found a greater likelihood of recurrence within 1 year for formerly depressed female adolescents compared with formerly depressed males (21% versus 9%; Lewinsohn et al., 1993a), the lack of a significant difference between time-to-recurrence curves for males and females was unexpected and further analyses were conducted. Although formerly depressed females were indeed more likely to develop a second episode before the conclusion of the study (29% of the females versus 16% of the males; $\chi^2[1, N = 336] = 5.99$, $p < .05$), the mean time to recurrence for the females (28.4 months, SD = 25.7) and males (21.1 months, SD = 18.4) did not significantly differ; $t(82) = -1.04$; not significant.

DISCUSSION

Limitations

Although the results of this investigation are based on a large sample of community-residing adolescents, several factors may limit the generalizability of our findings. Among these is the geographical location of the sample. The extent to which different findings might have been obtained from a national probability sample or from samples from other regions of the country is unknown. It is also important to note that this study is based on a sampling frame of adolescents attending school, and thus does not include youth who dropped out or were expelled from high school, groups that may include the most severely depressed.

However, the annual Oregon high school dropout rate is a relatively low 5.7% (Oregon Department of Education, 1993). In addition, it should be noted that diagnostic information was provided only by the adolescent; parental report of psychopathology was not obtained. This appears justified given that the reliability of parental report decreases as children become adolescents (e.g., Edelbrock et al., 1985).

The retrospective nature of the data is another consideration; the majority of MDD episodes (72%) were retrospective at T_1. It is likely that the veracity of this kind of information is affected by memory loss. However, because this sample consisted of adolescents, the reporting interval is, on the average, much shorter than in most studies with adults, including the Epidemiological Catchment Area study (Robins and Regier, 1991).

Despite these concerns, we believe that our results represent the most accurate estimates of the time course parameters for depression among community-residing, school-attending older adolescents that are currently available.

Onset Age

Comparison of our onset data with the previous literature is difficult because adults report on a much longer retrospective time span. Not withstanding, the present findings are consistent with data reported by Burke et al. (1990) and by Kessler et al. (1994), which indicate a great increase in the hazard rate for MDD onset between the ages of 13 to 19. Our findings regarding the general prevalence of MDD are also consistent with the findings reported by Kessler et al. (1994) for their youngest age group (13 through 24 years of age).

Recovery and Recurrence

The general recovery and recurrence data (Tables 3 and 4, respectively) are arguably the most useful product of this investigation. These data permit investigators to compare recovery functions of other groups (e.g., bipolar teenagers; adolescents treated with a new intervention) with the unipolar depression recovery function in this community sample. For clinicians, these data provide a yardstick for making prognoses for client episode duration, especially when paired with mediating variables data which identify patients with poor prognosis.

To our knowledge, this is the first report of episode duration and recurrence functions for a large community-based sample of depressed adolescents. In a sample of 100 psychiatric patients aged 7 to 17, McCauley et al. (1993) recently reported a first MDD episode mean duration of 35.6 weeks, which is close to the mean MDD duration of 39.6 weeks for those adolescents from our sample who received treatment. Of the 65 youth who completed a prospective 3-year follow-up with McCauley and colleagues, 35 (54%) developed another episode of depression, double the projected 3-year relapse rate (23%) reported in our study. Similarly, Kovacs et al. (1984b) found a higher cumulative recurrence rate (44%) for adolescent patients prospectively followed for a 3-year period. It will be remembered that obtaining treatment was not associated with recurrence in the present study; however, any number of factors may be responsible for the substantially higher recurrence rates reported by McCauley et al. and Kovacs et al. in their patient samples.

Negative Findings

Contrary to expectation, several of the independent variables were not associated with MDD onset age, duration, or recurrence. Pending independent cross-validation, these negative findings need to be interpreted with caution. Nonetheless, the negative results regarding gender and endogeneity merit comment. Given the large gender difference in depression prevalence among adolescents (e.g., Lewinsohn et al., 1993a), the failure of female gender to be associated with duration and time to recurrence was unexpected. In essence, while the formerly depressed females were almost twice as likely to have a recurrence in a given time period, the well-time between episodes did not significantly differ between genders. A clinical implication is that while females may be more likely candidates for recurrence prevention interventions, there need not be gender-specific timing of entry into maintenance treatment, as females do not have a recurrence any sooner than males.

Endogeneity failed to emerge as a significant mediator of age at onset, duration, or recurrence. This finding is at variance with other studies such as those by Lavori et al. (unpublished) and McCauley et al. (1993). One explanation for this discrepancy may be the often-noted poor correspondence between various operational definitions of endogeneity (e.g., Costello, 1993). While

we used the *DSM-III-R* melancholia subtype as the endogeneity definition, both Lavori et al. (unpublished) and McCauley et al. (1993) used the Research Diagnostic Criteria endogenous subtype.

Positive Findings

Perhaps the most striking overall result is that, with the exception of suicidal behavior, no one mediating factor contributed to the prediction of each of the three time parameters (onset age, duration, and recurrence). Clearly the three parameters are mediated by different factors. In general, onset age was mediated by adolescent/parent demographics (gender, parent education), comorbidity with other disorders, and suicide attempts; these may be broadly characterized as representing the preexisting demographic and psychiatric "background" or environment in which the first MDD episode emerges. These factors apparently do not affect the subsequent course (duration, recurrence) of depression. However, only female gender actually predicted *early* onset age among those who developed an episode of MDD. Previous adult and adolescent studies have not made the distinction between risk factors that predict onset and those that predict early onset.

In contrast to the findings regarding onset, the predictors of duration and recurrence (severity, receiving treatment, duration [for recurrence], onset age, and suicidal ideation and attempt) may be broadly characterized as parameters of the first episode itself. This pattern suggests that the factors responsible for the occurrence of first MDD episode are different from those that determine the length of the episode and the time to recurrence. Etiological models need to incorporate these unanticipated complexities. Clinically, these findings have implications for both treatment and prevention interventions.

Suicidal behavior emerged as an important determinant of each of the three disorder parameters. Our data indicate that adolescents with suicidal ideation were more likely to become depressed earlier in life, to have longer lasting episodes, and to have a shorter time to recurrence. Youth who made a suicide attempt were more likely to become depressed during childhood and had a shorter time to recurrence. The findings emphasize the importance of suicidal behavior in clinical assessment and treatment and in recurrence prevention efforts.

Although treatment utilization was associated with episodes of longer duration, this should not be interpreted as implying that treatment iatrogenically prolonged the depressive episodes. Rather, those for whom treatment was sought probably had longer lasting episodes because they were more severely depressed. However, even after statistically controlling for severity, treatment utilization was still significantly associated with longer durations. We suggest that mental health treatment utilization is a consequence, rather than a cause, of the protracted MDD episode (i.e., the probability of seeking treatment increases as the episode persists).

The finding that episodes that occurred early during childhood had longer durations lends support to the hypothesis that early-onset depression may differ in important ways from depression that occurs later during adolescence and during adulthood. This is not an artifact of sample characteristics; e.g., since all participants were interviewed between the ages of 14 and 18, those with earlier onset ages had potentially more time for longer episodes. The survival analysis methods control for this confound by accommodating subjects with different periods of observation. These findings are consistent with the hypothesis advanced by some (e.g., Weissman et al., 1987) that early onset signals a more serious form of the disorder.

Consistent with results reported by Kovacs et al. (1984b), early onset was also significantly associated with time to recurrence, but in a direction opposite from the above-mentioned hypothesis: earlier age was associated with a longer time to recurrence. Contrary to the results for duration, this finding is inconsistent with the assumption that early onset is an indicator of a more serious form of the disorder. Obviously the finding needs to be cross-validated. However, one explanation is that later- and earlier-onset MDD may represent different subtypes, at least within the child-adolescent age span. The findings (i.e., shorter duration and quicker recurrence with later onset) suggest an increase in the proportion of "rapid cycling" depressions (e.g., Angst and Wicki, 1990) among those with a later onset, compared to children with early onset whose depression more often exhibits classic MDD features of relatively longer duration and longer well-time. It is important to note that the negative association between onset age and recurrence (early onset age associated with longer time to relapse) was very robust ($p < .001$). These issues deserve further exploration.

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Journal of Abnormal Psychology
1986, Vol. 95, No. 4, 378-383

0021-843X/86/$00.75

Age at First Onset for Nonbipolar Depression

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The purpose of this study was to describe the onset age distribution for first episodes of unipolar depression for men and women. From a total of 6,742 participants ranging in age from 18 to 88 years, 2,046 were selected for a diagnostic interview on the basis of elevated scores on a self-report depression inventory and were diagnosed as per the Schedule for Affective Disorders and Schizophrenia and Research Diagnostic Criteria procedures. Of those interviewed, 1,012 were diagnosed as having suffered from a previous episode of depression. The Life Table method was used to describe the risks associated with different ages for developing an initial episode of depression. The results indicate that the hazard rates are very low through age 14 years, increase during adolescence (15-19 years) and young adulthood (20-24 years), peak between 45 and 55 years, and then decrease with increasing age, becoming zero at 80 years or older. The hazard rates for men and women differed, with women between the ages of 9 and 69 years having higher hazard rates than men between the same ages. The average age at onset for first episodes of depression for men and women did not differ.

The age at which disorders have their initial onset is important epidemiological information. The potential importance of age at onset is recognized by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III; American Psychiatric Association, 1980), which devotes a section to this aspect for each disorder even though in most instances relatively few empirical data are available for estimating the age of first onset distributions for the various disorders.

Many theoretical and practical issues can be addressed if the age at onset distribution for a disorder is known. Such knowledge would have important public policy and planning implications for directing services toward the vulnerable age groups. In addition, there is evidence that the age at first onset for a disorder can have etiological implications. For example, with affective disorders there appears to be a stronger genetic component in those individuals who develop the disorder earlier in life relative to those who develop the disorder later in life (Gershon, Bunney, Leckman, vanEerdewegh, & DeBauche, 1976; Mendlewicz & Baron, 1981; Winokur, 1974).

Knowledge concerning the modal age at first onset for depression may be particularly important for several additional reasons. It would be useful to know whether there are certain ages that are more vulnerable to depression since early symptoms of the disorder are difficult to recognize (Hopkinson, 1963, 1965). The literature also suggests that the age at first onset of affective disorders is related to the morbidity risk in the relatives of the affected patients. Thus, in a recent study, Weissman et al. (1984) found a substantial inverse relationship between the age at onset of major depression in the probands and the risk of major depression in their first-degree relatives. Individuals with the highest risk of major depression were the relatives of probands whose first onset of major depression occurred when they were younger than 20 years of age compared with the relatives of probands who had later ages of onset.

A review of the literature revealed that there is little consensus concerning the age range at greatest risk for the initial onset of an episode of depression. The reported average age at first onset varies widely from study to study (Beck, 1967), with many ages having been thought to be at elevated risk for depression. Thus, Kraepelin (1913) reported a peak incidence of depression (i.e., age at which the first episode occurs) during the decade of 20 to 30 years, whereas Cassidy, Flanagan, and Spellman (1957) and Ayd (1961) designated the decade of 30 to 40 years for this distinction. Weissman and Myers (1978b) found that women peaked in rates of prevalence at the age range of 35 to 45 years, whereas the rates for men increased with age. Rennie (1942) believed 45-55 years and Lundquist (1945) and Post (1968) believed 50 years and older were times of peak incidence, while in a recent review, Levitt, Lubin, and Brooks (1983) suggested that "depression, by comparison with all other functional mental illnesses, is an ailment of the aging" (p. 23).

The above-mentioned discrepancies concerning the age at onset distribution for depression may reflect three major problems with the earlier studies. First, many investigators did not differentiate between unipolar and bipolar depression. As has been noted (e.g., Depue & Monroe, 1978), there are important differences between these two forms of depression, including the age of initial treatment. Typically, bipolar patients are first treated or hospitalized at an earlier age than unipolar depressives. In the present study we have addressed this problem by restricting ourselves to cases of unipolar depression.[1]

This research was supported in part by Research Grant No. MH35672 from the National Institute of Mental Health.

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[1] It should be noted, however, that this strategy may not have been completely successful with young subjects who have had a depressive but not yet a manic episode. One would expect the number of such undetected bipolars to be small. Their effect on the onset age distribution would be to overestimate the hazard rate for unipolar depression for the younger years.

A second problem with many age at first onset studies is that only treated or hospitalized patients were counted. However, most individuals with unipolar depression do not seek or receive treatment (Roberts & Vernon, 1982; Weissman, Myers, & Thompson, 1981). Consequently, many of the earlier studies are based on a restricted subset of cases of unipolar depression. In the present study we dealt with this sampling problem by selecting a large sample from the general population and screening the sample in order to interview only those individuals with a high probability for the presence of a current or past episode of depression.

The third problem with the earlier studies is that their results are probably strongly influenced by the particular age characteristics of the study samples. Thus, for example, studies that have reported relatively early onset age values may have obtained such results because there were few older individuals in the sample rather than because late onset depression is rare. The fact that the demographic structure of a particular sample has a strong effect on the age of onset distribution has been recognized by Batschelet (1963); Crowe and Smouse (1977); Heimbuch, Matthysse, and Kidd (1980); and Wendt, Landzettel, and Unterreiner (1959). Batschelet (1963) and Wendt et al. (1959) suggested solving this problem by either restricting oneself to older individuals (who are presumably beyond the age at risk) or increasing the proportion of older individuals in the sample. Unfortunately, restricting oneself to older individuals is neither practical nor theoretically defensible because such populations may be biased by differential mortality. In the present study we have tried to solve this problem by using the Life Table method (Anderson et al., 1980; Kalbfeisch & Prentice, 1980) to analyze the results. As noted by Lavori, Keller, and Klerman (1984), the Life Table method is designed to analyze incomplete sets of observations in which a large proportion of participants who are at risk are lost because they drop out of the study or fail to become depressed before the termination of data collection (i.e., the participant's *current* age).

Several recent articles suggest a possible pattern of results for the present study. First, although there is an emerging consensus that depression occurs in young children (Carlson & Cantwell, 1980), it also appears to be relatively rare during early childhood and difficult to differentiate from normal transitory childhood problems (Lefkowitz & Burton, 1978). On the basis of the observations of Rutter, Maughan, Mortimore, and Ousten (1979) and Rutter (1983), one might hypothesize that somewhere between childhood and adulthood there is a dramatic increase in the prevalence of depression. Support for this hypothesis comes from epidemiological studies (Albert & Beck, 1975; Leslie, 1974; Schoenbach, Kaplan, Grimson, & Wagner, 1982) in which adolescent populations have been shown to have substantially elevated means on self-report depression measures.

We thus expected an increase in the incidence of depression as a function of age during young adulthood. For adults it is more difficult to predict any particular pattern of results because of the number of conflicting findings. However, we expected to find a decrease in the incidence of first onset of depression with increasing age for individuals 50 years or older on the bases of our own (Teri & Lewinsohn, 1983) and other recent studies (e.g., Robins et al., 1984) which indicate that the prevalence of depression (i.e., the proportion of the population suffering from the disorder at a given point in time) decreases slightly with increasing age. Finally, in view of the large difference in the prevalence of depression in males relative to females (Weissman & Klerman, 1977), it was of interest to determine if the distributions of the age at first onset of depression values differ for males and females.

Method

Participants

Data were available for 2,046 subjects who had participated in four epidemiological studies for which they had been recruited via announcements inviting paid participation in psychological research. The goals and demand characteristics of the four studies were similar in that each was designed to identify the psychological characteristics of persons vulnerable to depression and each had been presented to the participants as a community-wide study aimed at pinpointing the correlates of psychological health.

From the total sample of 6,742 participants in the four epidemiological studies, the present 2,046 subjects were selected to be interviewed on the basis of elevated scores on the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is a self-report measure of frequency of occurrence of 20 depressive symptoms designed for use with general community samples. The CES-D has been shown to possess adequate psychometric properties and to correlate substantially with other measures of depression (Radloff, 1977). This method of selecting subjects was not intended to generate a random or representative subset of the larger samples but was designed to increase the density of interviewing individuals with a current or past episode of depression. However, by restricting ourselves to people with elevated CES-D scores, we may have eliminated subjects who were symptom free at the time of the study but had a previous history of depression.

The cutoff scores for selecting participants to be interviewed varied among the samples based on the respective distributions of the CES-D scores (> 18 for Sample 1; > 10 for Sample 2; > 16 for Samples 3 and 4). The cutoff score was lower for the second sample because these participants generally provided low scores on the CES-D. Written informed consent was obtained from all participants.

The first sample (Amenson & Lewinsohn, 1981) consisted of 566 individuals who were a subset of 998 volunteers. These participants were interviewed between September 1978 and June 1979. The second sample (Finnell, 1980) consisted of 114 older (60+ years) individuals who were a subset of 1,197 volunteers for a study by the anthropologist Martin Horeis. The subjects for the third and fourth samples were recruited from a list of licensed drivers in the Eugene/Springfield (Oregon) area who were 50 years of age or older. For Sample 3, 484 subjects were interviewed between April 1980 and March 1982 from an initial sample of 2,724 subjects. For Sample 4, 882 subjects were interviewed between June 1982 and June 1984 from an initial sample of 1,823 subjects. Across the four studies, 2,046 (30.3%) of the total participants were interviewed.

Table 1 presents the demographic characteristics of the 2,046 participants. The sample differs from the larger population in that the participants had more education and higher incomes than the general population. Additionally, females were overrepresented.

Assessment of Depression

Information was gathered from the participants in interviews conducted as per the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978) and evaluated for the presence of current and past episodes of unipolar depression and other mental disor-

Table 1
Comparison of Demographic Characteristics of Sample (N = 2046)

Characteristic	%
Race	
Caucasian	99.0
Other	1.0
Sex	
Female	62.7
Male	37.3
Age (years)	
18–24	2.8
25–34	11.5
35–44	4.4
45–54	15.0
55–64	34.3
65 and older	32.0
Marital status	
Married	68.9
Divorced/separated	11.4
Widowed	12.3
Never married	7.4
Employment	
Employed	43.8
Unemployed and seeking	9.6
Retired/unemployed and not seeking	46.6
Education	
Less than high school	6.9
High school diploma	25.9
Some college	36.3
College degree	30.8
Income (per year)	
≤$4,000	13.8
$4,001–$8,000	19.2
$8,001–$12,000	21.6
$12,001–$16,000	19.9
>$16,000	25.4

Note. Income data were unavailable for Sample 4.

ders. Regardless of whether a subject met criteria for a present episode, the interviewer probed for past episodes. The diagnoses were based on the criteria provided by the Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978). Earlier studies (Mazure & Gershon, 1979; Spitzer et al., 1978; Weissman & Myers, 1978a) have indicated that the SADS–RDC procedure provides a moderately reliable and valid method for making retrospective diagnoses of psychiatric disorders for both psychiatric patients and for nonpatient samples, with measures of reliability generally ranging from .8 to above .9.

The training of the interviewers and other details of the procedure have been described by Amenson and Lewinsohn (1981) and Finnell (1980). Interrater reliability was comparable to that reported by Spitzer et al. (1978). Approximately 25% of all interviews were observed and independently rated by reliability coders, and interrater agreement was evaluated by means of the weighted kappa statistic (Cohen, 1960). Kappas were .91 for Samples 1 and 2, .84 for Sample 3, and .88 for Sample 4.

In the present study a subject was considered to be or to have been depressed if the RDC criterion for major, minor, or intermittent depressive disorder (i.e., pure unipolar depression) was met. Persons were excluded if a current or past diagnosis of bipolar depression or schizoaffective disorder was made. Of the 2,046 subjects who were interviewed, 1,012 were diagnosed as having at least one current or previous episode of unipolar depression. The mean age of the 1,012 subjects was 52.0 years (SD = 15.4; range = 18–88), and 73.5% were female.

The majority of the subjects did not report being in treatment during an episode. Those who indicated that they had received treatment reported themselves as being in different types and combinations of treatments (antidepressants, hospitalization, counseling, psychotherapy, marital therapy, assertion training, etc.) for varying periods of time, and no attempt was made to incorporate treatment as a variable into the statistical analyses.

Statistical Considerations: Life Table Method

The Life Table method (Anderson et al., 1980; Kalbfeisch & Prentice, 1980) was used to describe the risks associated with different ages of experiencing an initial episode of depression. The Life Table method is applicable when a sample of subjects is followed longitudinally either to the occurrence of a response (e.g., an episode of depression) or to the termination of data collection (i.e., no experience of a depressive episode before or at the time of the interview). The Life Table method is unique in its ability to use data from cases for whom the response has not occurred at the time of the interview (i.e., censored cases). The method calculates the probability of a first episode of depression during different age ranges based on the number of participants who become depressed out of the total number of participants at risk. By convention, participants who are censored during a given age interval are counted as at risk for half of the interval.

The Life Table method can also be used to compute the cumulative probability of surviving as a function of age. The cumulative proportion surviving is the probability of survival from the first interval at risk to the last interval of the follow-up. At any given age range, the cumulative proportion surviving is calculated as the product of all previous interval-specific probabilities of survival. The survival pattern for two or more groups may be compared by several different methods (Fleiss, 1981). In the present study, the survival curves obtained for the men were compared to those obtained for the women at all points simultaneously by using a summary chi-square procedure (Mantel, 1966). The statistic used, the Mantel-Cox Test (Benedetti, Yuen, & Young, 1983), incorporates a correction for discontinuity and may be evaluated by means of chi-square tables with one degree of freedom to test for the significance of the differences between the two groups.

The Life Table technique also permits the calculation of a hazard rate and its standard error for any age interval. The hazard rate is a conditional density rate in that it is the probability that an individual becomes depressed during an age interval given that the individual has survived to the beginning of the age interval (Gross & Clark, 1975). The hazard rate describes the "instantaneous" risk of depression at each age interval for persons still at risk. As per the null hypothesis, the hazard rate would be expected to be constant across the age intervals, indicating that the risk for a first episode of depression is constant across the life span.

The Life Table analysis was conducted on the present data by use of the BMDP1L program (Benedetti et al., 1983). The program provided separate survival and hazard functions for the female and male subjects. In the present analysis, the life span was divided into 18 age intervals. Each interval was 5 years in length except for the last interval (85 years and older).

Results

The major focus of the present study was to determine if the probability of developing an initial episode of depression changes as a function of age. This question can be answered most directly by examining the hazard function, because the latter describes the way in which the probability for a first episode of depression changes with age. Figure 1 is a presentation

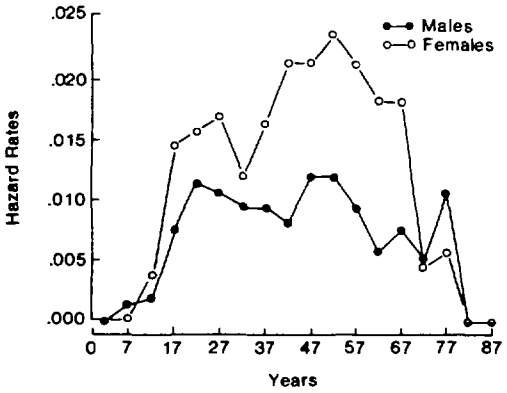

Figure 1. Probability that an individual will become depressed during an age interval given that the individual has not been depressed prior to the age interval.

of the hazard functions associated with the male and female participants in each of the 18 age intervals.[2] The hazard functions associated with the male and female participants were examined by separate chi-square tests in order to determine if either set of hazard rates differed as a function of age. The null hypothesis was that the expected hazard rates would not change across the age intervals. Both chi-squares were calculated for the 17 age intervals from 0 to 84 years. The last interval (85 years and over) was omitted because its range was not fixed at 5 years. Both chi-squares were highly significant: For the females, $\chi^2(16, N = 1{,}287$ females, 757 males$) = 44.38, p < .001$; for the males, $\chi^2(16, N = 1{,}287$ females, 757 males$) = 22.75, p < .001$. Clearly, the chi-square tests indicate that the hazard rates varied widely as a function of age for both males and females.

Visual inspection of the hazard functions reveals certain similarities in the overall patterns for males and females. For both sexes, the hazard rates are very low for the first three age intervals (0–4, 5–9, and 10–14 years) and then increase in the next two age intervals (15–19 and 20–24 years). For both the males and females, the hazard rates peak in the age range of 45 to 55 years and then decrease until the hazard rates are zero for all individuals 80 years and older. Thus, for both males and females, the ages at the lowest risk for a first episode of depression are under 20 years and over 75 years of age.

Despite the similarity in the hazard functions of males and females at the very young and very old ages, there are several important differences between the hazard functions associated with each sex. First, the overall hazard rates are much higher for females than males. A comparison of the survival curves of the males and females as per the Mantel-Cox statistic shows this difference to be statistically significant, $t(1) = 69.9, p < .001$. The difference in the hazard rates and the survival curves between the sexes reflects the fact that 57% of the females who were interviewed were diagnosed as having a current or past episode of depression whereas only 37% of the males received such a diagnosis.

An additional analysis was performed in order to determine if the mean age at the first onset of depression differed for males and females. Because the ages of the male and female participants at the time of the interviews were not the same, and because any differences in onset age might be due to differences in the ages at the time of the interviews, an analysis of covariance was performed on the first onset ages for depression with age at the time of the interview serving as the covariant. This analysis revealed that there was no difference in the mean first onset age of depression for males (35.1 years) compared to females (36.7 years), $F(1, 1010) = 3.4$.

A second important difference in the hazard functions of the male and female participants is found in the changes that occur in the hazard rates between the ages of 20 and 75 years. For the females, the hazard rates increase during adolescence and continue to increase until approximately age 30. At the 30- to 34-year interval, there was a slight decrease in the hazard rates, which was then followed by a dramatic increase in the hazard associated with the age intervals 35–39 and 40–44 years. The hazard rates peaked during the age interval 50–54 years and remained high until the 65–69 age interval. For males there was also a steep increase in the hazard rates during adolescence but, unlike the females, the hazard rates remained relatively stable from the age of 20 until the age of 54 years. The hazard rate peaked between the ages of 45 and 55 years for the males and then decreased until the age interval 75–79 years.

Discussion

The main finding of this study is that the risk for developing an initial episode of unipolar depression is very low during childhood, increases dramatically during adolescence, peaks at the middle years, and decreases during the elderly years. There were also interesting similarities and differences in the results for males and females. These findings, however, should be treated cautiously, and a number of limitations of the sample, and the retrospective nature of the data, need to be recognized.

Our subjects were a largely self-selected community sample that was not representative of the population at large. In order to maximize individuals with a history of depression, the subjects had been screened for high scores on a scale of depression symptoms and thus were a high-risk sample. Not surprisingly, the lifetime prevalence of depression in our sample (30.3%) contrasts sharply with the much lower figures (e.g., 9.9% for New Haven, 5.8% for Baltimore, and 9.3% for St. Louis) reported by Robins et al. (1984) for the Epidemiological Catchment Area Program. Our sample also did not include individuals who were hospitalized at the time of the study. For all of these considerations the hazard rates reported in our study probably overestimate the values that would have been obtained with a randomly selected sample.

[2] The exact proportions for each interval (number of initial episodes/number at risk) for the data in Figure 1, from youngest to oldest interval, were as follows: 1/1,287, 2/1,286, 25/1,284, 87/1,258, 86/1,166, 87/1,065, 55/958, 69/890, 81/814, 74/724, 68/613, 48/474, 29/336, 17/199, 2/88, 1/36, 0/12, and 1/2 for females and 0/757, 4/757, 8/753, 28/744, 38/710, 35/660, 27/608, 26/570, 22/537, 30/508, 26/454, 17/376, 8/276, 6/168, 2/86, 2/38, 0/14, and 0/4 for males.

Another limitation of the present study concerns the definition of a depressive episode. To be counted as an episode, the depression had to meet the fairly rigorous criteria of the RDC (Spitzer et al., 1978), and thus milder episodes of depression were not counted. It is unknown if vulnerability to depressive symptoms or mild episodes of depression differs from that associated with depressive episodes meeting the RDC criteria.

The final limitation of the present study concerns the use of retrospective interviews to make clinical diagnoses. The validity of retrospective information is dependent on the accuracy of the memories of those who are interviewed. Because it is reasonable to assume that older memories are less accurate than more recent ones, it is possible that hazard rates for the young years may have been underestimated.

There does not appear to be a simple solution to all of these problems. Ideally, epidemiological data should be collected in prospective studies in which cohorts are followed over many years.

Despite the above limitations, the present data strongly suggest that one's vulnerability to an initial episode of unipolar depression varies as a function of age. Overall the Life Table analysis indicates that the risk of developing an initial episode of unipolar depression is very low during childhood, increases during adolescence, and decreases during the elderly years. Consequently, the results suggest that the lowest risks for first episode of unipolar depression occur at the extremes of the life span. This conclusion is consistent with results obtained by other investigators. Thus, Kashani and Simonds (1979) found that the incidence of depression is relatively low in early childhood, and Gurland (1976), on the basis of a review of various epidemiological studies, concluded that the least vulnerable ages for depression are before 10 and after 60 years. The counterintuitive decrease of the incidence and prevalence of depression beyond a certain age has also been found in several recent studies (Comstock & Helsing, 1976; Craig & Van Natta, 1979; Teri & Lewinsohn, 1983; Robins et al., 1984). It is clear that theories of unipolar depression must account for what appears to be a curvilinear relationship between the incidence or vulnerability for depression and age.

The results also revealed interesting similarities and differences in the findings for males and females. First of all, in spite of the overall elevated hazard rates for females, the average onset age for males and females did not differ. Thus, the elevated prevalence of unipolar depression among women cannot be explained on the basis of an earlier age at first onset. It is also noteworthy that the hazard rates for males and females did not differ before 9 and after 69 years of age. Between those two ages, however, the relationship between age and the probability of an initial episode of unipolar depression varied as a function of gender. Examination of the hazard function revealed that for females the hazard rates increased during adolescence and generally continued to increase during adulthood until the rates peaked at approximately 50 years of age. For males, the hazard rates increased during adolescence but generally stabilized at 20 years and remained level throughout adulthood except for a small peak at the age range of 45 to 49 years. As with the females, the male hazard rates began to decrease after the age of 50. These age patterns are generally consistent with results obtained by other investigators. For example, Weissman and Myers (1978b) found that the prevalence of depression in women peaked during the age range of 35 to 45 years. For men, the pattern was less evident. Essen-Möller and Hagnell (1961) found that women peak in incidence of depression between the ages of 30 and 50; in men incidence rates are more stable across the adult years.

The results of the present investigation need to be cross validated, ideally in prospective studies. In the meantime they raise a number of interesting theoretical as well as clinical questions: What is responsible for the elevated vulnerability to depression during the middle years? How does one account for the different pattern of results for males and females? Are there significant clinical and etiological differences in persons who become depressed at different points in the life cycle?

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Received February 13, 1986
Revision received June 11, 1986 ■

Journal of Abnormal Psychology
1993, Vol. 102, No. 1, 133-144

0021-843X/93/$3.00

Adolescent Psychopathology: I. Prevalence and Incidence of Depression and Other *DSM-III-R* Disorders in High School Students

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Data were collected on the point and lifetime prevalences, 1-year incidence, and comorbidity of depression with other disorders (*Diagnostic and Statistical Manual of Mental Disorders* [3rd ed., rev.]) in a randomly selected sample (n = 1,710) of high school students at point of entry and at 1-year follow-up (n = 1,508). The Schedule for Affective Disorders and Schizophrenia for School-Age Children was used to collect diagnostic information; 9.6% met criteria for a current disorder, more than 33% had experienced a disorder over their lifetimes, and 31.7% of the latter had experienced a second disorder. High relapse rates were found for all disorders, especially for unipolar depression (18.4%) and substance use (15.0%). Female subjects had significantly higher rates at all age levels for unipolar depression, anxiety disorders, eating disorders, and adjustment disorders; male subjects had higher rates of disruptive behavior disorders.

In the past 25 years, substantial progress has been made in the understanding of depression among adults. This progress has been facilitated by a number of conceptual and methodological advances, the more important of which have been (a) explicit diagnostic criteria such as the Research Diagnostic Criteria (RDC; Spitzer, Endicott, & Robins, 1978) and the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*; American Psychiatric Association, 1980); (b) accompanying structured and semistructured standardized interview schedules such as the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978), the Diagnostic Interview Schedule (DIS; Robins, Helzer, Crougham, Williams, & Spitzer, 1981), and the Longitudinal Interval Follow-Up Evaluation (LIFE; Shapiro & Keller, 1979); and (c) the distinction between bipolar and unipolar depression and the further partition of the latter into major depression and dysthymia.

The study of affective disorders in children and adolescents may be said to have begun when a number of investigators (Carlson & Strober, 1978; Cytryn & McKnew, 1972; Kovacs & Beck, 1977; Poznanski & Zrull, 1970; Puig-Antich & Chambers, 1983; Rutter, Schaffer, & Shepherd, 1975; Weinberg, Rutman, Sullivan, Penick, & Dietz, 1973) showed that depressive disorders can and do occur in children and adolescents.

The study of depression among adolescents is important because adolescence is a crucial period of life that strongly influences a person's options for critical life choices. Adolescent depression predicts future adjustment problems in the areas of marriage, dropping out of school, unemployment status, involvement with drugs, delinquent behavior, being arrested, being convicted of a crime, and being in a car accident (Carlson & Strober, 1979; Chiles, Miller, & Cox, 1980; Kandel & Davies, 1986; Newcomb & Bentler, 1988; Paton, Kessler, & Kandel, 1977). Moreover, having an episode of depression early in life substantially increases the risk for future episodes during adolescence (Kovacs, Feinberg, Crouse-Novack, Paulauskas, & Finkelstein, 1984) and later in life (Harrington, Fudge, Rutter, Pickles, & Hill, 1990).

Given the serious consequences of adolescent depression, knowledge about the magnitude of depression in this population is important. Therefore, it is not surprising that a fairly large number of epidemiological studies have been conducted. These studies have been evaluated in several recent reviews (Angold, 1988; Fleming & Offord, 1990; Offord, 1985; Rutter, 1988; Schwartz-Gould, Wunsch-Hitzig, & Dohrenwend, 1981). Unfortunately, with some exceptions (Canino et al., 1987; Kashani, Beck, et al., 1987; McGee et al., 1990; Velez, Johnson, & Cohen, 1989; Whitaker et al., 1990), most of the studies using rigorous diagnostic procedures and criteria have been conducted with younger children and information about the epidemiological dimensions of depression in adolescents is sparse. The prevalence rates reported in studies of depression among adolescents ranged from 8.7% for 14- to 16-year-old adolescents in Puerto Rico (Bird et al., 1988) to 2.3% for 15-year-olds in the Dunedin, New Zealand, study (McGee et al., 1990). These inconsistencies were probably attributable to differences in case definition, sample composition, and sample size. For example, in the New Zealand study, children could receive a "strong,

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This research was partially supported by National Institute of Mental Health Grant MH40501. Preliminary findings were presented at the annual meeting of the American Public Health Association held in Boston in November 1988.

We wish to thank Beth Blackshaw, Debbie Blanchard, Jackie Bianconi, Barb Eisenhardt, Sheila Foulkes, Tina Hazzard, Jeanette Healey, Trish Hoerth, Wendy Hogan, Candance Holcomb, Sue Jordan, Patrice Kangas, Mara Levin, Renee Marcy, Katie Newman, Laila Pettersen, Julie Redner, Susan Reno, Diane Rosen, Mary Schnebly, Pat Stamps, Keith Smolkowski, Kevin Smolkowski, Nancy Stevens, Heidi Walker, and Jean Wilson for their contribution to this project.

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pervasive" diagnosis if they met revised *DSM-III* (*DSM-III-R*: American Psychiatric Association, 1987) criteria from more than one informant, a "situational" diagnosis if they met criteria from only one informant, or a "weak, pervasive" diagnosis by combining symptoms reported by all informants. The number of subjects also varied markedly and sample sizes were often too small to yield stable results and to permit fine-grained comparisons between age and gender groups. Thus, the Kashani, Carlson, et al. (1987) prevalence of 8% was based on a sample size of 150, and the Bird et al. (1988) sample was based on 777 children (aged 4–16), 386 of whom were interviewed. It is also important to note that none of these researchers presented information about the incidence of depression (i.e., the rate of *new* cases of depression in the population during a specified period of time) for which a prospective design is needed. Similarly, none of the researchers provided basic information on things such as the duration of episodes and multiple episodes.

In this article we report findings from the Oregon Adolescent Depression Project (OADP), a large-scale, community-based investigation of the epidemiology of depression and other psychiatric disorders among a high school population. The distinguishing characteristics of the OADP are as follows: (a) a community-based epidemiological survey; (b) a longitudinal, prospective design, with follow-up assessments reported after 1 year; (c) the use of contemporary diagnostic criteria (*DSM-III-R*); and (d) the inclusion of diagnostic information encompassing a broad range of psychiatric disorders. The research satisfies the criteria outlined by Angst, Dobler-Mikola, and Binder (1984), Fleming and Offord (1990), Hirschfeld and Cross (1982), and Mitchell, McCauley, Burke, and Moss (1988) for generating more reliable and valid data on the epidemiology of affective and other psychiatric disorders.

We present data on the prevalence (point and lifetime), incidence (1 year), and comorbidity for affective and selected other psychiatric disorders in middle-to-older (14–18) adolescents. We also present information on other epidemiological characteristics such as severity, onset age, and duration, as well as the association of the occurrence of depression with age and gender. Given that adolescents had significantly more depressive disorders than children in studies that included both age groups (Bird et al., 1988; Fleming, Offord, & Boyle, 1989; Rutter, Tizard, Yule, Graham, & Whitmore, 1976) and that the percentage of deaths attributable to suicide increased sharply between 15 and 19 years of age (National Center for Health Statistics, 1989), we hypothesized an increase in depression during adolescence. Furthermore, given that there was no gender difference at the youngest ages (Fleming et al., 1989; Kashani et al., 1983; Velez et al., 1989) and that by adulthood there was a 2:1 female preponderance (Weissman & Myers, 1978), we also hypothesized an interaction between age and gender such that prevalence rates for female subjects would increase disproportionately with increasing age.

Method

Overview

A diagnostic interview was conducted with each adolescent at point of entry into the study (Time 1). Immediately prior to the interview, subjects completed a questionnaire that included measures of psychosocial constructs (Hops, Lewinsohn, Andrews, & Roberts, 1990). A screening instrument was also completed twice, once as part of the questionnaire and again approximately 1 week later. Parents provided information regarding their education and occupation via short mail questionnaires. Approximately 1 year after their initial assessment (Time 2), participants were reassessed via interviews and questionnaires. Written informed consent was obtained from all adolescent participants and from parents or guardians. Each participant received $25 and had $5 placed into their school fund for each assessment. This sample has been previously described in Lewinsohn, Rohde, Seeley, and Hops (1991); Rohde, Lewinsohn, and Seeley (1991); and Roberts, Lewinsohn, and Seeley (1991).

Subjects

The population for this study was the total enrollment (approximately 10,200) of nine high schools (Grades 9–12) in two urban communities (metropolitan populations of approximately 200,000) and three rural communities in west central Oregon. Schools were chosen because of their location (within 100 miles of the project). All of the 10 schools we approached agreed to participate, although 1 declined later.

Three cohorts were recruited in 1987, 1988, and 1989 and consisted of 352, 864, and 494 students, respectively. The total completed Time 1 sample size was 1,710 and the completed Time 1–Time 2 panel was 1,508. The following sampling strategy was used.

1. At the beginning of each academic year, parents of all (including those in special classes) students enrolled in each of the participating schools were sent a letter describing the proposed research and asking for permission for their offspring to be included in the potential sample.

2. Students whose parents did not return the "decline" card (passive consent procedure) constituted the sampling frame. The proportion declining at this stage ranged from 4% (Cohort 3) to 8% (Cohorts 1 and 2).

3. Sampling fractions of 10%, 18.5%, and 20% were used for each cohort, and sampling within each school was proportional to the size of the school, the size of the grade within school, and the gender within the grade.

The selected students and their parents received two letters, the first welcoming them to the study and a second informing them that they would receive a phone call within the next few days. The caller attempted to schedule the adolescent for an interview. Participants without phones were sent a note asking them to contact the institute. If there was no response, a member of the staff was sent to the student's home or school to explain the project and to schedule an interview.

Response Rates

Because parental involvement in the diagnostic interview was required in Cohort 1, the decline rate among those for whom passive consent had been obtained earlier was relatively high (48%). This requirement was dropped for Cohorts 2 and 3, and the respective decline rates dropped to 38% and 32%, respectively, resulting in an overall participation rate of 61%. To assess differences between participants and decliners, we obtained brief demographic information on key variables from the latter by telephone, including reasons for decline. In most cases, adolescents expressed disinterest; 12% were overruled by their parents, 12% thought the assessment was too personal, and 4% provided various other explanations, including being too shy, too busy, and so forth. We found a significant but small relation between grade level and the reason for decline, $\chi^2(9, N = 938) = 21.4$, $p < .05$. Younger students were more likely to be overruled by their parents, whereas

older students were more likely to decline because they were not interested.

Representativeness of the Sample

Several checks on the representativeness of the sample were made. First, we compared the demographic characteristics of the sample with the 1980 census and found no differences on gender, ethnic status, or parental education level. Not surprisingly, our sample had significantly more children under 18 years of age in the home and a slightly higher proportion of two-parent families. Second, we compared our participants with those who declined on demographic information obtained from decliners by telephone. Differences were minimal. Families were similar on gender of head of household, family size, and number of parents in the household. Although the decliners' mean socioeconomic status (SES) was significantly lower than that of the participants, $F(1, 2023) = 97.0$, $p < .001$, both represented the middle class. Significant effects were found for grade and gender; 12th graders (67%) were more likely to participate than 9th graders (59%), $\chi^2(3, N = 2,571) = 10.5$, $p < .05$, and female students (68%) were more likely to participate than male students (60%), $\chi^2(1, N = 2,575) = 17.3$, $p < .001$.

As an additional check on the representativeness of the sample, we assessed 100 Cohort 3 subjects who refused initially but responded to a $100 inducement. This sample did not differ on type or number of current and lifetime clinical diagnoses, number or extent of clinical symptoms, race, current employment status of parents, and questionnaire variables. However, compared with 100 randomly selected participants, decliners were less likely to be from two-parent families (66% vs. 74%), $\chi^2(1, N = 200) = 6.86$, $p < .05$; their parents had less education, $F(1, 175) = 6.5$, $p < .05$; and they reported a lower grade point average (2.9 vs. 3.1), $F(1, 189) = 4.6$, $p < .05$. All of these analyses suggested that, with minor exceptions, the students in our sample were representative of high school students in western Oregon.

To evaluate the degree to which the Time 1–Time 2 panel ($n = 1,508$) might have become biased, we compared those who did not participate at Time 2 ($n = 202$) with the panel subjects on critical Time 1 variables. There were small but statistically significant differences. The Time 2 participants were slightly higher on parental SES, $F(1, 1431) = 11.6$, $p < .001$; number in household, $F(1, 1683) = 4.0$, $p < .05$; proportion of female students (54% vs. 40%), $\chi^2(1, N = 1,710) = 13.2$, $p < .001$; and parental educational level, $F(1, 1544) = 14.1$, $p < .001$. However, the two groups did not differ on measures of psychopathology (e.g., number of suicide attempts, number of episodes of current and past disorders including depression), the self-report depression measures, race, or grade level. Significantly higher attrition rates were noted, however, for subjects who had a history of disruptive behavior disorders (16.8% vs. 10.8%), $\chi^2(1, N = 1,710) = 30.7$, $p < .001$. Also, male students with a history of substance use disorders had a significantly higher attrition rate (26.1% vs. 13.7%), $\chi^2(1, N = 819) = 7.7$, $p < .01$.

Differences between high schools in rural and urban districts and between cohorts on prevalence (point and lifetime) of depression and other disorders and scores on the Beck Depression Inventory (BDI) and the Center for Epidemiological Studies Depression Scale (CES-D) were small and did not attain statistical significance. Consequently, we combined schools and cohorts into a single group.

The demographic characteristics of the Time 1 sample were as follows: Their mean age was 16.6 years ($SD = 1.2$), 52.9% were female, 8.9% were non-White, 71.3% were living with two parents, 53% were living with biological parents, 14.9% were in the 9th grade, 27.2% in the 10th grade, 26.3% in the 11th grade, 31.6% in the 12th grade, and overall 12.3% had repeated a grade. Parents' occupational status consisted of 2.5% unskilled, 8.0% semiskilled, 21.2% skilled, 57.9% minor professional, and 10.3% professional. Parental education consisted of 16.5% who did not complete high school, 16.5% who completed high school, 35.5% with partial college education, and 20.3% with an academic or professional degree.

Diagnostic Interview at Time 1

A semistructured diagnostic interview was conducted with each adolescent using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Chambers et al., 1985; Puig-Antich & Chambers, 1983). Our version of the K-SADS combined features of the Epidemiologic Version (K-SADS-E; Orvaschel, Puig-Antich, Chambers, Tabrizi, & Johnson, 1982) and the K-SADS-P (Present Episode). With the assistance of Puig-Antich, we developed an interview schedule that used the K-SADS-E strategy to assess past episodes and the K-SADS-P strategy to assess current episodes as per *DSM–III–R* criteria. Our protocol included symptom severity ratings for all episodes, past or present. Following the procedures developed by Endicott, Cohen, Nee, Fleiss, and Sarantakos (1981), the interviewers also completed a 14-item version of the Hamilton Rating Scale for Depression (Hamilton, 1960) for any current or past episode of depression basing their ratings on responses to the depression items of the K-SADS-E. The K-SADS interviews with the adolescents provided the information for the ratings for the presence of symptoms, diagnoses for any current and past episodes of depression and other disorders, age at onset, and the duration of each episode of disorder.

Most of our 27 interviewers had advanced degrees in clinical or counseling psychology or social work and completed a 70-hr didactic and experiential course in diagnostic interviewing. Prior to conducting interviews, all interviewers were required to demonstrate a minimum kappa of .80 across all symptoms for at least two consecutive training interviews and on one videotaped interview of an adolescent with evidence of psychopathology. Procedures were set up to minimize interviewer drift and maintain adequate reliabilities across the length of the study. All interviews were videotaped. Reliability ratings were obtained on a randomly selected 12% by an experienced interviewer. In addition, a child psychiatrist[1] who was unaware of subjects' diagnoses provided symptom ratings and diagnoses of videotapes for seven participants randomly selected over time by the interviewer supervisor. The percentage of agreement between the interviewers and the experienced interviewer, and the kappas for each of the major disorders for current, lifetime, and between Time 1 and Time 2 diagnoses were computed. With the exceptions of diagnoses for current and lifetime anxiety disorders (κs = .60 and .53, respectively), and for lifetime diagnoses of dysthymia (κ = .58) and eating disorders (κ = .66), all of the kappas were equal to or greater than .80. The degree of agreement between the symptom ratings of our interviewers and the child psychiatrist on the seven videotaped cases was reflected by averaged kappas of .83 (range = .69–1.0) and .72 (range = .44–.90) for the current and for the worst past episode, respectively. Within 2 weeks of an interview, the symptom checklist and corresponding diagnoses were evaluated for consistency. Discrepancies were discussed with individual interviewers, and weekly discussion sessions were held between the supervisor and the interviewers to review the interview procedures and diagnostic criteria.

Diagnostic Interview at Time 2

At the second (Time 2) diagnostic interview, scheduled approximately 1 year after Time 1 (the mean duration of interval was 13.8 months, $SD = 2.3$), the LIFE (Shapiro & Keller, 1979) was conducted individually with each participant. The LIFE interview elicits detailed information about the longitudinal course of all *DSM–III–R* disorders

[1] We wish to express our appreciation to William Sack.

present at Time 1, in addition to the onset of new disorders, by asking respondents to provide detailed information about their mental status since Time 1. Using careful probing, the interviewer establishes the approximate dates for critical transition points (i.e., offset of a previous episode, onset of a new episode). On the basis of this information, the interviewers made weekly ratings of symptom levels for each diagnosis assigned during the initial (Time 1) interview for each new episode of disorder. These ratings were made on a 6-point scale that indicated, for each week, if the participant (a) had continued to meet the *DSM-III-R* criteria for the index disorder (5 or 6); (b) had marked or moderate symptoms without meeting criteria (4); (c) experienced partial remission (3); (d) was in a residual state (2); or (e) had no residual symptoms (1). An existing episode was assumed to have ended by symptom ratings of 1 or 2 for 8 consecutive weeks. The interviewers also made symptom severity ratings for all episodes of disorder since Time 1. The interrater reliability of these diagnoses was high and comparable to that reported by the LIFE's authors (Keller et al., 1987). Because of the low frequencies of many disorders, we computed kappas across all disorders. The kappas for any versus no disorder at Time 2 and between Times 1 and 2 were .87 and .72, respectively.

By providing a rigorous definition of recovery, the SADS-LIFE methodology allowed for the relatively precise determination of the duration of episodes of disorder that existed at Time 1. The LIFE also probed for the occurrence of new disorders (i.e., since Time 1), the date of onset of new episodes of disorder, and intervals between different episodes of disorder. At the Time 2 interview, the interviewers also elicited information about and rated the presence and severity of depression symptoms and completed the Hamilton Rating Scale for Depression (Hamilton, 1960) for current symptoms and worst past symptoms in the Time 1–Time 2 interval.

The interviewers also made Axis V Global Assessment of Functioning (GAF; *DSM-III-R*, American Psychiatric Association, 1987) ratings for the current level of functioning (i.e., at the Time 2 evaluation) and the highest level of functioning during the period between Times 1 and 2. The interviewers followed the *DSM-III-R* direction to give an overall judgment of the adolescent's psychological, social, and occupational (academic) functioning and need for treatment. Thus, the GAF is a global judgment that combines symptom severity, social role functioning, and perceived need for treatment. The scale ranges from 1 to 90. Scores of 81–90 represent very good functioning in all areas, whereas 1–10 represents severely impaired functioning.

Ratings by Clinical Child Psychiatrists

To provide information about the clinical significance of episodes of *DSM-III-R* affective disorders detected by the K-SADS methodology, three child psychiatrists' rated all subjects with a current diagnosis of affective disorder at Time 1 ($n = 50$) and those who developed an episode of affective disorder between Times 1 and 2 ($n = 121$) for (a) "current level of functioning," (b) "highest level of functioning during the past year," (c) "severity of depression," and (d) "need for treatment." These ratings were done on specially developed and carefully anchored 6- or 7-point scales for each of the dimensions. The psychiatrists were instructed to use the adolescent patients from their clinical practices as a frame of reference. Our scales were closely modeled after existing scales (e.g., the Children's Global Assessment Scale; Shaffer et al., 1983). The ratings were made on the basis of the intake notes written by the K-SADS interviewers. These notes (two–three pages) included a listing of all current and past diagnoses and symptoms; onset age; episode duration; and a summary of the subjects' educational, social, and health history and of the family environment. About one third were rated by more than one psychiatrist and interrater reliabilities—averaged across rater pairs—ranged from .88 (for severity) to .58 (for need for treatment).

Other Measures

The Center for Epidemiologic Studies-Depression Scale (Radloff, 1977). The CES-D was included as a self-report measure of depressive symptomatology. This 20-item scale assesses the occurrence of depressive symptoms during the past week. The scale has been shown to have adequate psychometric properties on an adolescent sample (Roberts, Andrews, Lewinsohn, & Hops, 1990).

The Beck Depression Inventory (Beck, 1967; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The BDI, another self-report measure of depression, was also included. This 21-item scale assesses the presence of depressive symptoms during the past week and has good psychometric properties when used with adolescent samples (Teri, 1982; Roberts et al., 1990, 1991).

Results

Point and Lifetime Prevalence of DSM-III-R Disorders

Tables 1 and 2 show the point and lifetime prevalence by gender, respectively, for each of the major *DSM-III-R* diagnostic categories at Times 1 and 2. In interpreting the results of Tables 1 and 2, it is important to keep in mind that the point and lifetime prevalences for specific disorders included subjects who had more than one disorder. Of those with a lifetime history of a mental disorder ($n = 634$), 31% reported having experienced another mental disorder; among the adolescents with a lifetime history of unipolar depression ($n = 348$), 42% reported having experienced another mental disorder; and among those with a current (at Time 1) diagnosis of unipolar depression ($n = 50$), 66% had a history of another mental disorder, and 34% reported having experienced a previous episode of depression. The degree of comorbidity (over the lifetime) between all of the major *DSM-III-R* disorders is shown in Table 3. As can be seen, there was substantial comorbidity between all of the disorders except for adjustment disorder, which was comorbid only with substance dependence and abuse. A diagnosis of adjustment disorder made it less likely that subjects would have had diagnoses of unipolar depression, disruptive behavior disorders, bipolar disorders, or eating disorders. A likely explanation is that, as per the *DSM-III-R*, meeting criteria for any specific mental disorder is an exclusion criterion for adjustment disorder.

Comparisons of the Time 1 and Time 2 point prevalence rates for the Time 1–Time 2 panel ($n = 1,508$), by means of the critical ratio z, indicated that at Time 2, when the participants were 1 year older, there had been an increase in the point prevalence of alcohol dependence and abuse ($z = 2.60$, $p < .01$) and a decrease in the point prevalences for anxiety ($z = 3.65$, $p < .001$) and disruptive behavior disorders ($z = 3.03$, $p < .01$). None of the other Time 1–Time 2 comparisons was significant. In the presentation and discussion of results, we focus on the Time 1 data. The Time 1 sample was larger and some additional biases were introduced into the Time 1–Time 2 panel.

Almost 10% of the sample met criteria for a current psychiatric disorder as defined by the *DSM-III-R*, and more than 33% experienced a disorder over their lifetime. Major depressive dis-

[2] We wish to express our appreciation to Susan Colasurdo, Jerome Vergamini, and William Sack.

Table 1
Point Prevalence Rates (PPRs) of DSM-III-R Disorders by Gender

	Time 1 (%)						Time 2 (%)					
	Female[a]		Male[b]		Total[c]		Female[d]		Male[e]		Total[f]	
Psychiatric diagnosis	PPR	*SE*	PPR	*SE*	PPR	*SE*	PPR	*SE*	PPR	*SE*	PPR	*SE*
Unipolar depression	3.82	0.64*	1.95	0.48	2.92	0.41	3.70	0.66	2.58	0.60	3.18	0.45
Major depression	3.37	0.60*	1.71	0.45	2.57	0.38	3.58	0.65	2.58	0.60	3.12	0.45
Dysthymia	0.56	0.25	0.49	0.24	0.53	0.18	0.25	0.17	0.00	0.00	0.13	0.09
Bipolar disorder	0.45	0.22	0.12	0.12	0.29	0.13	0.25	0.17	0.14	0.14	0.20	0.11
Anxiety disorders	4.71	0.71***	1.47	0.42	3.16	0.42	1.98	0.49*	0.57	0.29	1.33	0.29
Panic	0.45	0.22	0.24	0.17	0.35	0.14	0.62	0.28	0.00	0.00	0.33	0.15
Agoraphobia	0.67	0.27	0.12	0.12	0.41	0.15	0.12	0.12	0.00	0.00	0.07	0.07
Social phobia	1.57	0.42**	0.24	0.17	0.94	0.23	0.37	0.21	0.00	0.00	0.20	0.11
Simple phobia	2.02	0.47*	0.73	0.30	1.40	0.28	0.62	0.28	0.43	0.25	0.53	0.19
Obsessive–compulsive	0.11	0.11	0.00	0.00	0.06	0.06	0.00	0.00	0.00	0.00	0.00	0.00
Separation anxiety	0.34	0.19	0.00	0.00	0.18	0.10	0.12	0.12	0.00	0.00	0.07	0.07
Overanxious	0.67	0.27	0.24	0.17	0.47	0.17	0.12	0.12	0.14	0.14	0.13	0.09
Disruptive behavior disorder	*1.01*	*0.34***	*2.69*	*0.57*	*1.81*	*0.32*	*0.25*	*0.17*	*0.72*	*0.32*	*0.46*	*0.18*
Attention-deficit hyperactivity	0.34	0.19	0.49	0.24	0.41	0.15	0.00	0.00	0.14	0.14	0.07	0.07
Conduct	0.34	0.19	0.85	0.32	0.13	0.09	0.12	0.12	0.14	0.14	0.13	0.09
Oppositional defiant	0.45	0.22**	1.47	0.42	0.94	0.23	0.12	0.12	0.57	0.29	0.33	0.15
Substance use disorders	2.13	0.48	2.56	0.55	2.34	0.37	1.60	0.44**	3.87	0.73	2.65	0.41
Alcohol dependence and abuse	1.12	0.35	0.85	0.32	0.99	0.24	1.11	0.37	2.15	0.55	1.59	0.32
Drug dependence and abuse	1.57	0.42	2.08	0.50	1.81	0.32	0.62	0.28**	2.29	0.57	1.39	0.30
Cannabis	1.35	0.39	2.08	0.50	1.70	0.31	0.49	0.25**	2.15	0.55	1.26	0.29
Hard drugs	0.34	0.19	0.49	0.24	0.41	0.15	0.12	0.12	0.29	0.20	0.20	0.11
Cocaine	0.00	0.00	0.12	0.12	0.06	0.06	0.00	0.00	0.14	0.14	0.07	0.07
Amphetamines	0.22	0.16	0.24	0.17	0.23	0.12	0.12	0.12	0.00	0.00	0.07	0.07
Eating disorders	0.34	0.19	0.00	0.00	0.18	0.10	0.49	0.25	0.00	0.00	0.27	0.13
Anorexia nervosa	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Bulimia nervosa	0.34	0.19	0.00	0.00	0.18	0.10	0.49	0.25	0.00	0.00	0.27	0.13
Adjustment disorder	*1.12*	*0.35**	*0.24*	*0.17*	*0.70*	*0.20*	*1.36*	*0.41**	*0.29*	*0.20*	*0.86*	*0.24*
Other disorders	0.00	0.00	0.12	0.12	0.06	0.06	0.00	0.00	0.14	0.14	0.07	0.07
Any diagnosis	11.22	1.06*	7.81	0.94	9.59	0.72	8.02	0.96	7.76	0.69	7.82	0.69

Note. *DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders* (rev. 3rd ed.).
[a] $n = 891$. [b] $n = 819$. [c] $n = 1{,}710$. [d] $n = 810$. [e] $n = 698$. [f] $n = 1{,}508$.
* $p < .05$. ** $p < .01$. *** $p < .001$.

order (MDD) had the highest lifetime prevalence rate, followed by anxiety disorders. By contrast, anxiety disorders were the most prevalent at Time 1, followed by MDD. Psychoactive substance use and disruptive behavior disorders ranked third and fourth, respectively, for both point and lifetime rates.

The overall distributions of lifetime mental disorders for female and male students, respectively, with one or more episodes was 28.2% versus 22.5% for one, 9.8% versus 7.3% for two, 3.6% versus 1.8% for three, and 0.7% versus 0.2% for four or more episodes. The difference in the distribution between female and male students was significant, $\chi^2(5, N = 1{,}710) = 22.4$, $p < .001$, with more female subjects (42.3%) than male subjects (31.8%) having at least one disorder. The percentage of female and male students with one or more current and lifetime episodes of unipolar depression was 22.3 versus 11.4 for one and 4.9 versus 1.6 for two or more episodes. Although there was a trend for female students to be overrepresented in the multiple-episode group (17.8% vs. 12.3%), the trend was not significant, $\chi^2(2, N = 348) = 2.0$, $p > .05$.

The respective mean onset ages of MDD and dysthymia for female and male students were 13.9 ($SD = 2.7$) versus 14.2 ($SD = 2.5$) for MDD and 10.9 ($SD = 3.0$) and 11.3 ($SD = 2.7$) for dysthymia. Differences between the sexes on onset age were not significant for either MDD or dysthymia. Onset age for dysthymia was significantly lower than for MDD, $F(1, 345) = 56.2$, $p < .001$.

Mean duration (in weeks) was significantly longer for dysthymia ($M = 134.1$, $SD = 116.5$) than for MDD ($M = 23.6$, $SD = 51.4$), $F(1, 312) = 114.2$, $p < .05$. The duration of episodes of dysthymia was significantly longer for female students ($M = 157.5$, $SD = 129.5$) than for male subjects ($M = 82.3$, $SD = 55.1$), $F(1, 43) = 4.3$, $p < .05$. The difference in duration between female students ($M = 25.6$, $SD = 55.0$) and male students ($M = 18.8$, $SD = 41.1$) for MDD was not significant, $F(1, 267) = 0.97$, $p > .05$.

Incidence of Depression and Other Mental Disorders

Following Eaton et al. (1989) we distinguished between *first incidence*, the number of subjects who developed an episode for the first time in their lives divided by the total number of subjects who had never had the disorder at Time 1, and *total inci-*

Table 2
Lifetime Prevalence Rates (LPRs) of DSM-III-R *Disorders by Gender*

	Time 1 (%)						Time 2 (%)					
	Female[a]		Male[b]		Total[c]		Female[d]		Male[e]		Total[f]	
Psychiatric diagnosis	LPR	*SE*	LPR	*SE*	LPR	*SE*	LPR	*SE*	LPR	*SE*	LPR	*SE*
Unipolar depression	27.16	1.49***	12.94	1.17	20.35	0.97	32.96	1.65***	16.33	1.40	25.27	1.12
Major depression	24.80	1.45***	11.60	1.12	18.48	0.94	31.60	1.63***	15.19	1.36	24.01	1.10
Dysthymia	4.04	0.66*	2.32	0.53	3.22	0.43	4.07	0.70**	1.72	0.49	2.98	0.44
Bipolar disorder	0.56	0.25	0.61	0.27	0.58	0.18	0.62	0.28	0.72	0.32	0.66	0.21
Anxiety disorders	11.67	1.08***	5.62	0.81	8.77	0.68	12.35	1.16***	5.44	0.86	9.15	0.74
Panic	1.12	0.35	0.49	0.24	0.82	0.22	1.73	0.46*	0.57	0.29	1.19	0.28
Agoraphobia	1.12	0.35*	0.24	0.17	0.70	0.20	0.99	0.35*	0.14	0.14	0.60	0.20
Social phobia	2.36	0.51**	0.49	0.24	1.46	0.29	2.35	0.53**	0.43	0.25	1.46	0.31
Simple phobia	2.81	0.55*	1.10	0.36	1.99	0.34	2.96	0.60*	1.15	0.40	2.12	0.37
Obsessive-compulsive	0.34	0.19	0.73	0.30	0.53	0.18	0.37	0.21	0.86	0.35	0.60	0.20
Separation anxiety	5.84	0.79***	2.44	0.54	4.21	0.49	6.05	0.84***	2.29	0.57	4.31	0.52
Overanxious	1.80	0.45	0.73	0.30	1.29	0.27	1.98	0.49**	0.29	0.20	1.19	0.28
Disruptive behavior disorder	4.71	0.71***	10.13	1.06	7.31	0.63	4.20	0.71***	9.17	1.09	6.50	0.63
Attention-deficit hyperactivity	1.80	0.45**	4.52	0.73	3.10	0.42	1.73	0.46**	4.15	0.76	2.85	0.42
Conduct	1.68	0.43***	4.88	0.75	3.22	0.43	1.60	0.44**	4.01	0.74	2.72	0.42
Oppositional defiant	1.80	0.45	3.17	0.61	2.46	0.37	1.60	0.44	2.58	0.60	2.06	0.37
Substance use disorders	8.19	0.92	8.42	0.97	8.30	0.67	10.00	1.05	11.75	1.22	10.81	0.80
Alcohol	4.83	0.72	4.27	0.71	4.56	0.50	5.93	0.83	6.59	0.94	6.23	0.62
Drugs	5.84	0.79	6.72	0.88	6.26	0.59	7.65	0.93	8.74	1.07	8.16	0.71
Cannabis	4.26	0.68*	6.59	0.87	5.38	0.55	5.31	0.79*	7.88	1.02	6.50	0.63
Hard drugs	2.69	0.54	2.44	0.54	2.57	0.38	3.95	0.68	3.30	0.68	3.65	0.48
Cocaine	0.34	0.19	0.37	0.21	0.35	0.14	0.49	0.25	0.72	0.32	0.60	0.20
Amphetamines	1.80	0.45	1.22	0.38	1.52	0.30	2.47	0.55	1.29	0.43	1.92	0.35
Eating disorders	1.35	0.39**	0.12	0.12	0.76	0.21	2.35	0.53***	0.14	0.14	1.33	0.29
Anorexia nervosa	0.45	0.22	0.00	0.00	0.23	0.12	0.74	0.30*	0.00	0.00	0.40	0.16
Bulimia nervosa	0.90	0.32**	0.12	0.12	0.53	0.18	1.60	0.44**	0.14	0.14	0.93	0.25
Adjustment disorder	7.07	0.86	5.25	0.78	6.20	0.58	11.36	1.12***	6.45	0.93	9.08	0.74
Other disorders	0.34	0.19	0.24	0.17	0.29	0.13	0.37	0.21	0.29	0.20	0.33	0.15
Any diagnosis	42.09	1.65***	31.62	1.63	37.08	1.17	49.01	1.76***	35.67	1.81	42.84	1.27

Note. *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders* (rev. 3rd ed.).
[a] $n = 891$. [b] $n = 819$. [c] $n = 1{,}710$. [d] $n = 810$. [e] $n = 698$. [f] $n = 1{,}508$.
* $p < .05$. ** $p < .01$. *** $p < .001$.

dence, the total number of subjects who developed an episode of disorder (some of whom might have had an episode before) divided by the total number of subjects who were not in an episode at Time 1. In Table 4, we also provide the relapse rate, which indicates the incidence of depression in those who had a previous episode from which they had recovered at Time 1.

Selected Characteristics of Adolescents With a Diagnosis of Depression at Times 1 and 2

Adolescents with a diagnosis of MDD at Time 1 were compared with those with no current diagnosis of any disorder on a number of selected characteristics. MDD subjects were more likely to be female (68.2% vs. 51.2%), $\chi^2(1, N = 1{,}588) = 5.0$, $p < .05$; to have higher scores on the CES-D (33.0 vs. 16.1), $F(1, 1586) = 122.0$, $p < .001$, the BDI (19.7 vs. 6.4), $F(1, 1586) = 160.0$, $p < .001$, and the Hamilton Rating Scale for Depression (12.5 vs. 0.7), $F(1, 1575) = 1{,}660.8$, $p < .001$; to have reduced functioning according to the GAF (76.3 vs. 86.5), $F(1, 1386) = 90.0$, $p < .001$; and more likely to be in treatment (34.1% vs. 0.8%), $\chi^2(1, N = 1{,}588) = 284.1$, $p < .001$. The ratings by the child clinical psychiatrists indicated that approximately 15% of those with MDD had poor role functioning (defined as moderate to severe impairment) during the past year, with about 33% currently having poor role functioning. Most (88.6%) of the MDD adolescents were estimated to have moderate to severe depression, and 93.2% were judged to be in need of treatment. The Time 2 results were highly similar to the Time 1 results.

Effects of Gender and Age

We examined the associations of gender, age, and the interaction between age and gender with the point and lifetime prevalence and incidence of each of the psychiatric disorders using logistic regression. For each analysis, the criterion variable was the presence or absence of the disorder during the specified period. The significant associations of gender for point prevalence, lifetime prevalence, and total incidence have been noted in Tables 1, 2, and 3, respectively. As can be seen, female students were more likely to be diagnosed with a disorder than were male students, particularly unipolar depression, anxiety disorders, eating disorders, and adjustment disorder. By con-

Table 3
Lifetime Comorbidity Between the Major DSM–III–R *Disorders Occurring During Childhood and Adolescence (n = 1,710)*

	Disorder A							
Disorder B	Any n = 634 (37.1%)	Unipolar depression n = 348 (20.4%)	Anxiety n = 150 (8.8%)	Disruptive behavior n = 125 (7.3%)	Substance use n = 142 (8.3%)	Adjustment n = 106 (6.2%)	Bipolar n = 10 (0.6%)	Eating n = 13 (0.8%)
Any								
Prevalence ratio	—	42.8/20.9 = 2.0	61.3/31.0 = 2.0	60.0/32.1 = 1.9	66.2/31.3 = 2.1	29.2/32.9 = 0.9	70.0/36.7 = 1.9	76.9/36.6 = 2.1
Odds ratio	—	2.8* (2.2, 3.6)	3.5* (2.5, 5.0)	3.2* (2.2, 4.6)	4.3* (3.0, 6.2)	0.8 (0.5, 1.3)	4.0* (1.0, 15.6)	5.8* (1.6, 21.1)
Unipolar depression								
Prevalence ratio	34.3/15.6 = 2.2	—	48.7/17.6 = 2.8	34.4/19.2 = 1.8	49.3/17.7 = 2.8	12.3/20.9 = 0.6	30.0/20.3 = 1.5	69.2/20.0 = 3.5
Odds ratio	2.8* (2.2, 3.6)	—	4.4* (3.1, 6.3)	2.2* (1.5, 3.2)	4.5* (3.2, 6.4)	0.5* (0.3, 0.9)	1.7 (0.4, 6.5)	9.0* (2.2, 20.7)
Anxiety								
Prevalence ratio	16.0/5.1 = 3.1	21.0/5.7 = 3.7	—	16.0/8.2 = 2.0	16.2/8.1 = 2.0	8.5/8.8 = 1.0	40.0/8.6 = 4.7	38.5/8.5 = 4.5
Odds ratio	3.5* (2.5, 5.0)	4.4* (3.1, 6.3)	—	2.1* (1.3, 3.6)	2.2* (1.4, 3.6)	1.0 (0.5, 1.9)	7.1* (2.0, 25.4)	6.7* (2.2, 20.7)
Disruptive behavior								
Prevalence ratio	12.9/4.4 = 2.9	12.4/6.0 = 2.1	13.3/6.7 = 2.0	—	25.4/5.7 = 4.5	6.6/7.4 = 0.9	10.0/7.3 = 1.4	7.7/7.3 = 1.1
Odds ratio	3.2* (2.2, 4.6)	2.2* (1.5, 3.2)	2.1* (1.3, 3.6)	—	5.6* (3.7, 8.7)	0.9 (0.4, 2.0)	1.4 (0.2, 11.2)	1.1 (0.1, 8.2)
Substance use								
Prevalence ratio	16.1/4.3 = 3.7	20.1/5.3 = 3.8	15.3/7.6 = 2.0	28.8/6.7 = 4.3	—	10.4/8.2 = 1.2	20.0/8.2 = 2.4	30.8/8.1 = 3.8
Odds ratio	4.3* (3.0, 6.2)	4.5* (3.2, 6.4)	2.2* (1.4, 3.6)	5.6* (3.7, 8.7)	—	1.3 (0.7, 2.5)	2.8 (0.6, 13.2)	5.0* (1.5, 16.5)
Adjustment								
Prevalence ratio	5.6/6.5 = 0.9	3.7/6.8 = 0.5	6.0/6.2 = 1.0	5.6/6.2 = 0.9	7.7/6.1 = 1.3	—	0.0/6.2 = 0.0	0.0/8.2 = 0.0
Odds ratio	0.8 (0.5, 1.3)	0.5* (0.3, 0.9)	1.0 (0.5, 1.9)	0.9 (0.4, 2.0)	1.3 (0.7, 2.5)	—	0.9* (0.9, 1.0)	0.9* (0.9, 1.0)
Bipolar								
Prevalence ratio	1.1/0.3 = 3.7	0.9/0.05 = 1.8	2.7/0.4 = 6.8	0.8/0.6 = 1.3	1.4/0.5 = 2.8	0.0/0.6 = 0.0	—	0.0/0.6 = 0.0
Odds ratio	4.0* (1.0, 15.6)	1.7 (0.4, 6.5)	7.1* (2.0, 25.4)	1.4 (0.2, 11.2)	2.8 (0.6, 13.2)	0.9* (0.9, 1.0)	—	1.0 (1.0, 1.0)
Eating								
Prevalence ratio	1.6/0.3 = 5.3	2.6/0.3 = 8.7	3.3/0.5 = 6.6	0.8/0.8 = 1.0	2.8/0.6 = 4.7	0.0/0.8 = 0.0	0.0/0.8 = 0.0	—
Odds ratio	5.8* (1.6, 21.1)	9.0* (2.8, 29.4)	6.7* (2.2, 20.7)	1.1 (0.1, 8.2)	5.0* (1.5, 16.5)	0.9* (0.9, 1.0)	1.0 (1.0, 1.0)	—

Note. *DSM–III–R* = *Diagnostic and Statistical Manual of Mental Disorder* (rev. 3rd ed.). The numerator in the prevalence ratios is the percentage of adolescents with Disorder A who also have Disorder B. The denominator is the percentage of adolescents without Disorder A who have Disorder B. Numbers in parentheses in the odds ratio rows indicate the 95% confidence bounds.
* $p < .05$.

Table 4
One-Year First Incidence, Relapse, and Total Incidence Rates of DSM-III-R *Disorders by Gender*

	First incidence (%)						Relapse (%)						Total incidence					
	Female[a]		Male[b]		Total[c]		Female[a]		Male[b]		Total[c]		Female[a]		Male[b]		Total[c]	
Psychiatric diagnosis	Rate	*SE*	Rate	*SE*	Rate	*SE*	Rate	*SE*	Rate	*SE*	Rate	*SE*	Rate	*SE*	Rate	*SE*	Rate	*SE*
Unipolar depression	6.32	1.01	4.25	0.82	5.26	0.65	21.76	2.98*	9.59	3.47	18.42	2.38	10.15	1.08***	4.82	0.82	7.66	0.70
Major depression	7.14	1.05*	4.35	0.82	5.72	0.66	21.11	3.05*	9.09	3.57	17.89	2.45	10.36	1.09***	4.80	0.82	7.76	0.70
Dysthymia	0.13	0.13	0.00	0.00	0.07	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.12	0.00	0.00	0.07	0.07
Bipolar disorder	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Anxiety disorder	0.84	0.34	0.30	0.21	0.58	0.20	1.75	1.75	0.00	0.00	1.18	1.18	0.90	0.34	0.29	0.20	0.61	0.20
Panic	0.38	0.22	0.14	0.14	0.27	0.13	0.00	0.00	0.00	0.00	0.00	0.00	0.37	0.21	0.14	0.14	0.27	0.13
Agoraphobia	0.12	0.12	0.00	0.00	0.07	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.12	0.00	0.00	0.07	0.07
Social phobia	0.13	0.13	0.00	0.00	0.07	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.13	0.13	0.00	0.00	0.07	0.07
Simple phobia	0.00	0.00	0.14	0.14	0.07	0.07	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.14	0.14	0.07	0.07
Obsessive-compulsive	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Separation anxiety	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Overanxious	0.25	0.18	0.00	0.00	0.13	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.18	0.00	0.00	0.13	0.09
Disruptive behavior disorder	0.26	0.18	0.78	0.35	0.49	0.19	4.00	4.00	2.33	2.33	2.94	2.06	0.37	0.22	0.88	0.36	0.61	0.20
Attention deficit	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.12	0.29	0.20	0.20	0.12
Conduct	0.13	0.13	0.15	0.15	0.14	0.10	0.00	0.00	4.76	4.76	3.13	3.13	0.00	0.00	0.00	0.00	0.00	0.00
Oppositional defiant	0.25	0.18	0.58	0.29	0.40	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.18	0.58	0.29	0.40	0.16
Substance use disorders	2.54	0.58	4.33	0.80	3.37	0.48	17.39	5.65	11.76	5.61	15.00	4.02	3.40	0.64	4.70	0.81	4.00	0.51
Alcohol dependence and abuse	1.30	0.41	2.68	0.62	1.94	0.36	24.14	8.09	4.76	4.76	16.00	5.24	2.12	0.51	2.74	0.62	2.41	0.40
Drug dependence and abuse	2.22	0.53	2.44	0.60	2.32	0.40	3.03	3.03	10.71	5.95	6.56	3.20	2.26	0.53	2.78	0.63	2.50	0.41
Cannabis	1.16	0.38	1.53	0.48	1.33	0.30	4.35	4.35	3.57	3.57	3.92	2.75	1.25	0.39	1.61	0.48	1.42	0.31
Hard drugs	0.13	0.13	0.59	0.29	0.34	0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.12	0.12	0.58	0.29	0.33	0.15
Cocaine	0.25	0.17	0.43	0.25	0.33	0.15	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.17	0.43	0.25	0.33	0.15
Amphetamines	0.75	0.31	0.29	0.20	0.54	0.19	0.00	0.00	0.00	0.00	0.00	0.00	0.74	0.30	0.29	0.20	0.53	0.19
Eating disorders	1.00	0.35**	0.00	0.00	0.53	0.19	0.00	0.00	0.00	0.00	0.00	0.00	0.99	0.35**	0.00	0.00	0.53	0.19
Anorexia nervosa	0.25	0.18	0.00	0.00	0.13	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.17	0.00	0.00	0.13	0.09
Bulimia nervosa	0.75	0.30*	0.00	0.00	0.40	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.74	0.30*	0.00	0.00	0.40	0.16
Adjustment disorder	3.72	0.69**	1.36	0.45	2.61	0.42	2.04	2.04	0.00	0.00	1.22	1.22	3.62	0.66**	1.29	0.43	2.54	0.41
Other disorders	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Any diagnosis	10.25	1.40	7.76	1.21	8.96	0.92	26.19	2.78	17.72	3.05	22.93	2.08	15.79	1.36**	10.19	1.19	13.14	0.91

Note. *DSM-III-R* = *Diagnostic and Statistical Manual of Mental Disorders* (rev. 3rd ed.).
[a] $n = 810$. [b] $n = 698$. [c] $n = 1,508$.
* $p < .05$. ** $p < .01$. *** $p < .001$.

trast, Time 1 point and lifetime prevalence rates for disruptive behavior disorders for male students were more than twice as large as the rates for female students.

At Time 1, older adolescents were more likely to have a diagnosis of dysthymia (odds ratio [OR] = 1.87; 95% confidence bounds = 1.03, 3.40), and younger adolescents were more likely to have a diagnosis of a disruptive behavior disorder (OR = 1.47; 95% confidence bounds = 1.07, 2.01). As expected, age was associated with the lifetime prevalence of most of the disorders, with the exception of childhood disorders, particularly disruptive behavior disorders and some anxiety disorders (e.g., separation anxiety, overanxious). The only significant age effect for the total incidence was found for the omnibus test of developing any disorder: Older adolescents were more likely to develop a disorder between Times 1 and 2 (OR = 1.19; 95% confidence bounds = 1.03, 1.37). No age effects for disorder-specific incidence rates were found.

The interaction between age and gender for the occurrence of unipolar depression was not significant. Thus, the hypothesis that the difference in occurrence of depression between male and female students would increase as a function of age was not supported. However, significant Age × Gender interactions were found for Time 1 point prevalence of the omnibus test of any disorder (OR = 1.32, 95% confidence bounds = 1.01, 1.74) and anxiety disorders (OR = 2.16; 95% confidence bounds = 1.23, 3.77) as well as for Time 1 lifetime prevalence of anxiety disorders (OR = 1.43; 95% confidence bounds = 1.06, 1.93). Post hoc comparisons revealed that female students under 16 years of age were significantly higher than male students on the point prevalence of any disorder, $\chi^2(1, N = 613) = 4.77$, $p < .05$, and anxiety disorders, $\chi^2(1, N = 613) = 13.61$, $p < .001$, as well as for the lifetime prevalence of anxiety disorders, $\chi^2(1, N = 613) = 16.85$, $p < .001$. Gender differences were in the same direction for such rates in the older adolescents (16 years and older); however, the post hoc comparisons failed to attain statistical significance ($ps > .05$).

Discussion

The main purpose of our study was to provide estimates for the prevalence and incidence of depression and of other mental disorders in high school students. Because there have been few other community studies using *DSM-III-R* criteria and the K-SADS interview, it is important to consider potential sources of bias. Systematic biases might have been introduced into the study by the case ascertainment method, nonresponse at Time 1, and Time 1–Time 2 attrition.

Our relatively high nonresponse rate at Time 1 was a potential source of bias. However, our response rate increased over the three cohorts, reaching 68% for the last one. Differences between the three cohorts were small, and our efforts to collect data on the nonresponders indicated that they did not differ substantially from participants. The attrition from Time 1 to Time 2 was a modest 12%, and differences between the Time 1 sample and the Time 1–Time 2 panel were minor, except for the loss of a disproportionately large number of participants with a history of disruptive behavior and substance use disorders at Time 2. Thus, the relapse rates for disruptive behavior and substance use disorders (shown in Table 3) need to be interpreted with caution because they are based on a small sample.

Our population consisted of students enrolled in high schools in west central Oregon, which may not be representative of high schools in the United States. Our sample did not include those who had dropped out of high school (less than 10%) before Time 1; we tried to follow everyone after Time 1. It is likely that adolescents who dropped out before we could include them had an elevated prevalence of disorders. We also did not include adolescents in institutions (e.g., juvenile detention, mental hospitals). The effect of the biases just discussed probably was that the most severely disturbed and the most seriously delinquent adolescents were underrepresented.

The methodology used for case ascertainment consisted of the K-SADS at Time 1 and the LIFE combined with K-SADS at Time 2 to elicit information about the presence of symptoms that formed the basis for *DSM-III-R* diagnoses. Both the K-SADS and the LIFE have been used extensively in research. In our use of the K-SADS–LIFE procedures we attained high interrater reliability, indicating that we had a reliable symptom-determination method.

An important characteristic of our study was that we relied exclusively on diagnostic information provided by the adolescent. This differed from the standard procedure for the K-SADS (Puig-Antich & Chambers, 1983), which calls for diagnostic information elicited from the adolescent to be combined with information from a parent (typically the mother) for a summary diagnosis. We felt justified relying exclusively on the information provided by the adolescent because recent findings have shown that the reliability of diagnostic information from the child increases with age, whereas the reliability of the parents' report decreases sharply (Edelbrock, Costello, Dulcan, Kalas, & Conover, 1985) and that the amount of agreement between adolescents and parents declines with age (Kazdin, 1989). Nevertheless, it is likely that information from both teachers and parents would have identified additional cases.

Our point prevalence for unipolar depression (2.9%) was at the lower end of the range of values reported in previous studies (Canino et al., 1987; Fleming & Offord, 1990; Kashani, Beck, et al., 1987; Robins & Regier, 1991). By contrast, our lifetime prevalence of 20.4% at Time 1 and 25.3% at Time 2 was substantially higher than the Epidemiologic Catchment Area (ECA) overall lifetime rate of 7.8% for adults. This discrepancy between our results and the ECA lifetime rates for depression clearly deserves careful scrutiny and discussion.

How can it be that our adolescents had a substantially higher lifetime rate than the adults in the ECA? Because adults have lived longer with more opportunities to become depressed, their lifetime prevalence should be higher. For consideration of this issue, it is important to recognize that the lifetime rates in our study, as well as in other previous studies, were based on retrospective information that is subject to recall biases (e.g., Pearson, Ross, & Dawes, 1991). Equally relevant is the likelihood that the age at which people are asked about the occurrence of episodes of disorder has an effect on the age at which such episodes are reported. Thus, Angold, Weissman, John, Wickramaratne, and Prusoff (1991) found that the 16–18-year-old group reported more early onsets than younger (< 15) and older (19–21) subjects.

There are two directions from which one can approach the

issues we have outlined: Why is the ECA rate so low? On the other hand, why is our rate so high? The low lifetime rates by the ECA have been recognized as problematic (Parker, 1987; Roberts, 1988), and it has been suggested that the DIS methodology used in the ECA might have seriously underestimated lifetime rates. The ECA also contained the paradoxical finding of a gradual diminution of the lifetime rate as a function of age, with older people having lower rates than younger people (Robins & Regier, 1991). To resolve the discrepancy between the ECA and our lifetime rates for affective disorder, we suggest four hypotheses:

1. The prevalence of depression has been increasing and is now as high as indicated by the lifetime rates of the adolescents in our study.

2. The prevalence of depression has always been as high as indicated by our data, and the ECA data grossly underestimated the real lifetime prevalence of depression in adults and especially in older people.

3. Adolescents experience and report many relatively transient and short-lived episodes that, although meeting *DSM-III-R* criteria, are not recalled or reported later in life.

4. Our interviewers systematically "overdiagnosed" depression (i.e., their thresholds for determining the presence of various depression symptoms was lower than in other studies).

Although it is difficult to rule out this last hypothesis, we think that it is implausible because (a) our interviewers rigorously applied *DSM-III-R* criteria; (b) our point prevalence figure of 2.9 was within the range of values reported by other studies; (c) the mean number of depression symptoms rated as present by a child clinical psychiatrist (albeit on a small number of cases) was higher (5.8) than those of our interviewers (5.5; this difference was not significant); (d) the ratings by the child clinical psychiatrists who rated all cases of depression at Times 1 and 2 indicated that they considered approximately 90% of them to be moderately to severely depressed and in need of treatment; and (e) our point prevalence for any disorder of 9.7% was at the low end of the range of values (6.6%–37%) that has been reported and was close to the 10% estimated by Schwartz-Gould et al. (1981). Whether the lifetime prevalence was as high as suggested by our study or as low as in the ECA has important implications that can be resolved only by future research.

There are few studies in the literature that provide incidence data. As Eaton et al. (1989) pointed out, incidence data are hard to come by because, ideally, such data should be based on a longitudinal, prospective study design. Because the incidence of depression—and of most other mental disorders—is low, such a study must start with a large number of people who are not in an episode at the beginning of an observation period in order to generate a reasonable number of incidence cases over a 1-year period.

Comparing our annual first incidence rate of 5.7% for MDD with that reported in the literature, we found that ours was substantially higher than (a) the 1.6% reported by Eaton et al. (1989) for the ECA data; (b) the 0.52% reported by Hagnell, Essen-Möller, Lanke, Öjesjö, and Rorsman (1990) for the Lundby study; and (c) the 0.23% reported by Murphy, Olivier, Monson, Sobol, and Leighton (1988). Although a longitudinal, prospective design is the method of choice for determining incidence, it can be estimated if the point prevalence and the mean episode duration are known, as incidence is equal to prevalence divided by mean duration (Kleinbaum, Kupper, & Morgenstern, 1982). The formula determines how many people have to develop the disorder over a period of time to keep the prevalence rate constant. For example, if the point prevalence is 4% and the episode duration is 6 months, then 8% of the population have to become depressed every year in order to keep the prevalence at 4%. If we apply this formula, we obtain an estimated incidence for MDD of 5.8% for the adolescents from the present study (the prevalence was 2.6% and mean duration was 5.4 months). It thus seems that our 1-year incidence rates are close to what can be expected mathematically.

Whether one looks at first incidence, total incidence, or the relapse rate, our results suggest that the number of high school students who become depressed during a 1-year period is high. Projected onto a high school with 1,000 students, our data indicate that during a 1-year period, approximately 42 students would become depressed for the first time in their lives and that among those with a previous history of depression but who were not depressed initially at Time 1 (n = 174), 32 would become depressed again. Thus, in our hypothetical school, 74 cases of depression would be expected to occur during the 1-year period. The fact that the number of adolescents who become depressed over a 1-year period apparently is this large has important implications for the need for programs to detect, refer, and treat this age group.

The degree of comorbidity between all of the major *DSM-III-R* disorders was found to be substantial (i.e., those with a disorder have a markedly elevated probability of also having another disorder). There have been previous reports on the comorbidity of major depression with dysthymia (Lewinsohn et al., 1991) and between unipolar depression and other disorders (Rohde et al., 1991) for the OADP sample. In the future we will examine the effects of comorbidity on psychosocial functioning, suicidal behavior, treatment seeking, and other outcome measures.

Having a previous episode of any disorder is a strong risk factor for having another episode of mental disorder (OR = 1.74; 95% confidence bounds = 1.31, 2.31). The only disorder that did not seem to fit this pattern was adjustment disorder. However, data for 11 of the 12 subjects with a lifetime diagnosis of adjustment disorder for whom follow-up data were available indicated that 5 of them had developed an episode of major depression between Times 1 and 2. Thus, adjustment disorder is a strong risk factor for major depression. Another important finding was that there were no new cases of bipolar disorder and that all of the cases of bipolar disorder at Time 1 (most of whom were cyclothymic) had remitted by Time 2.

The effect of age on prevalence and incidence of depression was not significant. Thus, our hypothesis of an increase in depression between 14 and 18 years of age was not supported. That there was no increase as a function of age over this age span was consistent with recent findings on self-report measures such as the CES-D and the BDI (Roberts et al., 1990, 1991). As expected, female students scored substantially higher than male students on all indexes of unipolar depression, which was consistent with other studies such as those by Kashani, Carlson, et al. (1987), McGee et al. (1990), and Kandel and Davies (1982). On the other hand, the critical interaction between age and gender on depression prevalence and incidence was not significant. In other words, female students scored

higher on the depression measures for the total age range that we tested; the gap that already existed at age 14 between female and male students did not widen. Thus, to find the age at which female adolescents *begin* to surpass male adolescents will require studies of early adolescents.

Disruptive behavior disorders were more frequent in male students regardless of age. This was consistent with the findings of many studies, such as those by Offord et al. (1987), who found that male adolescents had a higher prevalence of conduct disorders regardless of age. Similarly, the point prevalence for substance use disorders was consistent with other studies (e.g., Robins & Regier, 1991) in showing higher levels by male adolescents. For the Time 1 lifetime prevalence and 1-year incidence results, the trends were in the same direction but were not significant.

As indicated earlier, it is important that the high lifetime and 1-year incidence rates we obtained for unipolar depression be cross-validated in other studies. Pending cross-validation, we suggest that our results can be generalized to adolescents in high school in small- and medium-sized urban areas of predominantly middle- and upper-middle-class people.

The long-term consequences of having an episode of depression or another mental disorder during adolescence need to be studied. By following our sample, we hope to provide more information about the course of episodes of disorders during adolescence and to contribute to the understanding of the antecedents and the consequences of mood and other mental disorders during adolescence, as well as the implications for depression in later life.

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Received July 8, 1991
Revision received June 25, 1992
Accepted July 10, 1992 ■

Brief Reports and Reviews—

The Brief Psychiatric Rating Scale for Children[1]

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Introduction

The Brief Psychiatric Rating Scale for Children (BPRS-C) has been developed to provide a parsimonious description of childhood emotional and behavioral disorders. Beginning with an extended description of the symptom and behavior characteristics associated with some 18 Diagnostic and Statistical Manual-III (DSM-III) categories, the methodology of factor analysis was used to identify clusters of symptoms that define major independent dimensions of difference among the diagnostic groups. Whereas the DSM-III includes specific, and sometimes rather arbitrary, criteria for a large number of childhood diagnoses, it is important to recognize that a relatively few major symptom and behavior dimensions separate those more numerous diagnostic groups. The BPRS-C is designed to characterize individual patients, and to evaluate treatment responses, in terms that are relevant for a variety of different diagnostic classifications. Thus, the multidimensional BPRS-C is considered appropriate for description of major differences among child and adolescent patients and for characterizing such patients according to major syndrome groupings, as well as for the evaluation of treatment responses in longitudinal research designs.

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Factor Analysis

In the factor analysis that provided the basis for development of the BPRS-C, the original data consisted of descriptions of hypothetical typical patients in some 18 diagnostic groups recorded on the 63-item Children's Psychiatric Rating Scale (CPRS) (Guy, 1974) by five experienced child and adolescent psychiatrists. The 18 diagnostic groups were selected from the DSM-III in an attempt to represent the range of clinical conditions most likely to be seen in the practice of child psychiatry. The five judges were asked to record what they considered from personal clinical experience to be the most likely level of symptom severity for typical patients in each of the 18 diagnostic groups. This produced 5 × 18 = 90 symptom and behavior rating-scale profiles representing a range of different types of childhood disorders. It is relevant to note that the CPRS rating scale on which the diagnostic stereotypes were recorded antedates the newly revised DSM-III, and that it includes symptom and behavior manifestations that span a broad domain of childhood psychopathology. The factors resulting from the analysis are thus conceived to be primary dimensions of symptom and behavior manifestations useful for describing differences among childhood psychiatric disorders in terms other than the specific diagnostic criteria of the DSM-III.

Intercorrelations among the 63 CPRS symptom variables across the 5 × 18 = 90 diagnostic profiles provided by the five expert judges were first factor-analyzed by a cluster-oriented powered vector method (Overall & Porterfield, 1962) to identify seven relatively independent

variables which represent distinct domains in the symptom measurement space. An oblique marker variable factor analysis (Overall, 1974) was then accomplished, starting with marker variables identified in the preliminary orthogonal powered vector factor analysis. This resulted in a good oblique simple structure in which most of the 63 variables projected substantially on only one of the seven oblique reference axes. The results from this factor analysis have been reported in some detail elsewhere (Pfefferbaum & Overall, 1981).

The BPRS-C includes three key variables to represent each of the seven empirically-identified factors. Care was exercised to avoid logical redundancies in the selection of symptom variables associated with each factor. That is, the several variables that projected primarily on each factor were inspected, and three variables were chosen for incorporation into the BPRS-C that appear to represent conceptually distinct manifestations of psychopathology that should be susceptible of separate evaluation even though they relate to a single primary factor in the larger symptom domain. In some cases, highly related symptom variables were combined into a single new rating construct for inclusion into the BPRS-C. Each of the seven empirically identified factors is thus represented by three conceptually distinct symptom constructs which appear in consecutive sequence in the BPRS-C format. A facsimili of the 21-item BPRS-C is presented in Figure 1.

BRIEF PSYCHIATRIC RATING SCALE FOR CHILDREN (BPRS-C)

Patient _____

Rater _____

Date _____

		Not Present	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extremely Severe
1.	Uncooperativeness - negative, uncooperative, resistant, difficult to manage.	☐	☐	☐	☐	☐	☐	☐
2.	Hostility - angry or suspicious affect, belligerence, accusations and verbal condemnations of others.	☐	☐	☐	☐	☐	☐	☐
3.	Manipulativeness - lying, cheating, exploitive of others.	☐	☐	☐	☐	☐	☐	☐
4.	Depressive Mood - sad, tearful, depressive demeanor.	☐	☐	☐	☐	☐	☐	☐
5.	Feelings of Inferiority - lacking self-confidence, self-depreciatory, feeling of personal inadequacy.	☐	☐	☐	☐	☐	☐	☐
6.	Suicidal Ideation - thoughts, threats, or attempts of suicide.	☐	☐	☐	☐	☐	☐	☐
7.	Peculiar Fantasies - recurrent, odd, unusual, or autistic ideations	☐	☐	☐	☐	☐	☐	☐
8.	Delusions - ideas of reference, persecutory or grandiose delusions.	☐	☐	☐	☐	☐	☐	☐
9.	Hallucinations - visual, auditory, or other hallucinatory experiences or perceptions.	☐	☐	☐	☐	☐	☐	☐
10.	Hyperactivity - excessive energy expenditure, frequent changes in posture, perpetual motion.	☐	☐	☐	☐	☐	☐	☐
11.	Distractibility - poor concentration, shortened attention span, reactivity to peripheral stimuli.	☐	☐	☐	☐	☐	☐	☐
12.	Speech or Voice Pressure - loud, excessive, or pressured speech.	☐	☐	☐	☐	☐	☐	☐
13.	Underproductive Speech - minimal, sparse inhibited verbal response pattern, or weak low voice.	☐	☐	☐	☐	☐	☐	☐
14.	Emotional Withdrawal - unspontaneous relations to examiner, lack of peer interaction, hypoactivity.	☐	☐	☐	☐	☐	☐	☐
15.	Blunted Affect - deficient emotional expression, blankness, flatness of affect.	☐	☐	☐	☐	☐	☐	☐
16.	Tension - nervousness, fidgetiness, nervous movements of hands or feet.	☐	☐	☐	☐	☐	☐	☐
17.	Anxiety - clinging behavior, separation anxiety, preoccupation with anxiety topics, fears or phobias.	☐	☐	☐	☐	☐	☐	☐
18.	Sleep Difficulties - inability to fall asleep, intermittant awakening, shortened sleep time.	☐	☐	☐	☐	☐	☐	☐
19.	Disorientation - confusion over persons, places or things.	☐	☐	☐	☐	☐	☐	☐
20.	Speech Deviance - inferior level of speech development, underdeveloped vocabulary, mispronunciations.	☐	☐	☐	☐	☐	☐	☐
21.	Stereotypy - rhythmic, repetitive, manneristic movements or posture.	☐	☐	☐	☐	☐	☐	☐

FIGURE 1

Factor Scoring of the BPRS-C

The 21 symptoms of the BPRS-C are rated for severity on 7-point scales ranging from "not present" to "extremely severe." The items are grouped into subsets of three to form a basis for the scoring of the composite factors which are conceived to represent the major ways in which one type of childhood disorder differs from another. Factor scores are calculated by summing the ratings on the successive subsets of three consecutive scales. This consecutive grouping of items representing each factor was chosen, not only to facilitate factor scoring, but to provide for considered comparison of the relative levels of severity of closely related symptoms. Although the symptoms within each group of three relate to the same factor, it is important to recognize that they may differ in severity in individual patients. Such differences are easier to consider when the symptom constructs are adjacent in the rating scale format. Each symptom should be rated separately, with severity in relation to associated symptoms considered carefully.

The breadth of the domain of psychopathology spanned by the BPRS-C suggests that not all factors are relevant for description of each type of patient. The seven major factor constructs and the symptom rating variables that are combined to define the associated factor scores are presented on the left-hand side of the Table. The DSM-III childhood diagnoses for which each major factor is considered to be particularly relevant are listed on the right. These diagnostic relevances were identified empirically from factor score profiles in the original 63-item data set that was analyzed to define the seven factors.

Brief Psychiatric History for Children

For both research and clinical purposes, it is useful to have selected history and demographic information recorded in a standard format. The relevant background data in the case of children with emotional and behavioral problems include demographic characteristics of the family as well as the child. In our own research, the background data form shown in Figure 2 is used to ensure the systematic recording of at least these minimum

Table

Factor Scoring of the Brief Psychiatric Rating Scale for Children and the Childhood Psychiatric Diagnoses in Which Each Factor Is Represented

Factors	Diagnoses
I. *Behavior Problems*	
Uncooperativeness	Conduct Disorders
Hostility	(all types)
Manipulativeness	Attention Deficit Disorders
	Oppositional Disorders
	Pervasive Developmental Disorder
	Infantile Autism
	Schizophrenic Disorder
	Major Depression
II. *Depression*	
Depressive Mood	Major Depression
Feelings of Inferiority	Agitated Depression
Suicidal Ideation	Retarded Depression
	Depression (other)
III. *Thinking Disturbance*	
Peculiar Fantasies	Pervasive Developmental Disorder
Delusions	Infantile Autism
Hallucinations	Schizophrenic Disorder
IV. *Psychomotor Excitation*	
Hyperactivity	Attention Deficit Disorder
Distractibility	Pervasive Developmental Disorder
Speech or Voice Pressure	Infantile Autism
	Schizophrenic Disorder
	Agitated Depression
V. *Withdrawal Retardation*	
Underproductive Speech	Avoidant Disorder
Emotional Withdrawal	Schizoid Disorder
Blunted Affect	Elective Mutism
	Retarded Depression
VI. *Anxiety*	
Tension	Separation Anxiety
Anxiety	Overanxious Disorder
Sleep Difficulties	Identity Disorder
	Anorexia Nervosa
	Agitated/Anxious Depression
VII. *Organicity*	
Disorientation	Traumatic Brain Injury
Speech Deviance	Organic Brain Disorder (other)
Stereotypy	Infantile Autism
	Pervasive Developmental Disorder
	Schizophrenic Disorder

items of background information. The Brief Psychiatric History for Children (BPH-C) is printed on the reverse side of the BPRS-C for convenience in use. As the data base grows, numerous interesting questions concerning the relationships of manifest psychopathology in children to background characteristics and family context can be answered. For comparative purposes, it may be useful to have similar information collected in different settings.

It will be noted that a section has been included for recording a tentative DSM-III diagnosis. Although a diagnosis made on the basis of brief contact with the child and parents is at best tentative, such a diagnostic impression is another way of characterizing or describing the patient. The fact that the symptom description recorded on the BPRS-C is not intended to be sufficient for diagnosis is emphasized. In children, as in adults, symptom descriptive classification and diagnosis are two different things. Examination of the phenomenological heterogeneity within major diagnostic categories may lead to eventual refinement of diagnostic concepts. The relationships between manifest psychopathology in children and DSM-III diagnosis should in fact be an interesting focus of future research with the BPRS-C.

Interviews with Parent and Child

The interviews used to obtain information necessary for completing the BPH-C and the BPRS-C rely heavily on the interviewing skills of the experienced clinician, who may be a child psychiatrist, child clinical psychologist, or other mental health professional with training and experience in working with children. The interviewer will be described as a psychiatrist in this discussion simply to avoid redundancy in reciting a list of qualified professionals.

An individualized style which allows the interviewer to maximize rapport is considered most important. Clinical skills unique to the individual can be capitalized on in a flexible semi structured interview. Nevertheless, a format that may help to eliminate extreme variation in the mode of data acquisition will be proposed here. It should allow ample opportunity for assessment in a reasonably short period of time. The use of such flexible, semistructured interviews has been documented to produce adequate reliability and validity in the assessment of children (Graham & Rutter, 1968; Rutter & Graham, 1968) as well as adults (Hedlund & Vieweg, 1980).

An interview with one or both parents, or a guardian, is required. The interviewer is encouraged to begin with open-ended questions regarding the child's presenting emotional and/or behavioral problems. Each identified problem is covered in depth with specific regard to onset, duration, and severity of symptoms. Once each problem has been discussed, a more structured format is used to obtain information for the BPH-C and the various symptoms to be rated on the BPRS-C. Specific queries should relate to activity level, attention span, speech development and possible abnormalities, emotional relationships, mood, suicidal ideation, self-concept, tension or anxiety, vegetative symptoms, fantasies, and delusions or hallucinations. A medication history should also be obtained in the interview with the parent. This interview can usually be completed in 35 minutes.

The interview with the child includes an assessment of the child's perception of his problems and an age appropriate mental status examination. As with the parent interview, this interview begins in an unstructured format allowing the interviewer to establish rapport and observe the child's behavior. Play or other modes of relating may be used depending on the child's age and condition. In the unstructured portion of the interview, the clinician can pay particular attention to activity level, attention span, peculiar mannerisms, speech production and abnormalities, manner of relating, mood, affect, self-concept, preoccupations, tension or anxiety, and delusional thinking or hallucinations that are spontaneously manifest.

During the structured portion of the examination, specific tasks may be assigned to the child in order to ascertain the child's developmental level, attention span, and ability to accept direction. Specific questions regarding friendships, school progress, mood, suicidal ideation, preoccupations, fears, fantasies, and unusual experiences or perceptions should be asked. The nature and severity of any positive findings should be explored in detail.

Since the BPRS-C is intended for research use, it is important to standardize the source of infor-

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BRIEF PSYCHIATRIC HISTORY

Patient _____ **Date** _____

Patient Present Age
- ☐ 0-1
- ☐ 2-5
- ☐ 6-10
- ☐ 11-13
- ☐ 14-16
- ☐ 17-19
- ☐ 20 or above

Ethnicity
- ☐ White
- ☐ Black
- ☐ Mexican American
- ☐ Other Minority _____

Sex
- ☐ Male
- ☐ Female

Pregnancy, Delivery, Neonatal
- ☐ Uncomplicated
- ☐ Complicated pregnancy _____
- ☐ Complicated delivery _____
- ☐ Complicated neonatal period _____

School (level)
- ☐ None
- ☐ Preschool
- ☐ Kindergarten
- ☐ Grade 1-3
- ☐ Grade 4-6
- ☐ Grade 7-9
- ☐ Grade 10-12
- ☐ Greater than grade 12

School (performance)
- ☐ Retarded
- ☐ Borderline
- ☐ Average
- ☐ Superior

School (interest)
- ☐ Negative
- ☐ Indifferent
- ☐ Normal interest
- ☐ Excess involvement

Patient living with
- ☐ Mother
- ☐ Father
- ☐ Grandparent(s)
- ☐ Sib(s)
- ☐ Stepparent
- ☐ Step/half sib(s)
- ☐ Other _____

Sibs of Patient
- ☐ None
- ☐ One sib
- ☐ 2-4 sibs
- ☐ More than 4

Birth Order of Patient
- ☐ Oldest
- ☐ Middle
- ☐ Youngest

Family Religious Attitude
- ☐ Atheist
- ☐ Agnostic (doubting)
- ☐ Indifferent
- ☐ Moderate Positive
- ☐ Strong Positive or Fanatic

Present Family Problems
- ☐ Marital conflict
- ☐ Separation or divorce
- ☐ Death of parent(s)
- ☐ Death of sib(s)
- ☐ Criminal victimization
- ☐ Criminal apprehension
- ☐ Work problems
- ☐ Financial problems
- ☐ Alcohol abuse
- ☐ Drug abuse
- ☐ Physical illness
- ☐ Organic CNS involvement
- ☐ Other _____
- ☐ None

Major Patient Problem Areas
- Developmental
- Social interpersonal
- Antisocial behavior
- School
- Poor impulse control
- Alcohol abuse
- Drug abuse
- Sleep problems
- Physical problems
- CNS dysfunction
- Other _____

Father's Education
- ☐ Less than high school
- ☐ High school graduate
- ☐ Some college

Mother's Education
- ☐ Less than high school
- ☐ High school graduate
- ☐ Some college

Duration of This Episode
- ☐ Less than 1 month
- ☐ 1-6 months
- ☐ 6-12 months
- ☐ 1-2 years
- ☐ More than 2 years
- ☐ Life long

Course of Illness
- ☐ Chronic stable
- ☐ Slow decline
- ☐ Recurrent acute episodes
- ☐ First episode

Previous Psychiatric Hospitalization
- ☐ No previous admission
- ☐ Single previous admission
- ☐ Multiple previous admission

Previous Outpatient Psy. Treatment
- ☐ None
- ☐ Non-psychiatric Rx
- ☐ Psychiatrist
- ☐ Psychologist

Nature of Previous Episodes
- ☐ None
- ☐ Same as current
- ☐ Other _____

Family Psychiatric History
- ☐ Father
- ☐ Mother
- ☐ Siblings
- ☐ Other relatives _____

Patient Perception of Problem
- ☐ Mental ☐ Mood
- ☐ Character ☐ Physical
- ☐ Interpersonal adjustment
- ☐ No problem (denial)
- ☐ Other _____

Diagnosis
- ☐ Attention deficit disorder
  - ☐ with hyperactivity
  - ☐ without hyperactivity
- ☐ Conduct disorder
- ☐ Separation anxiety disorder
- ☐ Overanxious disorder
- ☐ Schizoid disorder
- ☐ Avoidant disorder
- ☐ Elective mutism
- ☐ Oppositional disorder
- ☐ Identity disorder
- ☐ Anorexia nervosa
- ☐ Infantile autism
- ☐ Pervasive developmental disorder
- ☐ Schizophrenic disorder
- ☐ Major depression
  - ☐ with psychomotor excitation
  - ☐ with psychomotor retardation
- ☐ Other _____

Past medications _____

Current medications _____

New medications _____

Figure 2

mation used in making the ratings. We recommend that the symptom and behavior ratings be based on direct observation of the child, although important leads derive from the prior interview with the parent. Some research protocols may specifically authorize the use of information derived from other sources; however, in general, the psychopathology should be verified in the interview with the child.

After completing the history and BPRS-C, the psychiatrist is asked to make an initial diagnosis of the child. It is understood that the diagnosis may be based on all information available to the psychiatrist, even though the symptom ratings on the BPRS-C are restricted to information verified in the child interview. The initial diagnosis should be recorded by checking the most appropriate DSM-III diagnosis in the box at the lower right-hand corner of the BPH-C form. In addition to providing past and current medication use, the psychiatrist is also asked to list medications which he intends to start after this initial assessment. If he decides to discontinue any current medications, that should also be noted under new medications.

Conclusion

Much work needs to be done to establish the BPRS-C as a reliable and valid instrument for characterizing childhood psychopathology. We believe that the initial development based on factor analyses of ratings descriptive of a wide range of diagnostic entities has produced an instrument with desirable balance for the representation of different types of psychopathology. Because the BPRS-C is intended for use with different types of patients, it is not expected that all symptoms and behaviors will be present in each patient. Preliminary work has suggested, however, that some of the symptoms, and their combinations into factor scores, are relevant in assessing the severity of psychopathology in each of the major diagnostic groups that were considered in development of the instrument.

Because appropriate evaluation of a new assessment device is best accomplished in the context of ongoing research, we have chosen to present the BPRS-C at this time so that it can be considered in the public domain — an instrument that can be used and evaluated by anyone who has a research program into which it can be usefully integrated. Data for assessing internal consistency reliability and concurrent or predictive validity can also be obtained by the use of the BPRS-C and BPH-C in routine clinical practice, where those data can provide standard descriptive information not inappropriate for retention in the patient's file.

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0271-0749/82/0202-0107$02.00/0
Journal of Clinical Psychopharmacology

Vol. 2, No. 2
Printed in U.S.A.

BRIEF REPORTS

Imipramine Treatment of Depressed Children: A Double-Blind Pilot Study

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DEPRESSION in children continues to command major attention from child psychiatrists, both as a diagnostic enigma and an area of early attempts at comprehensive treatment.[1-7] Many noncontrolled or partially controlled studies have demonstrated the clinical efficacy of antidepressants in the treatment of depressed children and of target symptoms related to depression, but the vast majority lack experimental rigor.[1, 3, 7] A few studies have selected subjects who met research criteria for depression.[3, 8-11] No double-blind controlled study documents the superiority of imipramine (Tofranil) over placebo in moderately depressed children who meet research criteria for depression. A pilot study that demonstrates this superiority is described here.

Patients and Methods

Seven children, ages 6 to 12 years, newly admitted to a psychiatric unit and designated as depressed by the Bellevue Index of Depression (BID) and Weinberg Index of Depression, were studied.[11, 12] The patients were drug free for 2 weeks, during which time routine laboratory studies, electroencephalograms, cardiograms, and neurological, psychiatric, psychological, and educational assessments were conducted. Active milieu therapy, individual dynamic psychotherapy, and initial family work were also provided.[13] During the 3rd week of hospitalization, each child was given the Children's Depression Inventory (CDI) (M. Kovacs, N. G. Betof, J. E. Celebre, and associates, unpublished manuscript, 1977) and a structured interview, the School Age Depression Listed Inventory (SADLI).

The SADLI consists of 17 items rated on a scale from 1, absent, to 7, very severe. A rating of 4 would indicate moderate severity. The first 5 items, rated by direct observations in the interview setting, include irritability, depressed appearance, withdrawn behavior, hyperactivity, and oppositional behavior. The next 11 items, rated according to the child's response to questions posed within a semistructured format, are anhedonia, sleeping difficulties, somatic complaints, social withdrawal, loneliness, helplessness, exclusion, depressed mood, self aggression-suicide, worthlessness, and hopelessness. Item 17 is a global depression rating that is based on the clinical judgment of the rater, using both subjective and objective data obtained from the interview. The SADLI was explicitly developed to assess the response of depressed children to various therapeutic interventions delivered in a hospital setting. The initial scale consisted of 28 items and was reduced over 4 years to the present form. The interviews were videotaped and rated independently by two judges. High interrater reliability had been previously obtained.

One child failed to be rated as moderately or more severely depressed on the SADLI and was eliminated from the study. The other six children were randomly assigned to either the imipramine or the matched placebo conditions. The assignment was unknown to the investigators and to the unit staff. The number of pills was constant throughout the 6 weeks of treatment for both groups and was equal to that necessary to provide approximately 5 mg/kg/day in three doses. Cardiograms were routinely done after the children reached the dosage of 3.5 mg/kg/day. The maximum dosage was reached at the end of 1 week and maintained for 3 weeks; the dosage was then tapered and stopped over the last week of the study. At the end of the last week on maximum dosage, repeat SADLI and CDI were conducted. During the following week, when medication was slowly discontinued, the child form of the BID was administered. Plasma

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tricyclic levels were also obtained during the drug phase.[10]

Results

Our earlier clinical impressions, which were based on open studies,[8] single case reports,[14, 15] and clinical experience[3] with imipramine treatment of depressed children at this dosage level and without monitoring tricyclic plasma levels, were confirmed. All three children of the drug group showed some or dramatic improvement on the three measures employed, while two of the three children on placebo worsened on two of the scales. All three children on placebo required and responded to imipramine treatment, which was instituted after completion of the controlled trial. Only subjective mild clinical improvement was shown by one drug-treated child (patient 2) during the trial, but he continued to show steady improvement and a complete remission shortly afterward. Surprisingly, this child had the highest plasma tricyclic levels of all three children (imipramine = 55 ng/ml; desipramine = 330.6 ng/ml; total = 385.6 ng/ml). Table 1 demonstrates ratings for the children, comparing predrug and drug phases. Because the sample size is small, statistics cannot be validly used for hypothesis testing. However, some statistics were calculated for descriptive purposes. The imipramine group did look more disturbed on the initial BID and SADLI ratings. Hence, *t* tests were performed to compare the initial ratings of the placebo children with those of the drug-treated children. The differences were not significant for the initial BID and SADLI. The placebo group appeared more depressed on the CDI, and there was a significant between-group difference for this measure. Significant differences were found only for the predrug-drug ratings of the imipramine group on the SADLI.

Because differences were noted for initial assessments between drug-treated and placebo groups, paired *t* tests were performed to see whether there was significant change within individuals over time. Analyzing specific items on the SADLI reveals significant improvement for the imipramine group in dysphoric mood and suicidal ideation. Strong trends for withdrawn behavior and helplessness on the two-tailed paired *t* tests were noted (Table 2). No significant differences during the treatment period were found in the placebo group, and actual worsening in certain symptomatology occurred (*e.g.*, dysphoric mood and depressed appearance). Dramatic changes on the child form of the BID were evident for two of the imipramine-treated children, but the extraordinary drop in patient 2's score prevented the values from reaching statistical significance. Highly significant interrater correlations were obtained on individual items for both the BID and SADLI scales. No untoward side effects or significant electrocardiographic changes were experienced by any of the children. One of the children on imipramine (patient 1) did show a marked drug withdrawal response to the 1-week discontinuation of medication. This consisted of agitation and severe gastrointestinal distress, along with irritability and some increase in depression and hostility.[16] Withdrawal symptoms were present to a more limited degree in the other two children. All six children in this study met Diagnostic and Statistical Manual of Mental Disorders III criteria for major depressive disorder when retrospectively rated.

Discussion

Few systematic studies have been conducted that assess the effects of intervention strategies on children meeting research criteria for depression. Most of these studies relate to psychopharmacological treatment.[7] This

TABLE 1. Basic data of children in the imipramine and placebo treatment groups including age, sex, and predrug and drug period ratings for three measures of depression[a]

Patients	Age (mo)	Sex	SADLI		BID		CDI[b]	
			Predrug	Drug	Predrug	Drug	Predrug	Drug
Imipramine treated								
1	94	M	97	35.5	35	5	3	1
2	93	M	68.5	50	63	0	17	7
3	114	M	77	50	26	16	10	7
Mean	100		80.8[c]	45.1	41.3	7	10	5
Placebo								
1	86	M	61.5	45.5	4	1	30	23
2	125	M	46	60.5	46	14	6	7
3	152	F	39	36	12	31	17	10
Mean	121		48.8	47.3	20.7	15.3	17.7	13.3

[a] SADLI = School Age Depression Listed Inventory; BID = Bellevue Index of Depression; and CDI = Children's Depression Inventory.
[b] Initial scores are significantly different between the drug-treated and placebo groups ($p < 0.03$).
[c] Predrug and drug period scores are significantly different in the imipramine group only ($p < 0.04$).

TABLE 2. Comparison of predrug and drug ratings on six items of the School Age Depression Listed Inventory for the imipramine and placebo groups[a]

	Imipramine group		Placebo group	
	Predrug	Drug	Predrug	Placebo
Dysphoric mood	6.2	2.0[b]	2.2	5.5
Suicidal ideation	4.2	1.0[c]	2.7	2.3
Hopelessness	5.8	2.8	4.0	4.0
Withdrawal	6.2	2.7	3.8	3.0
Helplessness	6.0	2.7	1.2	2.3
Depressed appearance	7.0	4.6	3.7	4.3

[a] Results are given as means.

[b] Predrug and drug scores are significantly different ($p < 0.05$; two-tailed paired t test).

[c] Predrug and drug scores are significantly different ($p < 0.02$; two-tailed paired t test).

article presents a double-blind pilot study that demonstrates the superiority of imipramine over placebo in the comprehensive multimodality inpatient treatment of children who did meet the research criteria for depression. The small sample size and the consequent failure to achieve truly matched groups are significant shortcomings of this pilot study. Employing the paired t test corrects for part of this deficiency. Although plasma levels for tricyclic antidepressants were obtained, they did not play a role in drug management and were revealed to the investigators well after the clinical ratings had been completed. The imipramine children responded in this study in a like manner to a large number of similar children whom we have treated clinically and for whom plasma levels were not used.[8]

Depression experienced by children, even for those with suicidal ideation, may not be as potentially lethal as the major depressive disorders experienced by adults. Even though side effects such as seizures,[17] cardiac arrhythmias,[18] death with excessive dosage,[19] and withdrawal symptoms upon discontinuation[16, 20] have been reported, the depressed child and his or her family do suffer to an extent that justifies consideration of antidepressant medication as part of a total comprehensive treatment plan. It was also the impression of the staff clinicians that the imipramine-treated children showed progressive improvement even after the drug was discontinued at the end of the trial, while the placebo children responded only marginally to intensive treatment until they were given the active drug.

The placebo children were older and seemed less severely depressed on two of the measures; this could possibly account for their lack of significant response to placebo. However, the results of a positive response to the drug are supported for the following reasons: (1) such major indicators of depression as dysphoric mood and suicidal ideation decreased significantly in the drug group, and similar very strong trends indicating improvement in hopelessness, withdrawal, and helplessness were also found in the drug group as compared to a lack of change in the placebo group; and (2) these results are similar to earlier reports and our own clinical experience. Given the small number (N = 6) of this pilot study, the results support the further large scale investigation of imipramine in conjunction with intensive treatment for moderately depressed children who meet research criteria for major depressive disorder. Such research will be difficult to conduct because, even though the number of moderately to severely depressed children is high, the etiology and clinical presentation are complex, populations of depressed children are not homogeneous, and the response to imipramine treatment is diverse. Groups of well controlled, single case, designed studies may be a most appropriate methodology to employ in such research.[21] Data from the present study demonstrate that widely divergent change patterns as measured by different types of clinical instruments do occur in the same subject. Such discrepancies can provide useful clinical insights into both the nature of depression in children and its treatment, but they often get lost in large group or extensive case designs.[21] Future research in this important area should keep these considerations in mind.

Acknowledgments

This work was supported in part by Grant MH-30915 from the National Institute of Mental Health. The authors wish to express their appreciation to S. Wilson, RN, MSN, K. E. Dawson, MEd, B. Rautner, ACSW, C. Konkoleski, RN, B. Levinson, RPh, and the staff of the Children's Psychiatric Intensive Care Service, Western Psychiatric Institute and Clinic, University of Pittsburgh, for their assistance and to D. Wagener, PhD, for performing the statistical analysis.

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Suicidal Children Grow Up: Demographic and Clinical Risk Factors for Adolescent Suicide Attempts

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Abstract. This longitudinal study reports rates and demographic and clinical risk factors for adolescent suicide attempts during a 6- to 8-year follow-up period of an initial sample of 106 preadolescent and young adolescent psychiatric inpatients and 101 preadolescent and young adolescent nonpatients. Survival analysis was used to evaluate risk for a first suicide attempt in the follow-up period for 133 subjects who were interviewed. No deaths occurred. Suicidal inpatients, compared with nonpatients, had earlier first suicide attempts in the follow-up period. Adolescents who attempted suicide in the follow-up period were seven times more likely to have a mood disorder during the follow-up period than those who did not attempt suicide. Implications for clinical practice and research are discussed. *J. Am. Acad. Child Adolesc. Psychiatry*, 1991, 30, 4:609–616. **Key Words:** adolescent suicide attempts.

With the recognition of youth suicide as a national mental health problem (Alcohol, Drug Abuse, and Mental Health Administration, 1989), there has been increased public health, clinical, and research interest in youth suicide attempts. The present paper on adolescent suicide attempts is a companion to a paper (Pfeffer et al., submitted for publication) that reported on suicidal episodes during a 6- to 8-year follow-up period of a high-risk sample of preadolescents and young adolescents who had a history of suicidal ideation and/or acts. In the companion paper, suicidal episodes were operationalized to include suicidal ideation, threats, attempts, or suicide within yearly intervals. The present paper investigates suicide attempts as a subset of suicidal episodes.

Suicide attempts represent an unfortunate outcome; although, the most unfortunate outcome of a suicidal episode is death. The companion paper (Pfeffer et al., submitted for publication) reported that almost half of these high-risk preadolescents and young adolescents experienced at least one suicidal episode in the follow-up period, and a smaller percentage of the preadolescents and young adolescents attempted suicide during the first suicidal episode in the follow-up period. The present study aims to identify which preadolescents and young adolescents will be most likely to attempt suicide.

This paper reports on rates and demographic and clinical risk factors for suicide attempts in high-risk preadolescents and young adolescents participating in an ongoing prospective study (Pfeffer et al., 1986, 1988). Risk factors for a first suicide attempt in a 6- to 8-year follow-up period are identified, using survival analysis methods, a statistical technique that has not been utilized on data of child or adolescent suicidal attempts. It is hypothesized that preadolescents and young adolescents who report suicidal ideation and/or acts will have an earlier suicide attempt during the follow-up period.

Method

Design and Sample

The study was designed as a 6- to 8-year follow-up of 106 consecutively hospitalized preadolescent and young adolescent psychiatric inpatients (Pfeffer et al., 1986) who were at high risk for suicidal behavior. At the time of the initial assessment in 1979 to 1982, 84 (79.2%) of the inpatients reported suicidal ideation and/or attempts within 6 months of hospital admission (Pfeffer et al., 1986). A comparison group of 101 preadolescents was selected by stratified random sampling from a computer roster of 1,565 students in a large urban community to match the distribution of inpatients on age, gender, race/ethnicity, and social status (Pfeffer et al., 1986). Approximately 12% of the nonpatients reported suicidal ideation, threats, or attempts. The 207 subjects at the initial assessment were predominantly male (73%), white (75%), and from middle social status backgrounds (53%) (Hollingshead and Redlich, 1958). The majority of subjects were Catholic (56.5%). The mean age at the initial assessment for the 207 subjects was 10.5 ± 1.8 years (range, 4.6–14.7 years). This is a naturalistic longitudinal study. The subjects have not been assigned to interventions by the investigators.

Interview Procedures and Research Assessments

Subjects and their parents were interviewed separately at

Accepted November 15, 1990.

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This study was supported by USPHS Grant No. MH 142120, 1987–1990, from the National Institute of Mental Health. Appreciation is extended to Ms. Tammy Chung for research assistance.

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0890-8567/91/3004-0609$03.00/0

the 6- to 8-year follow-up assessment if each gave written informed consent. Interviews were conducted at their home or at the university by masters or Ph.D. level psychologists trained in the interviewing techniques. Interrater reliability was evaluated by comparing ratings of an interviewer and an observer of the same interviews, each making independent ratings of the interview data.

The research instruments included the Spectrum of Suicidal Behavior Scale (Pfeffer, 1986; Pfeffer et al., 1979, 1980, 1982, 1984, 1986), used also at the initial assessment, to measure past and present suicidal behavior in a hierarchy along a 5-point ordinal scale that included nonsuicidal behavior (rated 1), suicidal ideation (rated 2), suicidal threats (rated 3), mild suicidal attempts (rated 4), and serious suicidal attempts (rated 5). This scale was administered during separate semistructured interviews of the subjects and parents at the follow-up assessment. A final rating of the present and past spectrum of suicidal behavior during the follow-up period was obtained by utilizing the highest score reported as retrospective information by either the subject or parents. These final ratings were made separately by two members of the research staff who were not involved in the research interviews.

Interrater reliability on (N) interviewer/observer pairs, assessed with the kappa (κ) coefficient (Cohen, 1960), for subject suicide attempts during the follow-up period was adequate and significant ($\kappa = 0.55$, $p < 0.0001$, $N = 69$). Subject–parent concordance based on subject–mother or subject–father pairs, evaluated with kappa, for subject suicide attempts at the follow-up assessment was low but significant ($\kappa = 0.40$, $p < 0.0001$, $N = 143$). Inspection of the discrepancies revealed that subjects reported more suicide attempts than did parents.

Both the Kiddie Schedule of Affective Disorders and Schizophrenia-Present Episode (Chambers et al., 1985) and Epiodemiological Version (Orvaschel et al., 1982) were administered during separate, semistructured interviews of the subjects and parents at the follow-up assessment to classify current and past *DSM-III-R* psychiatric disorders during the follow-up period. Final psychiatric diagnoses and their onsets and durations were rated from the subject and parent data, using a best estimate consensus determined independently by two members of the research staff who were not involved in the research interviews. Psychiatric disorders at the initial assessment used *DSM-III* criteria.

Interrater reliability on 46 interviewer/observer pairs assessed with kappa for current psychiatric disorders was adequate and significant and ranged from $\kappa = 0.55$ to $\kappa = 0.99$ ($p < 0.0001$). Subject–parent concordance estimates ($N = 130$) for current psychiatric disorders were acceptable and significant and ranged from $\kappa = 0.23$ to $\kappa = 0.57$ ($p < 0.05$) and are similar to findings that were reported by other investigators (Apter et al., 1988, 1989; Weissman et al., 1987). Subject–parent concordance for past psychiatric disorders during the follow-up period ranged from $\kappa = 0.24$ to $\kappa = 0.66$.

Operational Criteria For Suicidal Episode

Ideally, a follow-up study should include assessments at frequent intervals in order to detect changes in clinical status, particularly suicidal behavior. There are methods, such as the Longitudinal Interval Follow-up Evaluation (Shapiro and Keller, 1979), to assess such changes. Frequent interval assessments were not incorporated into the design of the present study. As an approximation of such assessments, the retrospective data on suicide attempts are organized on a yearly basis.

A suicidal episode was defined as the occurrence of either suicidal ideation, threats or attempts or suicide within a 1-year period (Pfeffer et al., submitted for publication). A suicidal episode may include more than one suicidal behavior. For example, within a specific year, a subject may exhibit suicidal ideation or suicidal threats as well as a suicide attempt. This paper will report on suicide attempts during the follow-up period.

Statistical Methods

Survival analysis using the life table method (Kalbfleisch and Prentice, 1980; Lee, 1980) with yearly intervals was utilized to investigate risk factors associated with the cumulative probability of a first suicide attempt during the follow-up period. This analysis enabled the inclusion of data about subjects who did not exhibit a suicide attempt during the 6- to 8-year follow-up period and the inclusion of data on subjects who dropped out before a suicide attempt may have been evident. Hazard functions indicating the conditional probability of a suicide attempt within each yearly interval are reported. Differences in cumulative probability between groups of subjects were evaluated with the Log rank test, which identifies differences over the entire follow-up period. The Wilcoxon test, which is more sensitive to differences occurring in the earlier phase of the follow-up period, was also applied. Since results of these tests were identical, only results of the Log rank test are presented. Furthermore, all summary statistics on scores are presented as means ± standard deviations.

Cox proportional hazard regression models were used to estimate the effects of risk factors as covariates on the hazard functions. This process of analysis began with an evaluation of the effects of risk factors in bivariate models and subsequently included risk factors that had significant bivariate associations into multivariate models. The Cox proportional hazard regression analysis is based on the assumption that the proportional effects of risk factors on hazard functions for groups of subjects remain constant over time. Relative risks with 95% confidence intervals are reported to indicate the frequency a risk factor occurred in subjects with a suicidal attempt in the follow-up period relative to its frequency in subjects without a suicide attempt in the follow-up period.

Series of Cox proportional hazard regression models were computed to evaluate risk factors rated for various time periods. One series of models considered risk factors present at the initial assessment.

Another series of models considered risk factors after the initial assessment. This analysis was computed by indicating that a risk factor was present for those subjects with a suicide attempt if the risk factor was present at any time after the

initial assessment but estimated to be before the suicide attempt. For subjects who had no suicide attempt, a risk factor was rated as present if it was present at any time after the initial assessment.

A third series of models was computed to consider risk factors near the time of the suicide attempt. For subjects who had a suicide attempt, a risk factor was considered present if it was present within the year of the suicide attempt. For subjects who had no suicide attempt, a risk factor was rated as present if it was present at some time during the follow-up period.

A fourth series of models involved considering lifetime risk factors. For subjects who had a suicide attempt, a risk factor was rated as present if it was present at any time in the life of the subject and estimated to be before the time of the suicide attempt. A risk factor for subjects who did not have a suicide attempt was considered present if it was present at any time before the end of the follow-up period.

Risk factors that were present at the initial assessment and had significant bivariate associations were included in all models. This approach of evaluating risk factors in different time frames was used because it enabled analysis of risk factors that may have changed during the time period evaluated. It also enabled the assessment of whether risk factors present more proximal to the suicide attempt in the follow-up period were stronger than those present more distally. Considering a risk factor present during the entire follow-up period for subjects who did not have a suicide attempt may have overestimated the prevalence of a risk factor in this group of subjects. This approach may have an advantage in that if a risk factor was found to be significant, its effects may be large since this assignment strategy tended to overrepresent a risk factor in subjects without a suicide attempt.

Results

The Sample at Follow-up

Among the initial 207 subjects, 201 (97.1%) were located (102 [96.2%] of the 106 initial psychiatric inpatients and 99 [98.0%] of the 101 initial nonpatients). One hundred thirty-three adolescents (64.3% of the 207 initial subjects) and their parents were interviewed in the present study. They include 69 (65.1%) of the 106 former psychiatric inpatients and 64 (63.4%) of the 101 former nonpatients. Approximately 85% of the 133 subjects and 80% of the parents of these adolescents were interviewed.

The 133 adolescents were predominantly male (72.9%), white (72.1%), and from middle social status backgrounds (56.3%) (Hollingshead and Redlich, 1958). Most of the subjects were Catholic (60.2%) and the remainder included Jewish (20.3%), Protestant (12.8%), and other religions (6.8%). The mean age at the time of follow-up was 17.0 ± 2.2 years (range, 10.9–21.3 years). There were no differences in demographic features of the initial 53 suicidal inpatients, 16 nonsuicidal inpatients, and 64 nonpatients.

Distributions of age, gender, race/ethnicity, social status, religion, diagnoses, and suicidal status measured at the time of initial assessment for the 133 adolescents in the present study were similar to the distributions of these variables for the 74 adolescents for whom interview data was not obtained.

Deaths

There have been no deaths among the 201 located adolescents. Efforts have been undertaken to determine if the 6 unlocated adolescents died.

Suicide Attempts during Follow-up

Twenty (15.0%) of the 133 adolescents (16 [23.2%] inpatients and four [6.3%] nonpatients) attempted suicide at least once during the follow-up period (mean follow-up period = 7.16 ± 1.0 years). In general, the inpatients had a gradual increase in yearly rates of first suicide attempts, in contrast to a low rate of suicide attempts for the nonpatients. This is shown in Figure 1 for hazard functions of suicide attempts for inpatients and nonpatients. There was a total of 71 suicide attempts made during 40 (28.7%) of the 140 person years of follow-up for the group of 20 suicide attempters. This represents an average of 1.8 ± 1.3 (range, 1–6) suicide attempts per year for the suicide attempters. Fifty (70.4%) suicide attempts were considered mild because they did not have the potential to cause death and they did not necessitate medical attention. Twenty-one (29.6%) suicide attempts were serious because they could have caused death or required medical attention. The most frequent methods utilized to attempt suicide were self-cutting (39.4%), ingestion (18.4%), and hanging or choking (15.5%).

Ten (50%) suicide attempters made multiple suicide attempts, with a median of 3.5 suicide attempts (range, 2–14 suicide attempts). Among the 10 multiple suicide attempters, seven (70%) attempted suicide more than once within a 1-year period, and eight (80%) attempted suicide in several different years.

Risk Factors for Multiple Suicide Attempts

The 10 adolescents who attempted suicide once in the follow-up period were compared with the 10 multiple sui-

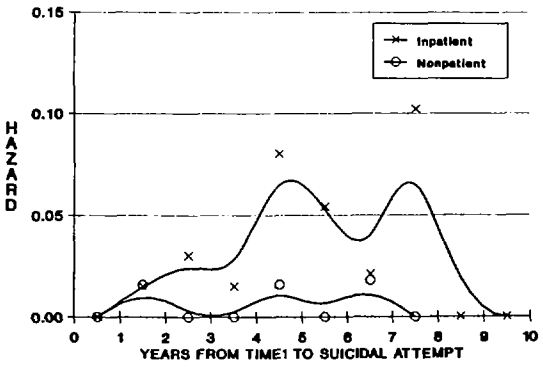

FIG. 1. Hazard functions for first suicide attempt during follow-up for inpatients and nonpatients.

TABLE 1. *Psychiatric Disorders among 133 Subjects at the Initial Assessment and during the Follow-up Period*

Psychiatric Disorder	Initial Assessment		Follow-up Period			
	N	%	*N*	%	*Z*	*p*
Any disorder	111	83.5	110	82.7	0.0	NS
Mood disorder	42	31.6	63	47.4	2.5	0.01
Major depressive	17	12.8	32	24.1	2.2	0.03
Dysthymic	25	18.8	34	25.6	1.2	NS
Bipolar	0	0.0	2	1.5	—	—
Disruptive disorder	54	40.6	77	57.9	5.1	0.0001
Attention deficit hyperactive	12	9.0	42	31.6	4.4	0.0001
Conduct	37	27.8	58	43.6	2.6	0.01
Oppositional defiant	12	9.0	23	17.3	1.8	NS
Schizophrenic disorder	11	8.3	8	6.0	0.5	NS
Anxiety disorder	27	20.3	56	42.1	3.7	0.0001
Separation anxiety	6	4.5	35	26.3	4.8	0.0001
Substance abuse disorder[a]	0	0.0	35	26.3	—	—
Alcohol abuse	0	0.0	25	18.8	—	—
Substance abuse	0	0.0	25	18.8	—	—
Other disorder	27	20.3	25	18.8	0.2	NS
Developmental disorder	41	30.8	15	11.3	3.7	0.0001

[a]Comparison of substance abuse disorders is not applicable since no subject had such disorders initially.

cide attempters on demographic and clinical variables. Six (85.7%) female suicide attempters, compared with four (30.8%) male suicide attempters, made multiple suicide attempts ($\chi^2 = 5.22$, $df = 1$, Fisher's exact test $p = 0.03$). The female suicide attempters made an average of 7.4 ± 5.6 attempts (range, 1–14), and the male suicide attempters made an average of 1.5 ± 0.8 suicide attempts (range, 1–3) ($t = 2.8$, $df = 6.1$, $p < 0.03$). There were no significant differences in other demographic variables, initial severity of suicidal behavior, initial or follow-up psychiatric disorders, or initial inpatient status between the adolescent single and multiple suicide attempters.

Initial Suicidal Behavior as a Risk Factor for Suicide Attempts

Twenty-six (19.5%) of the 133 subjects reported having attempted suicide at the time of the initial assessment. Among these 26 initial suicide attempters, eight (30.8%) attempted suicide in the follow-up period. A follow-up suicide attempt was made by 26.4% of the 53 suicidal inpatients, 12.4% of the 16 nonsuicidal inpatients, and 6.3% of the 64 nonpatients. More suicidal inpatients reported a first follow-up suicide attempt than the nonpatients ($\chi^2 = 10.1$, $df = 2$, $p < 0.006$). Considered in another way, among the 20 suicide attempters in the follow-up period, eight (40%) had attempted suicide before the initial assessment.

A significant difference was found in the cumulative probability of a first suicide attempt during the follow-up period between the suicidal inpatients, nonsuicidal inpatients, and nonpatients (Log rank, $\chi^2 = 9.78$, $df = 2$, $p < 0.008$). Suicidal inpatients had earlier first suicide attempts during the follow-up period than nonpatients (Log rank, $\chi^2 = 9.36$, $df = 1$, $p < 0.002$), but there was no significant difference in cumulative probability for a first suicide attempt during the follow-up period for the suicidal or nonsuicidal inpatients (Log rank, $\chi^2 = 1.28$, $df = 1$) or between the nonsuicidal inpatients and nonpatients (Log rank, $\chi^2 = 0.66$, $df = 1$).

Considering specific time intervals, there were a low number of subjects with a first suicide attempt in the early phases of the follow-up period. Three (5.7%) suicidal inpatients, 0 (0%) nonsuicidal inpatients, and 1 (1.6%) nonpatients reported a first follow-up suicide attempt by the time of the second follow-up year. Within 5 years after the initial assessment, 11 (20.5%) suicidal inpatients, 1 (6.3%) nonsuicidal inpatient, and 2 (3.1%) nonpatients reported a first follow-up suicide attempt. By the end of the 6- to 8-year follow-up period, the cumulative probability for a first suicide attempt was 30% for the suicidal inpatients, 17% for the nonsuicidal inpatients, and 5% for the nonpatients. The mean age at the first follow-up suicide attempt was 14.0 ± 2.3 years (range, 9–18 years).

Demographic and Clinical Risk Factors for Suicide Attempts during Follow-up

Demographic and clinical variables were evaluated as risk factors for a first suicide attempt during the follow-up period. The psychiatric disorders that were evaluated are shown in Table 1. Approximately 83% of the subjects had a psychiatric disorder at the initial assessment and/or in the follow-up period. Compared with the initial assessment, the follow-up period included as significantly higher prevalence of such psychiatric disorders as mood, disruptive, anxiety, and substance abuse disorders.

Table 2 shows the relative risk for factors that have significant unadjusted associations with the hazard function for a first suicide attempt in the follow-up period. These risk factors were present at the initial assessment, subsequent to the initial assessment, only within the year of the follow-up suicide attempt, or in the subject's lifetime. A risk factor was considered for analysis if it was present in at least 15 subjects. An exception was made for the diagnosis of schiz-

TABLE 2. *Risk Factors with Significant Unadjusted Associations with the Hazard Function of the First Suicidal Attempt in the Follow-up Period*

Risk Factor	Levels[a] Compared	At Initial Assessment RR	(95% conf)		After Initial Assessment RR	(95% conf)		Within Year of Suicide Attempt RR	(95% conf)		Lifetime RR	(95% conf)	
Suicidal severity	(2, 1)	2.21***	(1.29,	3.78)	—	—	—	—	—	—	—	—	—
	(3, 1)	4.88	(1.67,	14.28)	—	—	—	—	—	—	—	—	—
Being an inpatient		4.08**	(1.36,	12.21)	—	—	—	—	—	—	—	—	—
Number of disorders	(1–2, 0)	—	—	—	1.94***	(1.29,	2.94)	—	—	—	2.13****	(1.39,	3.27)
	(3–4, 0)	—	—	—	3.77	(1.65,	8.62)	—	—	—	4.55	(1.93,	10.72)
	(5–6, 0)	—	—	—	7.33	(2.12,	25.30)	—	—	—	9.71	(2.69,	35.08)
	(>6, 0)	—	—	—	14.24	(2.73,	74.26)	—	—	—	20.70	(3.73,	114.83)
Mood disorder	(1, 0)	3.54**	(1.35,	9.28)	7.24***	(2.12,	24.73)	5.28***	(1.76,	15.82)	6.36***	(1.86,	21.72)
Major depressive	(1, 0)	—	—	—	—	—	—	—	—	—	3.09**	(1.28,	7.45)
Dysthymic	(1, 0)	—	—	—	3.72***	(1.54,	9.00)	2.66*	(1.10,	6.44)	3.79***	(1.55,	9.29)
Disruptive disorder	(1, 0)	—	—	—	3.08*	(1.03,	9.21)	—	—	—	3.08*	(1.03,	9.21)
Conduct	(1, 0)	—	—	—	2.67*	(1.07,	6.71)	—	—	—	3.29**	(1.26,	8.57)
Anxiety disorder		—	—	—	—	—	—	—	—	—	—	—	—
Separation anxiety	(1, 0)	—	—	—	2.59*	(1.07,	6.25)	—	—	—	—	—	—
Substance abuse disorder	(1, 0)	—	—	—	2.84*	(1.18,	6.83)	2.84*	(1.18,	6.83)	2.84*	(1.18,	6.83)
Alcohol abuse	(1, 0)	—	—	—	3.42**	(1.40,	8.40)	—	—	—	3.42**	(1.40,	8.40)
Developmental disorder	(1, 0)	2.95*	(1.22,	7.12)	—	—	—	—	—	—	—	—	—
Specific developmental	(1, 0)	2.82*	(1.17,	6.77)	—	—	—	—	—	—	—	—	—
Other disorder	(1, 0)	2.89*	(1.18,	7.09)	—	—	—	—	—	—	—	—	—

Note: RR (95% conf) = relative risk (95% confidence interval).

[a] Levels compared indicates the variable ratings compared that range from the lowest score for variable to the highest score.

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.005$, **** $p \leq 0.001$.

ophrenia because of its potential importance in predicting suicide attempts. These analyses were computed using the 133 adolescents as a group.

Risk factors that had no significant associations with the hazard function for a suicide attempt were gender, age at the initial assessment, race/ethnicity, religion, social status, assaultive behavior at the initial assessment, and most diagnostic categories or specific disorders present at the initial assessment. However, major depressive, specific developmental, and other disorders were significantly associated with the hazard function for a first suicide attempt in the follow-up period. A variety of diagnostic entities was associated at other time periods, such as mood, disruptive, anxiety, and substance abuse disorders.

Multivariate Risk Models for Suicide Attempts during Follow-up

A series of Cox proportional hazard regression analyses were computed for the 133 adolescents, using the risk factors in Table 2 to identify models for the best combinations of risk factors for a first suicide attempt in the follow-up period (Table 3).

As shown in Table 3, the most significant risk factor present at the initial assessment for a suicide attempt during follow-up was the severity of suicidal behavior. A diagnosis of a mood disorder, either subsequent to the initial assessment or over the subject's lifetime, was the strongest diagnostic risk factor. Adolescents who attempted suicide in the follow-up period were more than seven times likely to have a mood disorder than adolescents who did not attempt suicide during follow-up. This is shown in Figure 2 where there was a significant difference between those with and without a mood disorder after the initial assessment in cumulative probability of a first suicide attempt during the follow-up period (Log rank, $\chi^2 = 13.95$, $df = 1$, $p < 0.0002$). Seventeen (85%) of those who attempted suicide and 45 (39.8%) of those who did not attempt suicide had a mood disorder after the initial assessment.

Having a mood disorder within the year of the suicide attempt during follow-up was the strongest risk factor for a first suicide attempt in the follow-up period. However, all suicide attempters had a psychiatric disorder within the year of the suicide attempt. The most prevalent psychiatric disorders at the time of the first suicide attempt in the follow-up period were mood (80%), disruptive (65%), substance abuse (50%), and anxiety (45%) disorders. No adolescent who was schizophrenic reported a suicide attempt in the follow-up period. This may be related to the fact that there were only eight adolescents with a diagnosis of schizophrenia in the follow-up period. The number of psychiatric disorders present in the subject's lifetime was also a significant risk factor.

Discussion

The findings of the present study support those of the companion paper (Pfeffer et al., submitted for publication) that reported that preadolescents and young adolescents with a history of suicidal ideation and/or acts had an earlier episode of suicidal ideation, threats, or attempts during the follow-up period. Specifically, the present report of suicide attempts suggests that preadolescent and young adolescent psychiatric inpatients with a history of suicidal ideation,

TABLE 3. *Best Combination of Factors for Risk of a First Suicide Attempt during Follow-up*

	Levels[a] Compared	RR	(95% conf)	Model R	(df)
Risk factor at initial assessment					
Model 1					
Suicidal severity	(2, 1)	2.21***	(1.29, 3.78)	0.185***	(1)
	(3, 1)	4.88	(1.67, 14.28)		
After initial assessment					
Model 1					
Mood disorder	(1, 0)	7.24***	(2.12, 24.73)	0.257****	(1)
Model 2					
Dysthymic disorder	(1, 0)	3.11**	(1.28, 7.58)	0.237****	(2)
Suicidal severity	(2, 1)	2.04**	(1.17, 3.55)		
	(3, 1)	4.15	(1.36, 12.61)		
Model 3					
Number of disorders	(1–2, 0)	1.94***	(1.29, 2.94)	0.210****	(1)
	(3–4, 0)	3.77	(1.65, 8.62)		
	(5–6, 0)	7.33	(2.12, 25.30)		
	(>6, 0)	14.24	(2.73, 74.26)		
Within year of suicide attempt					
Model 1					
Mood disorder	(1, 0)	5.28***	(1.76, 15.82)	0.223****	(1)
Lifetime					
Model 1					
Mood disorder	(1, 0)	6.36***	(1.86, 21.72)	0.236****	(1)
Model 2					
Dysthymic disorder	(1, 0)	3.07*	(1.24, 7.61)	0.235****	(2)
Suicidal severity	(2, 1)	1.99*	(1.13, 2.39)		
	(3, 1)	3.97	(1.29, 12.18)		
Model 3					
Number of disorders	(1–2, 0)	2.13****	(1.29, 3.27)	0.246****	(1)
	(3–4, 0)	4.55	(1.93, 10.72)		
	(5–6, 0)	9.71	(2.69, 35.08)		
	(>6, 0)	20.70	(3.73, 114.83)		

Note: RR (95% conf) = relative risk (95% confidence interval).

[a] Levels compared indicates the variable ratings compared that range from the lowest score for a variable to the highest score.

*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.005$, ****$p \leq 0.001$.

threats, or attempts had an earlier first suicide attempt during the follow-up period than did nonpatient preadolescents and young adolescents.

Recurrence of suicide attempts was common in this sample of subjects. Among the 26 preadolescents and young adolescents who attempted suicide at the time of the initial assessment, eight (30.8%) reported a suicide attempt in the follow-up period. Conversely, eight (40%) of the 20 suicide attempters in the follow-up period attempted suicide at the time of the initial assessment. Fifty percent of the 20 adolescent suicide attempters made multiple suicide attempts in the follow-up period. However, these results also suggest that although a history of suicide attempts enhances the risk for future suicide attempts, not all adolescents with such a history of suicidal acts will attempt suicide within a defined period of follow-up.

There were no deaths among the 201 adolescents who were located. This result agrees with other studies of suicidal children and adolescents reporting low suicide rates ranging from 0% to 4.3% during follow-up periods of 18 months to 12.5 years (Angle et al., 1983; Barter et al., 1968; Cohen-Sandler et al., 1982; Hawton et al., 1982; Mattsson et al., 1969; Nardini-Maillard and Ladame, 1980; Otto, 1972; Paerregaard, 1975; Pfeffer et al., 1988; Rydelius, 1984). Such findings suggest that suicidal children grow up. The lack of deaths in this study may be related to several considerations. This sample of subjects is just entering the high suicide risk period of 15 to 24 years of age (Shaffer, 1988). It is probable that as these subjects are followed through the second and third decade, the number of deaths will increase. Furthermore, because the absolute rate of suicide is low, large sample sizes in prospective studies are needed to predict suicide.

Assets and Limitations of This Study

There are a number of strengths of this study. This is a prospective study of an enriched sample at risk for suicide attempts by virtue of the fact that the majority of the total sample had a history of suicidal ideation, threats, or attempts at the initial assessment. In addition, these subjects are among the relatively few in longitudinal studies of preadolescents with high rates of mood disorders (Kovacs et al., 1984a,b, 1988), a factor that also enhances risk for future suicide attempts. A high rate (97.1%) of the initial sample

was located, and some information was obtained about them. The same research instruments were used throughout the course of investigation. This study demonstrated the feasibility of using survival analysis in evaluating risk for a first suicide attempt during the follow-up period.

This study has several limitations. Because it is uncommon for preadolescents to be psychiatrically hospitalized, it may not be possible to generalize the results of this study for risk models of adolescent suicide attempts in the general population. There were higher rates, both initially and in the follow-up period, of psychopathology among the nonpatients than were reported in other studies of community samples (Anderson et al., 1987; Bird et al., 1988). There are several reasons why this may have occurred. This nonpatient sample is not a probability sample of the general community especially because the nonpatients were selected by stratified random sampling to match the demographic characteristics of the former inpatients. Males, therefore, predominated, and it is known that rates of psychopathology are higher in preadolescent and young adolescent males. There may have been other selection biases especially with regard to personal issues involving psychological stress. However, an advantage gained by the higher rates of psychopathology among the nonpatients was to highlight the significance of the findings that distinguished the suicidal inpatients from the nonpatients. There were problems of attrition, with only 64.3% of the total initial sample completing the interview procedures.

Common to most studies (Angold et al., 1987; Apter et al., 1988, 1989; Edelbrock et al., 1986; Ivens and Rehm, 1988; Morkros et al., 1987; Weissman et al., 1987), there were low rates of concordance between subject and parent reports of suicide attempts and diagnostic factors. This emphasizes the difficulties in evaluating suicide attempts among children and adolescents. Because much of the data was retrospective, multiple informants and best estimate concensus of the data were utilized to minimize this problem. Finally, the low number of subjects with suicide attempts and with certain psychiatric disorders, such as substance abuse or schizophrenia, limited the possibility of identifying certain risk factors.

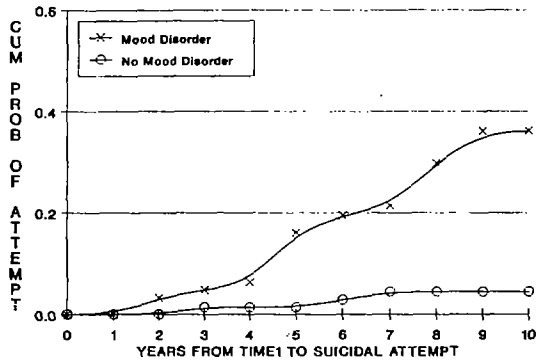

FIG. 2. Cumulative probability for first suicide attempt during follow-up for presence of mood disorder during the follow-up period.

Relation between Suicidal Episodes and Suicide Attempts

In a companion paper (Pfeffer et al., submitted for publication), suicidal episodes were delineated as the expression of suicidal fantasies and/or acts within a discrete time frame. Suicidal episodes are the most inclusive characterizations of suicidal impulses. Suicidal episodes involve the expression of suicidal ideation, threats, attempts, or suicide. In this high-risk sample of preadolescents and young adolescents, suicide attempts occurred less frequently than suicidal episodes in the follow-up period. For example, approximately 45% of the 133 adolescents reported at least one suicidal episode during the follow-up period (Pfeffer et al., submitted for publication). However, only 15% of the 133 adolescents reported a suicide attempt in the follow-up period.

The strongest risk factor for an earlier first suicidal episode in the follow-up period was a psychiatric disorder that was present in the follow-up period. Psychiatric disorders most associated with risk for an earlier first suicidal episode in the follow-up period were mood, disruptive, and schizophrenic disorders (Pfeffer et al., submitted for publication). However, the present study of suicide attempts suggests that mood disorders in the follow-up period is the strongest risk factor for a suicide attempt in the follow-up period. Adolescents who attempted suicide were seven times more likely to have a mood disorder than those who did not attempt suicide. More specifically, the combination of chronic depression diagnosed as a dysthymic disorder and a history of a suicidal episode are strong risk factors for an earlier suicide attempt in the follow-up period. The risk factors identified in the present study of adolescent suicide attempts are similar to those noted for adolescents who committed suicide especially with respect to mood disorders and history of suicidal behavior (Brent et al., 1988; Hoberman and Garfinkel, 1988; Shafii et al., 1985; Shaffer, 1988).

Clinical and Research Implications

This study highlighted that adolescents with histories of suicidal behavior have a high intensity of behavioral morbidity. For example, approximately 29% of all 140 follow-up years of the adolescent suicide attempters included at least one suicide attempt. In some cases, multiple suicide attempts were reported within the same year. Therefore, adolescents with histories of suicidal ideation and/or acts should be evaluated for early signs of suicide attempts.

The fact that all adolescents who attempted suicide in the follow-up period had a psychiatric disorder suggests that adolescents who attempt suicide are not normal youngsters responding primarily to environmental stresses. Since the strongest combinations of risk factors were more proximal to the first suicide attempt during the follow-up period, youngsters with a current episode of a mood disorder and/or a history of suicidal ideation, threats, or attempts should be followed closely throughout a current episode of psychiatric disorder. Furthermore, since not all adolescents with a history of suicidal ideation, acts, or psychiatric disorders will exhibit suicide attempts within a defined follow-up period, changes in risk factors should be monitored closely.

Several research implications can be derived from this study. The use of survival analysis techniques in this study enabled the identification of risk over time. A recommendation can be made that other prospective investigations of children and adolescents at risk for suicidal behavior or psychopathology utilize this statistical method.

This study evaluated suicidal risk during an important developmental transition from preadolescence to early adolescence. Additional prospective research is needed to identify whether there are unique risk factors for suicide attempts during other developmental periods, such as the transition from adolescence to young adulthood.

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Use of the Children's Depression Rating Scale in an Inpatient Psychiatric Population

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The Children's Depression Rating Scale is a useful and reliable instrument for measuring the severity of depression in children. The scale was initially used in a pediatric liaison population. This study reports its use in consecutive admissions to a child inpatient unit. Systematic evaluations of the children resulted in many diagnoses of depression which were missed by the clinical staff. Two relatively inexperienced raters did nearly as well as two raters who originated the scale, suggesting that the CDRS may have practical utility in many settings.
(J Clin Psychiatry 44:200-203, 1983)

The need for a childhood depression rating scale is reflected by the burgeoning literature about affective illness in this population.[1-4] Identification of characteristic behaviors of childhood depression and assessment of their intensity is important in both research and treatment. A rating scale, while not in itself a diagnostic tool, can alert the clinician to the possibility of depression and provide a more precise assessment of the severity of diagnosed depression.

Several workers have devised scales for research in childhood depression.[5-7] None of these investigators except Kovacs[5] has published a description of the population studied or given statistics on reliability and validity. The Kiddie-SADS, a structured interview analogous to the Schedule for Affective Disorders and Schizophrenia[9,10] for adults, does an excellent and thorough job of assessing the characteristics of depression in children. However, it takes 1-2 hours to complete this structured interview separately with the child and parent, and it is primarily a diagnostic instrument rather than a severity rating. The Children's Depression Rating Scale (CDRS), developed by Poznanski and Cook,[11] requires about 20 minutes of the psychiatrist's time and thus has the potential for repeated ratings. Like the Hamilton Depression Rating Scale[12] from which it is derived, the CDRS must be administered by a trained professional with clinical knowledge of children.

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This research was supported by National Institute of Mental Health grant MH-34196.

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The CDRS is designed for use with children between the ages of 6 and 12 years. We chose this developmental level since school-age children are a reasonably homogeneous group. While depression is also seen in adolescents and preschoolers, it is difficult to get verbal confirmation from preschoolers, and depressed adolescents are likely to have a mixture of childhood and adult clinical features of depression.

The CDRS was first checked for reliability and validity in a pediatric liaison population, chosen primarily for convenience. We were aware that this was a group in which any cases of depression were likely to be secondary. In the study reported here, two psychiatrists independently rated each child first with a global clinical rating of depression based on the clinician's judgment and then with the CDRS. The two total scores of the CDRS and the two global clinical ratings were correlated between ratings for reliability and across ratings for concurrent validity. Both reliability and validity were very acceptable. The next question was how the CDRS would perform in a psychiatric setting. The results reported in this study come from our preliminary findings with 30 children at Yorkwoods, the Youth Division of Ypsilanti Regional Psychiatric Hospital.

METHOD

Scale Construction

The CDRS resembles the Hamilton Depression Rating Scale (HAM-D) in its use of categories and subcategories (see Table 1), but with modifications to make it more useful for our age group. The scale has 15 categories, with a maximum score of 61 and a minimum score of 15. A score of 15 indicates no depression on the CDRS; the equivalent score on the HAM-D is zero.

Sample

The 30 children in this study were seen as part of a preadmission interview. We saw all consecutive preadmissions who were 12 years of age or under, excluding only mentally retarded and psychotically confused children. Although the CDRS had been used previously in the pediatric setting with 6- and 7-year-olds, no children in this age group were admitted to the hospital during the period of this study. In the sample of 30 children, the age distribution was as follows: 8 years, N = 1; 9 years, N = 5; 10 years, N = 8; 11 years, N = 11; 12 years, N = 5.

There were 6 girls and 24 boys in our sample. This

Continued

sex ratio is not surprising, in that boys are far more frequently referred for admission to a child inpatient psychiatric unit.

Procedure

Prior to the interview, informed consent was obtained from parents or guardians. Each child was seen by two child psychiatrists from a pool of four investigators: the two scale originators (E.O.P. and S.C.C.) are termed "experienced raters," and the other two raters, less familiar with the CDRS, are labeled "inexperienced raters."

One psychiatrist interviewed the child while the second psychiatrist observed the interview. The CDRS instructions specifically state that information can be obtained from multiple sources. Thus, parents and/or ward personnel were briefly interviewed on items where we thought the child was an unreliable source of information (e.g., irritability and social interaction). After the interview, the two psychiatrists independently made a global clinical assessment of depression (1 = definitely not depressed, 2 = doubtful depression; 3 = mild depression; 4 = moderate depression; 5 = severe depression) and filled out the CDRS.

The reliability of the scale was established by comparing the global ratings (and the item sums) made by the two psychiatrists. Construct validity such as can be provided by biologic measures or drug studies are unavailable in this age group of children. Concurrent validity was developed in the manner used by Beck et al.[12] The item scale rating was compared with the global rating from an independent source; thus, the global rating (GR) of each psychiatrist was compared with the item sum of the other psychiatrist, as follows.

	Experienced Raters: GR	Experienced Raters: Sum
Inexperienced Raters: GR	.83	.75
Inexperienced Raters: Sum	.74	.80

Each individual item in the scale was correlated with the global and sum scores of each psychiatrist to assay the strength of the individual items relative to both the global ratings of depression and the sum of the CDRS (see Table 2).

The clinical diagnosis of depression was made using diagnostic criteria developed by Poznanski et al.[11] for children. These criteria are as follows: (1) depressed mood, behavior, or appearance lasting one month or longer; and (2) four of the following items for probable depression and five for definite depression — anhedonia, lowered self-esteem, social withdrawal, impairment of schoolwork, difficulty with sleep, complaints of fatigue, hypoactivity, morbid ideation, suicidal ideation, or suicide attempt. These criteria differ from the Research Diagnostic Criteria[13] for adults in that nonverbal depressive affect can substitute for verbal reports of dysphoria, and social withdrawal replaces anorexia and weight loss.

TABLE 1. Comparison of Items on the Hamilton Depression Rating Scale (HAM-D) and the CDRS

HAM-D		CDRS	
Item	Rating	Item	Rating
Depressed mood	0-4	Depressed mood	1-5
		Weeping	1-3
Guilt	0-4		
		Self-esteem	1-5
Suicide	0-4	Suicidal ideation	1-5
		Morbid thoughts	1-4
Initial insomnia	0-2	Sleep	1-3
Middle insomnia	0-2		
Delayed insomnia	0-2		
Work & interest	0-4	Schoolwork	1-5
		Capacity to have fun	1-5
Retardation	0-4	Expressive communication	1-3
		Hypoactivity	1-3
Agitation	0-4		
Anxiety-psychic	0-4		
Anxiety-somatic	0-4	Frequent physical complaints	1-4
Gastrointestinal	0-2	Eating pattern	1-3
General somatic	0-2	General somatic	1-3
Genital	0-2		
Hypochondriasis	0-4		
Loss of insight	0-4		
Weight loss	0-2		
		Social withdrawal	1-5
		Irritability	1-5
Total	52	Total	61

TABLE 2. Individual Item Correlations with the Clinical Global Rating and the Sum of the CDRS

	Experienced Raters		Inexperienced Raters	
Item	Global	Sum	Global	Sum
Depressed mood*	.96	.90	.95	.88
Weeping	.65	.59	.65	.61
Self-esteem	.45	.60	.43	.59
Morbid thoughts	.43	.43	.44	.48
Suicidal ideation	.62	.63	.57	.59
Irritability	.10	.23	.04	.20
School performance*	.58	.72	.58	.72
Anhedonia*	.80	.86	.78	.80
Social withdrawal	.63	.69	.65	.69
Expressive communication*	.68	.85	.67	.80
Sleep	.19	.13	.09	.13
Disturbance of eating	.54	.52	.45	.48
Physical complaints	.42	.51	.37	.49
Somatic	.55	.62	.53	.61
Hypoactivity*	.67	.74	.67	.75

* Items most strongly correlated with the total CDRS scores.

RESULTS

The mean CDRS rating for the entire group of 30 children was 29.3, with a range of 17 to 45.5. (A score of 15 indicates no abnormality on each of the 15 items.)

Fourteen children were given a global rating of 1 or 2, i.e., definitely not depressed or doubtful depression. There were 28 ratings for these 14 children; 27 of the 28 ratings did not qualify as depressed by the research criteria. In this group of children, one diagnosis made by the clinical staff using DSM-II included the word "depression;" this child did not qualify for a diagnosis of depression by our research assessment.

Seven children had a global rating of mild or mild-moderate depression (3 or 3.5). Four of these children qualified as depressed using the research criteria, yet only 3 had the word "depression" as a possibility in their routine clinical diagnosis.

Nine children had a global rating of moderate to severe depression. Eight of these 9 fulfilled the research criteria for childhood depression, yet only 5 had the word "depression" in their routine clinical diagnosis, and this was often included as afterthought. It appears that depression in children often goes unnoticed, even in a psychiatric residential setting.

Analysis of variance for CDRS means by clinical global severity rating indicated a significant difference ($F = 72.55$, $df = 2, 27$, $p<.01$). Sheffé's multiple comparison test was then used to assess which groups differed. The results indicate that each group mean significantly differed from the others, in the expected direction ($p<.001$).

Our chief concern is that the scale reflect the severity of the depression. It can be seen in Figures 1 and 2 that the CDRS score increased in a linear fashion with increasing global severity of depression. The close correlation between the experienced and inexperienced rater on the CDRS is demonstrated in Figure 1.

DISCUSSION

The overall performance of the CDRS indicates that it does measure the severity of depression in children. A score of 15 is a completely normal baseline score on every item. Almost all children with CDRS scores under 25 were not globally rated as depressed, nor did they qualify for a research diagnosis of depression. The boundaries between mild, moderate, and severe depressions cannot be clearly delineated in this small sample; however, it appears that scores between 25 and 35 points are in the mild range and scores over 35 are in the moderate to severe category.

Morbid and suicidal ideation were included in this study but had not been used in the previous study of a pediatric liaison population, as we felt uneasy about asking these questions in a pediatric hospital. We wondered about the familiarity of children in our age range with the meaning of suicide and questioned the usefulness of morbid ideation and suicidal ideation as categories. Somewhat to our surprise, virtually all of the children at the state hospital knew the word "suicide." (Television is a significant teacher!) In interviews, two of three severely depressed children strongly denied thinking about suicide. These children were given ratings of 4 or 5 on this item, in accord with our operational definition. Later, we learned that both children had seriously discussed suicide with their ward attendants and/or teachers. Thus, children who are depressed but deny suicidal thoughts may well be suicidal, just as is the case with adults.

Morbid ideation occurred with or without suicidal thoughts. Therefore, it appeared advantageous to separate the two items to get a clearer picture. Both morbid ideation and suicidal ideation are important clinical feature of depression in children.

Figure 1. Correlation of CDRS scores with global rating of depression.

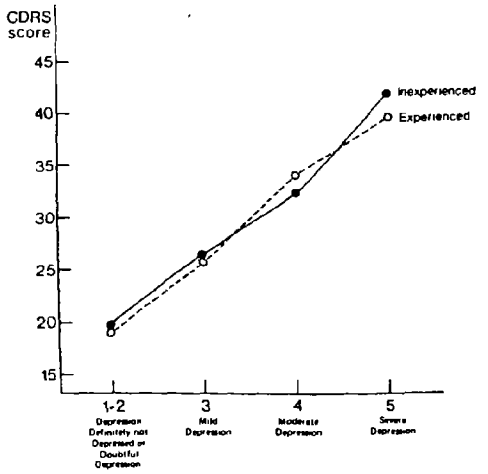
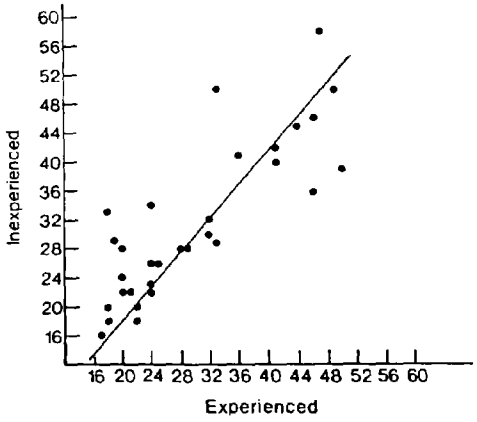


Figure 2. Linear regression curve for intragroup reliability on total CDRS scores: Experienced vs. inexperienced raters.



In the pilot study, three other items — reversal of affect, anxiety, and hyperactivity — were assessed for possible inclusion in the CDRS but were dropped because they did not show any correlation with depression in children. Hyperactivity had been previously thought to represent masked depression in children.[15] Hypoactivity, rather than hyperactivity, was characteristic in our group of depressed children. However, our sample is relatively small, and our findings do not rule out the possibility of a subgroup of hyperactive depressed children.

Children with severe separation anxiety were often difficult to rate. Some of these children had a depressed affect without manifesting the cardinal features of a depressive syndrome, while others showed the reverse picture. They also tended to widen the difference between the two raters' observations more than other subgroups of children. The interrater reliability was better in these children's assessment when the mother was present. Obviously, additional work needs to be done with this group of patients.

It is very clear that childhood depression is underrecognized. Of the children clinically assessed as having mild, moderate, or severe depression by our global rating of depression, only about half had the word "depression" in the clinical service records. None of these children were diagnosed as having a primary depression. The low reporting of depression in children probably stems from (1) failure to consider the possibility of depression in children aged 12 years and under; and (2) the interviewing techniques of child psychiatrists, which rarely involve questions in the areas of morbid ideation, suicidal ideation, sleep difficulties, and an assessment of the child's capacity to enjoy life.

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Children's Depression Rating Scale—Revised[1] (September 1984)

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Description of the Scale

The Childhood Depression Rating Scale—Revised (CDRS-R) is a clinician-rated instrument designed to measure the presence and severity of depression in children aged 6 to 12 years. The CDRS-R consists of 17 items. Fourteen of these items are rated on the basis of the subjects' responses to a series of standardized questions. This semi-standard interview can be administered to children ages 6 to 12, their parents, teachers, case workers, or other sources of information in approximately 30 minutes. The first 14 items are rated on the basis of this interview. The remaining 3 items of the CDRS-R are rated by the clinician on the basis of the *child's* nonverbal behavior. These 3 items are not rated when interviewing a subject other than the child.

The 17 items of the CDRS-R are scales from 1 to 5 for sleep, appetite, and tempo of speech items and from 1 to 7 for the remaining 14 items. A rating of 1 indicates no abnormality while a rating of 3 indicates mild symptomatology. A rating of 5 or more on all items indicates definite psychopathological symptomatology.

Reliability and validity studies on this instrument have been carried out in a hospitalized pediatric population, in a child psychiatric inpatient population, in three outpatient child psychiatric clinics, and in a elementary school sample.

[1]The CDRS-R was developed by E.O. Poznanski, M.D., with assistance of the staff of the Youth Affective Disorders Clinic. Investigators wishing to use or quote the CDRS-R should contact Dr. Poznanski at the address below.

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Administering the CDRS-R

Prior to administration of the scale, the clinician should familiarize himself or herself with the interview so that a freely flowing interview style is developed. Although the interview is designed so that the examination proceeds from less threatening areas of questioning to more emotionally evocative areas, some children spontaneously provide information for items out of the interview sequence. This should be accommodated in a manner that allows for the building of rapport between clinician and subject. The clinician should anticipate that some subjects are slow to become involved in the interview and may initially give bland and guarded responses. After more rapport has been developed, it may be necessary to re-question such a person about earlier items.

The developmental level of the subject being examined must always be considered in interpreting responses to questions on the CDRS-R. Some children cannot understand words such as guilt, irritability, or suicide. Suggestions are included in the interview for ways to rephrase these concepts in more concrete language that the child may better understand. The child's ability to understand time concepts must also be considered. Again, concrete time markers such as usual daily activities or meals may be helpful in assessing the duration of an unhappy, sad mood state. The clinician must make an effort to use language and time markers consistent with the child's developmental capacities throughout the interview and rating process.

The effect of various settings in which the CDRS-R may be administered must also be considered by the clinician rating the instrument. Children in psychiatric settings are more likely to give guarded responses or withhold information than those in nonpsychiatric settings such as schools. Within the pediatric liaison setting, where children have debilitating physical illness or fever, the physical state of subjects may promote apathetic withdrawn behavior, fatigue, or sleep disturbance. Children

may also suffer severe separation anxiety, appearing withdrawn, tearful, and socially isolative outside of their mother's presence, yet happily interact with peers when their mother is present. Gathering information from multiple sources is recommended to make the most valid CDRS-R rating. However, it is important to consider the source of information when determining the final, combined CDRS-R score. For example, the child's description of sleep disturbance is often more valid than the parental description since parents are often not aware of the child's sleep behavior after they have retired to bed. On the other hand, children may be reluctant to report behaviors that would promote reprimands from adults. Therefore, behaviors such as irritability and eating disturbances are more accurately reported by parents.

Determining Diagnosis

Prior experience with clinical populations indicate that a summary score of 40 or above on the CDRS-R is a strong indicator of the presence or potential for a Major Depressive Disorder. Although the score of 40 is a reliable indicator of depression, it should serve as a heuristic, not as a criterion by which a child is diagnosed Major Depressive Disorder or not. Other usual methods of psychiatric evaluation such as unstructured interviews, family history, pediatric examination, laboratory examinations, etc. may be used to determine the diagnosis using diagnostic criteria such as DSM-III (Diagnostic and Statistical Manual—3rd ed., 1980) or Research Diagnostic Criteria. When a diagnosis of depression is certain, the CDRS-R may be used as a measure of severity of the depression and to provide a basis for comparison over time.

The Individual Items

A. Schoolwork

A child's schoolwork is usually impaired while he or she is depressed. The cognitive impairment stems from a general lack of interest or enthusiasm, difficulty in concentrating, and negative cognitions (views of the world). The difficulty concentrating on external tasks is the result of a turning inward and a preoccupation with thoughts and worries rather than the result of distractibility by external stimuli. The child may be negative about the school environment and/or his or her school performance. He or she may perceive his or her schoolwork to be poorer than it objectively appears.

The depressed child's diminished academic performance represents a change as opposed to chronic and consistently poor schoolwork. There may also be variability in performance of schoolwork associated with mood shifts. Children with chronic learning problems also decline in performance relative to their usual capacity to achieve academically. Likewise, bright children may maintain high grades, but teachers or parents report a decrease in their usual enthusiasm for learning. It is necessary to assess the child's usual capability and motivation to perform academically, prior to the depressive episode, to accurately rate this item.

The rater should take care, further, to distinguish between general diminished school performance and disturbance with a specific subject or teacher.

If school is not in session, the clinician can assess difficulty attending to other activities, e.g., games, at-home reading, television.

Examples:

Rating of 1. "I like school, except for math. I got all B's except a C in Math—It's hard."

Rating of 3. "My teacher says I don't do enough effort . . . my mind wanders . . . I think of things people said, or about music."

Rating of 5. "I'm trying the best I can but my schoolwork is not good, I might have to go back to 5th grade . . . I don't finish homework . . . it's hard to keep what I remember in my head" (11-year-old who tested on the WISC-R in bright normal range).

Rating of 7. "I am failing all subjects . . . I don't like it . . . they ain't teaching me nothing . . . I hate my teachers and the kids."

B. Capacity to Have Fun

Loss of interest or pleasure in activities can be striking in a depressed child. Although adults

can remain very serious and get to enjoy a game of cards or chess, normal children rarely hide their pleasure and enthusiasm at their games. The presence and severity of this symptom can be assessed by the types and numbers of activities the child can enjoy, by the child's interest or enthusiasm expressed while describing the activity, and by the amount of boredom the child feels. While every child occasionally feels boredom, the depressed anhedonic child may say he or she feels bored 50 to 100% of the time. This loss of interest may be expressed more subtlely. For example, a child may describe pleasurable activities which only occur on rare occasions, or are only available in a different season of the year, e.g., ice skating in the summer. Some children cannot name any activity that they enjoy. Severely depressed children may become primarily passive watching others play without participating themselves or watch television with little awareness of the program playing. They may participate in games but only "go through the motions," not enjoying themselves.

Examples:

Rating of 1. "I like to go sledding and skating (in winter) or just play outside. Yeah, I get bored sometimes—on Sunday when I have to sit at church."

Rating of 3. "I go bike riding . . . about twice a week . . . oh, and Boy Scout outings can be fun . . . no, I don't think I'm bored *too* much."

Rating of 5. "Going fishing is fun, my Dad and I went fishing twice last year . . . I color and play with the dog. Oh yes, I got *really* bored . . . I got bored every day . . . a lot."

Rating of 7. "I don't like nothing, I want to be by myself." (Mother confirms child does not play and refused activities suggested by her.)

C. Social Withdrawal

Depressed children commonly have difficulty socializing with peers. They withdraw from peer activities, turn down opportunities to play with peers, or provoke peers to reject them. Unlike schizoid or avoidant children, depressed children usually have developed the capacity for interpersonal relationships and have been able to socialize with peers prior to the onset of the depressive episode. Therefore, it is necessary to distinguish between a chronically isolative personality style and a change in social behavior to rate this item. When the difficulty in social relating has been longstanding and unchanged, "2" is the appropriate rating for this item.

Examples:

Rating of 2. "He had a few friends in the neighborhood but they change every few weeks. He's never had any close friends."

Rating of 3. "Usually Sue calls me . . . sometimes I play with her but mostly I'd just rather stay home . . . "

Rating of 5. "He had friends in school last year and two boys he grew up with in the neighborhood—now they call him names and fight a lot . . . it's because he won't play with them anymore or he only plays with Alex."

Rating of 7. "I'd rather be alone . . . I like being by myself . . . It's better that way—all those kids smoke and drink now . . . I don't have friends any more."

D. Sleep

Although the total sleep time of depressed children is not different from that of normal children, depressed children often report initial, terminal, or middle-of-the-night insomnia. Many children have intermittent awakening because of anxiety, nightmares, etc. from which they return to sleep quickly. Depressed children have more consistent patterns of sleep disturbance and often stay awake more than 30 minutes after awakening.

Example:

Rating of 3. "About twice a week I wake up. It's dark and my parents are asleep . . . I stay awake for an hour!"

Rating of 5. "I can't sleep ever. They put me to bed at 9 p.m. but I don't go to sleep until 10 p.m. I get up at 2 a.m. and watch TV."

E. Appetite or Eating Patterns

Depressed children may have changes in their eating patterns during a depressive episode. These may be loss of appetite and weight loss or excessive appetite and weight gain. Children can describe changes in appetite. Usually

parents give more objective information regarding the child's food intake.

Examples:

Rating of 3. "I eat lunch and dinner, but I'm not really hungry . . . I lost 3 pounds on the scale."

Rating of 5. "I starve myself even though I'm hungry . . . I think the food is poisoned—and my clothes fit too big now."

F. Excessive Fatigue

While all children may feel tired during the day, depressed children feel unusually tired and heavy. They may complain frequently of fatigue or even nap frequently. Typically, even after a nap, a depressed child continues to feel tired or drowsy. The fatigue is not specifically related to boring schoolwork or a situation the child may wish to avoid, but instead is more pervasive and persists across environments or situations. When a child is persistently and frequently so tired that he or she prefers to sleep or rest, instead of to play, a severe rating of 7 is indicated.

Examples:

Rating of 1. "I feel tired sometimes like when my mother asks me to clean up my room . . . math homework makes me feel tired, too."

Rating of 3. "I usually take a nap after school . . . yeah, then I feel o.k. to do my homework (10-year-old boy).

Rating of 5. "I always go to sleep 3 times in the day" (child looks fatigued in the interview).

Rating of 7. "After school I'm too tired to play . . . I lay on the couch from 3 to 5 p.m. but I still feel tired after dinner."

G. Physical Complaints

Somatic complaints are common in depressed children and may represent either the gastrointestinal disturbances which occur in depression as well as physiological concommitants of anxiety. Pains may be subjectively experienced as more intense during a depressive episode. Since every child has occasional complaints, a pathological rating should not be considered unless the child's complaints seem excessive.

Examples:

Rating of 1. "I get headaches sometimes . . . they usually go away . . . no, I don't take an aspirin."

Rating of 3. "I get headaches . . . on hot days . . . they don't go away by themselves . . . I had a few leg aches, too. I get stomach aches a lot . . . no, I don't stop playing."

Rating of 5. "Every morning I wake up with a pain in my neck . . . my forehead hurts where a boy hit me last week."

Rating of 7. "I have pain all the time in my chest and stomach. I think I am dying because I am sick with headaches . . . my things are poisoned and there is Tylenol in my food."

H. Irritability

An irritable mood often accompanies or alternates with a depressed mood or is present in the depressive syndrome. This symptom is usually best assessed by observers—parents, teachers, or the clinician interviewing the child, but occasionally the child is also aware of feeling "grouchy," or can describe temper outbursts and can describe these feelings stated. When a child is irritable during the interview, we recommend rating a 5.

In assessing this item, the clinician should consider the duration of irritability; the appropriateness of the context in which irritability arises, as well as the appropriateness of the intensity of irritability in a given context; and the frequency of irritability. Again, as with schoolwork or social withdrawal the clinician should assess that the irritability being described represents a subjective feeling or behavioral change rather than a temperamental characteristic.

Examples:

Rating of 3. "He has little tiffs with his brother several times a week. It's because he's so grouchy . . . the brother doesn't do anything and he's mad for a half hour."

Rating of 5. "Whenever my sister talks to me I get so mad . . . I just go in my room and sit for an hour until I

feel better . . . Oh yeah, it happens 3 or 4 times a week."

Rating of 7. "Every day she gets angry and slams her door when she goes to her room . . . she says she hates Dr. H. and wants to kill him."

I. Guilt

Children can feel overwhelmingly guilty; but guilt is a difficult area to obtain consistent and reliable information from children. Developmentally, the concept of guilt is not cognitively accessible to a very young child. It is rarely grasped by a child under the age of 8 years. Lack of evidence of guilty does not necessarily mean the child does not feel guilt. A child may make a conscientious effort to make a good impression on the examiner, and not reveal misdeeds.

Pathological guilt is an important item to assess when the child is able to describe these feelings. Often, it is necessary to define guilt for the child and to be sure he or she understands the concept before proceeding with the interview. In assessing for pathological guilt—as opposed to guilty feelings appropriate for a misdeed—the clinician must evaluate the duration and intensity of the child's feelings in relation to the severity of the event reported.

It should be determined when a guilt-inducing event occurred and the length of time that the child continues to blame himself or herself for the outcome.

Example:

Rating of 1. "I broke a lamp . . . it was my fault . . . but I feel better about it now."

Rating of 3. "I hit my brother . . . I felt bad about it . . . yes, I do still think about it . . . "

Rating of 5. "I feel bad when I don't do something my mother tells me to do and then I lie and say I did it and I feel badly the *whole day*."

Rating of 7. "I said I hate my uncle . . . he died . . . it's all my fault that he died . . . why . . . because I said it!"

J. Self-Esteem

Feelings of self-reproach are common in depression. Loss of self-esteem may be difficult to determine, especially in 6- to 9-year-olds whose self-concept is less developed. Structured questions about the child's degree of satisfaction with his or her looks, personality, intelligence, and acceptance or rejection by peers yield more information than abstract questions such as "do you like yourself?." Observers often may report on the child's propensity to be teased, called names, or be picked on by other children; propensities which diminish a child's self-esteem.

Low self-esteem, however, is not specific to depression. It is seen in a variety of psychiatric diagnoses as well as in children who do not qualify for any psychiatric diagnosis.

Many children will spontaneously volunteer information about their self-concepts, but others may be modest and require encouragement before responding. If a child hesitates on every question about him or herself, or gives only half-hearted responses, we recommend a higher rating.

It is important to evaluate the overall affective tone of the child's responses. Some children will describe themselves negatively, calling themselves "stupid" or admit their peers call them nicknames such as "fatso" or "fag." Derogatory nicknames tend to lower a child's self-esteem. When children admit to being called such names, a higher rating is also recommended.

For this item, and the morbid ideation item, a pathological rating is 4 or more. A child must report two or more major areas of self-image in which he or she feels deficient to be scored a rating of 4.

Example:

Rating of 1. "Basically, I like my looks and wouldn't want to change anything . . . except maybe (offhandedly), I could be skinnier."

Rating of 3. "I'd like to change my nose. I'm smart more than dumb. Most kids like me" (mentions changing looks twice more to subsequent questions).

Rating of 4. "I wish I had my teeth straightened . . . I think I should be smarter . . . "

Rating of 5. "I hate my face . . . kids call me retardo."

Rating of 7. "I'd like to change my face, my hair, and my personality. They say I'm smart but I think I'm dumb . . . nobody likes me."

K. Depressed Feelings

This item rates *verbally* expressed depressed feelings. Since every child feels unhappy from time to time, the clinician must determine the intensity, duration, and degree of association of the sad feelings to an event. Higher ratings are indicated when either the intensity or duration of unhappiness are excessive. Lack of association with an event as well as lack of reactivity of the mood also elevates the rating score.

Examples:

Rating of 1. "I felt so sad when my dog ran away . . . I cried . . . I felt sad a lot until my mom gave me a new dog."

Rating of 2. "I cry when my mother goes away . . . I'm afraid she won't come back . . . no, I'm not sad if she's at home."

Rating of 3. "I tell my mom I feel moody . . . it's hard to shake that feeling when I feel moody . . . oh, a few times a week."

Rating of 5. "I feel sad a lot . . . I go in my room and lay down . . . nothing happened . . . I don't know why."

Rating of 7. "I feel sad a lot . . . it hurts my heart . . . I went to the doctor because my chest hurts . . . I feel so sad it hurts but they can't find anything wrong with me."

L. Morbid Ideation

Depressed children often have thoughts of death, passive wishes to die, and other morbid concerns. Concerns about one's own death are considered morbid rather than suicidal ideation, unless the child only considers his or her own death in the context of suicide. Most nondepressed latency children develop temporary fears of separation and death of the quality described in the child's prayer "If I should die before I wake, I pray the Lord my soul to take . . . ." These types of concerns should not be assessed as pathological and should receive ratings of only 1 or 2. Concerns or fears about death shortly after a traumatic environmental event, such as separation from death of a pet or family member, should not be rated pathologically (i.e., 4 or above).

Depressed children, on the other hand, may have exaggerated responses to reality events and remain excessively preoccupied with deaths which occurred in the distant past, or of people little known by the child. The thoughts may seem excessive because of the frequency or intensity with which the child recalls the precipitating event. If these thoughts are excessive but not bizarre and are related to the reality event, we recommend a rating score of 3. When the morbid thoughts preoccupy the child's thoughts and extend beyond external reality or become extensive or bizarre, we recommend a rating of 4 or higher.

Examples:

Rating of 2. "I worry that my grandfather might die." (Grandfather is in the hospital.)

Rating of 3. "Someone shot a bullet in our house . . . I'm still afraid I might die . . . I might get shot."

Rating of 4. "I worry that my father will get sick and lose his job . . . or he might die" (Father has been hospitalized twice—not currently ill or hospitalized.)

Rating of 5. "I don't think I should exist in the world . . . at night I can feel death's presence."

Rating of 7. "My dog might die . . . I have pain in my heart and stomach because I am dying . . . my food is poisoned . . . am I going to die?" (asks mother daily "am I going to die?")

M. Suicidal Ideation

Suicidal ideation, gestures, and attempts occur in childhood depression. Most children 7 years or older are familiar with the word suicide and its meaning or can readily understand once the meaning of the word is explained to them. However, the child's response to questioning about suicidal ideas is not always straightforward. Sometimes a child will deny or sharply deny suicidal thoughts when they are present. The child should be further questioned after attempts to put him or her more at ease. But, if sharp denial persists, we recommend a rating of 2. When a child admits

to thoughts of suicide, usually when angry, not accompanied by suicidal gestures or attempts, we recommend a rating of 3. Recurrent thoughts of suicide merit a rating of 5. Any child admitting to active suicidal thoughts or who has made a suicide attempt within the prior month, should be given a rating of 7.

Examples:

Rating of 3. "When my mother yelled at me and made me stay in my room, I told her "I'm going to kill myself."

Rating of 5. "Yeah, I think about walking in front of a car or jumping out of a high window . . . it makes me sad to think about it, so I try not to."

Rating of 7. "I want to kill myself . . . I think I'll go in front of a car . . . I tried to stab myself with a knife . . . last week."

N. Weeping

Weeping can be seen in childhood depression due to depressed or irritable moods. Most often, parents or other observers report excessive weeping. At times, depressed children themselves admit to feeling they are more depressed than other children, or that they often cry for no reason. Some children who have difficulty admitting to crying often, will admit to feeling like crying even though they do not cry. A mildly pathological rating of 3 is recommended for a child who cries slightly more often than peers. A rating of 5 is recommended if the child admits to crying for no reason and/or cries frequently. The severest rating of 7 is recommended for daily weeping.

O. Non-Verbal Items

The final 3 items of the CDRS-R are rated by the clinician using clinical judgment based on the child's appearance and non-verbal behavior. The guidelines for each rating on the non-verbal items are explained on the CDRS-R rating scale.

Childrens Depression Rating Scale—Revised

Schoolwork

Do you like school or dislike school? What parts do you like? What parts do you dislike? (Note: if teacher, peers, activities, e.g., recess, etc.)

What kind of grades do you get in school? Are they different now than they were last year? (Or most recent grading period.)

Do your parents or your teacher(s) think you ought to be doing better? What do they say? Do you agree or disagree with them?

If grades are a problem, ask: Do you have trouble paying attention? Why? Do you take longer to finish your assignments than other kids? Do you daydream?

Do other children bother you? Does the teacher often ask you to listen to what he/she is saying?

If not in school, ask about ability to concentrate on a TV program or game.

Ratings

1. Performance consistent with ability.
2.
3. Decrease in school performance.
4.
5. Major interference in most subjects.
6.
7. No motivation to perform.

Capacity to Have Fun

What do you like to do for fun? (Note interest, involvement, enthusiasm.) Discuss individual activities named.

How often do you have fun? (Note whether activities available daily, weekly, seasonally, or very infrequently.)

Are you ever bored? How often?

(If very inactive) What do you like to watch on TV? Discuss favorite TV shows. (Determine if active or passive viewer.)

Ratings

1. Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness. Any feelings of boredom are transient.
2.
3. Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm.

4.
5. Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude. May express interest primarily in activities that are (realistically) unavailable on a daily or weekly basis.
6.
7. Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches TV but shows little interest. Requires coaxing and/or pushing to get involved in activity. Shows no enthusiasm or real interest. Has difficulty naming activities.

Social Withdrawal

Do you have friends to play with? Are they at school or home? What games or things do you do? How often do you play with them?
Have you ever had a really close friend? Do you have one now?
Do your friends ever call for you and you just don't feel like going out to play? How often?
Have you ever lost friends? What happened?
Do children ever pick on you? How? What do they do? Is there anyone who will stick up for you?

Ratings

1. Enjoys friendships with peers at school and home.
2.
3. May not actively seek out friendships but waits for others to initiate a relationship or may occasionally reject opportunities to play without a describable alternative.
4.
5. Frequently avoids or refuses opportunities for desirable interaction with others and/or sets up situations where rejection is inevitable.
6.
7. Does not currently relate to other children. States he or she has "no friends" or actively rejects new or former friends.

Sleep

Do you have trouble sleeping?
Do you take a long time to go to sleep? (Differentiate from resisting going to bed.) How long? How often?
Do you wake up in the middle of the night? Do you go right back to sleep or stay awake? How often does this happen?
Do you ever wake up before you need to in the morning? How early? Do you go back to sleep or stay awake? What do you do? How often (or when) does this happen?

Ratings

1. No (or occasional) difficulty. (Goes to sleep within 1/2 hour or less.)
2.
3. Frequently has mild difficulty with sleep.
4.
5. Moderate difficulty with sleep nearly every night.

(If applicable, indicate time of difficulty)
a. Initial
b. Middle
c. Early morning awakening

Appetite or Eating Patterns

Do you like to eat?
At meals, are you hungry for some meals, most meals, all meals? Not hungry (if not hungry, record when and how often not hungry).
Does your mother complain about your eating?
Have you gained or lost weight? (If yes) How can you tell?

Ratings

1. No problems or change in eating pattern.
2.
3. Mild change from usual eating habits within onset of current behavioral problem.
4.
5. Is not hungry most of the time or has excessive food intake since onset of current behavioral problems or marked increase in appetite.

(If applicable, circle one)
Increased appetite Decreased appetite

Excessive Fatigue
(Consider age and activities of child)

Do you feel tired during the day? Even when you have had enough sleep? (During boring school subjects does not count.) After school?
How often do you feel tired after school?

Do you ever feel so tired you go and take a nap even if you don't have to? How often does this happen?

Ratings

1. No unusual complaints of "feeling tired" during the day.
2.
3. Complaints of fatigue which seem somewhat excessive and not related to boredom.
4.
5. Daily complaints of feeling tired.
6.
7. Complains of feeling tired most of the day. May voluntarily take long naps without feeling refreshed. Interferes with play activities.

Physical Complaints
(Complaints of a non-organic basis)

Do you ever get stomachaches, headaches, leg pains?
Do you get other aches and pains?
What are they like?
How often do these occur?
When you get _____ aches, how long do they last? Does anything make them go away? Do they keep you from playing? How often do they do this?

Ratings

1. Occasional complaints.
2.
3. Complaints appear mildly excessive.
4.
5. Complains daily. Some interference with the ability of the child to function.
6.
7. Preoccupied with aches and pains; interferes with play activities several times a week.

Irritability

What things make you get grouchy or mad?
How mad do you get?
Do you ever feel in a mood where everything bothers you? How long do these moods last? How often do these moods occur?

Ratings

1. Rare.
2. Occasional.
3. Several times a week for short periods.
4.
5. Several times a week for longer periods.
6.
7. Constant.

Guilt

Do you ever feel like it's your fault or blame yourself if something bad happens?
Do you ever feel bad or sorry about certain things you have done or wished you had done? What are they? (Note act and whether guilt is proportional to deed.)
Do you know what the word guilty means? Do certain things make you feel guilty?

Ratings

1. Does not express any undue feeling of guilt. Appears appropriate to precipitating event.
2.
3. Exaggerates guilt and/or shame out of proportion to the event described.
4.
5. Feels guilty over things not under his or her control. Guilt is definitely pathological.
6.
7. Severe delusions of guilt.

Self-Esteem

Do you like the way you look? Can you describe yourself? (With a young child, ask about hair, eyes, face, clothes, etc.) Would you want to change the way you look? What way?
Do you think you are smart or stupid?
Do you think you are better or worse from other kids?
Do most kids like you? Do any not like you? Why? Do you get called names? What are they? Do other kids put you down?
What things are you good at? Not so good? What?
Do you ever feel very down on yourself?
Would you like to change anything about yourself?

Ratings

1. Describes self in primarily positive terms.
2.
3. Describes self with one important area where the child feels deficit.
4.
5. Describes self in preponderance of negative terms or gives bland answers to questions.

6.
7. Refers to self in derogatory terms. Reports that other children refer to him/her frequently by using derogatory nicknames and child puts self down.

Depressed Feelings

What things make you feel unhappy?
When you feel unhappy how long does it last? An hour? A few hours? A whole day? How often do you feel like this? Every week? Every two weeks? (Note: for younger children, one hour may be equivalent of 1/2 day or more in older children.)
Do other people know when you are sad?
Do you feel sad just at certain times, like when you mother is away?
When you feel unhappy, how miserable do you feel? Do you ever feel so bad it hurts? How often does it feel bad? (Reactivity is an indicator of degree of depressed feelings.)

Ratings

1. Occasional feelings of unhappiness which quickly disappear.
2.
3. Describes sustained periods of unhappiness which appear excessive for events described.
4.
5. Feels unhappy most of the time without a major precipitating cause.
6.
7. Feels unhappy all of the time. Accompanied by psychic pain (e.g., "I can't stand it").

Morbid Ideation

Have you ever had a pet die? A friend? A relative? Do you think about it now? How often?
Do you ever think about someone dying in your family? Who? Describe. How often do you think about it?
Do you ever worry about everyone else? Who?
Do you ever think that you might die? Tell me about it.
How often do you have these kinds of thoughts?

Ratings

1. None.
2.
3. Has some morbid thoughts, all of which relate to a reality event but seem excessive.
4.
5. Preoccupied with morbid thoughts several times a week. Morbid thoughts extend beyond external reality.
6.
7. Preoccupied with death themes or morbid thoughts that are elaborate, extensive or bizarre on a daily basis.

Suicidal Ideation

Do you know what the word suicide means?
Have you ever thought of doing it? When? (If yes) How have you thought of doing it?
Have you ever said you would like to kill yourself even if you didn't mean it? Describe.
(If appropriate) Have you ever tried to kill yourself?

Ratings

1. Understands the word "suicide" but does not apply term to self.
2. Sharp denial of suicidal thoughts.
3. Has thoughts about suicide, usually when angry.
4.
5. Has recurrent thoughts of suicide.
6.
7. Has made suicide attempt within the last month or is actively suicidal.

Weeping

Do you ever cry very much?
Do you sometimes feel like crying even if you don't cry? What sort of things make you feel this way? How often do these occur?
Do you think you feel like crying more than your friends?
Do you ever feel like crying for no reason?

Ratings

1. Normal for age.
2. Suggestive statements that child cries, or feels like crying, more frequently than peers.
3. Child cries slightly more than peers.
4.
5. Cries or feels like crying frequently (several times a week). Admits to crying without knowing reason why.
6.
7. Cries nearly every day.

The following items are rated by the clinician based on the child's nonverbal behavior.

Depressed Affect

Ratings

1. Definitely not depressed. Facial expression and voice animated during interview.
2. Mild suppression of affect. Some loss of spontaneity.
3. Overall loss of spontaneity. Looks distinctly unhappy during parts of the interview. May still be able to smile when discussing non-threatening areas.
4.
5. Moderate restriction of affect throughout most of interview. Has longer and frequent periods of looking distinctly unhappy.
6.
7. Severe. Looks sad, withdrawn. Minimal verbal interaction throughout interview. Cries or may appear tearful.

Tempo of Speech

Ratings

1. Normal
2. Slow
3. Slow: delays interview.
4.
5. Severe. Low; marked interference with interview.

Hypoactivity

Ratings

1. None.
2.
3. Mild. Some body movements.
4.
5. Moderate. Definite motor retardation.
6.
7. Severe. Motionless throughout interview.

Preliminary Studies of the Reliability and Validity of the Children's Depression Rating Scale

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The Children's Depression Rating Scale, revised version (CDRS-R), is a reliable, clinician-rated scale which differentiates the depressed from the nondepressed child. The sum score of the CDRS-R appears to provide a better estimate of depressive symptomatology than does clinical impression. The relationship of the sum of the CDRS-R with global clinical ratings of depression indicates that the scale measures the severity of depression which is its primary purpose. The scale is not affected by the age of the child in our clinical sample, and the content of the items grouped as mood, somatic, subjective, and behavior all show good correlations with depression. The CDRS-R has been shown to be useful in a variety of settings, suggesting it is useful in both primary and secondary depressions.

Journal of the American Academy of Child Psychiatry, 23, 2:191–197, 1984.

The Children's Depression Rating Scale, revised version (CDRS-R), is a clinician-rated instrument for the assessment of the severity of depression in children ages 6–12 years. The majority of depression rating scales for children which have been published are self-report scales (Birleson, 1980; Kovacs, 1981). A self-report scale reliably quantifies subjective dysphoria but is less useful when the individual does not perceive his/her own affective state or rates himself or herself disproportionately high or low as compared to others in a given clinical state.

The general need for depression rating scales for children has become more evident as cross-sectional studies of the incidence of childhood depression show this is a common disorder in psychiatric populations. In addition, as treatment strategies emerge, the need to measure change both in an individual child and in groups of children is apparent.

The senior author's early stance that depression in children could be directly observed rather than inferred formed the basis from which the scale was developed (Poznanski and Zrull, 1970). The Children's Depression Rating Scale emphasizes the central importance of the child's ability to report verbally symptoms to their affective state and the direct observation of the child's behavior. Like other depression rating scales, the CDRS-R relates to the diagnosis of depression but cannot in itself make that diagnosis as information relating to other psychiatric diagnoses is lacking. The reliability of the child in reporting affective symptoms has been confirmed in several studies (Brumback and Weinberg, 1977; Carlson and Cantwell, 1979; Cytryn et al., 1980).

Review of the Literature

Rating scales can be divided into two types, namely, self-report and clinician-rated scales. Typically, a self-report protocol, with its obvious advantage of using less professional time, has not proven as reliable as clinician-rated scales. Carroll et al. (1973), in a review of the literature of depression rating scales, found a moderate correlation of self-reported symptoms of depression, with a clinician's rating of depression ($r = 0.42$) in a sample of adults. Prusoff et al. (1972) reported correlations between these two types of scales as ranging from 0.11 to 0.63. The majority of these studies have used different scales for the self-reported rating and clinician's rating. This presents a major methodological problem. The Hamilton Scale (Hamilton, 1960), which is clinician rated, is extensively used in clinical and research work with adults. The Carroll Scale (Carroll et al., 1981), which is a self-inventory, was specially designed to correspond with the Hamilton. As such, a comparison of the Carroll and Hamilton Scales overcomes the problem of using two unrelated instruments, and the correlation between these scales is higher than in the comparison of unrelated scales ($r = 0.67$) (Carroll et al., 1981).

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The authors wish to thank Lee Robins for his help in data collection.

This study was supported in part by the National Institute of Mental Health, Grant PHS MH 34196-02.

0002-7138/84/2302-0191 $02.00/0

Self-rating scales with young children need to be "interviewer-assisted" in that children can understand oral language before they can read it. Thus, most children under 9 years of age must have a scale read to them. The latter process introduces a potential bias in that the child's relationship to the adult reading the scale may influence the response. The influence and direction of this type of bias has not been studied in either adult or child populations.

The Children's Depression Inventory (CDI) (Kovacs, 1981) was the first and is the most widely used self-report measure used in childhood depression research. It was developed by Kovacs from the Beck Depression Inventory (Beck, 1969) for adults. The CDI has 27 items with a 3-point scale for severity. The CDI correlates moderately with global clinical depression rating ($r = 0.55$). Its main disadvantage is its reliability (Carlson and Cantwell, 1979), which has been a difficulty in any self-report measure.

In addition to the CDI, the only other self-report measure of depression in children that has had reported statistical analysis is a scale devised by Birleson (1980). His scale has 18 items which are simply and concretely worded and pose a forced choice situation, that is, a yes or no answer.

At least three clinical rating scales for depression in children are used in research. McKnew et al. (1979) developed and used the Children's Affective Rating Scale (CARS). The major drawback to this scale is that each item has a 10-point scale for severity without subcategory definitions, making it more difficult to obtain good interreliability. In addition, its subscale on fantasy is difficult to elicit and is subject to interpretation. Many mildly depressed children, as well as schizophrenic children with depressive affect, can provide fantasy material. However, reports by moderately to severely depressed children are characterized by slow, short answers. Therefore, eliciting fantasy material can be difficult to obtain.

Two diagnostic structured interviews, the Bellevue Index of Depression (Petti, 1978) and the Kiddies Schedule for Affective Disorders and Schizophrenia (K-SADS) (Puig-Antich et al., 1978) are used for both the diagnosis of depression in children and as a measure of severity. Both of these structured interviews for depression in childhood have been used diagnostically in clinical studies of depressed children. No statistical analyses of their data have been published relative to their use as severity rating measures of depression.

Review of the CDRS

A Depression Rating Scale for Children (CDRS) was devised and subsequently first used in a formal study of a random sample of children in an inpatient pediatric unit in a medical hospital (Poznanski et al., 1979). This population was selected primarily for ease of entry. The initial study of CDRS reliability and validity was done by two child psychiatrists, independently rating each child on a global rating of depression and the CDRS. The two sum scores of the CDRS had an inter-rater reliability of $r = 0.96$. As an index of convergent validity, the correlation of one rater's total CDRS score with a global clinical rating of depression from the other interviewer was $r = 0.89$.

Since the above study was conducted in a pediatric unit, a high occurrence of secondary depression was expected. The next step was to rate consecutive admissions to a Children's Unit of a Regional Mental Institution in the same manner as described above (Poznanski et al., 1983). In this study, four psychiatrists were used, two experienced and two inexperienced. The between-rater correlation was $r = 0.80$. Similarly, across-rater correlations (i.e. correlation between experienced and inexperienced raters) were $r = 0.75$ and $r = 0.74$. In this study, as well as in the study in the pediatric ward, a high correlation was found between global ratings of depression and the sum of the CDRS-R, indicating that the scale was indeed measuring severity.

Although the CDRS scale was performing well, since its inception 5 years of clinical research in childhood depression resulted in the recognition that several modifications would improve the clinical utility of the scale.

Scale Description and Modification

The CDRS-R is a clinician-rated scale for severity of depression of children ages 6–12 years. It usually takes about 20–30 min to interview a child in order to make a rating. Depressed children generally take longer to interview than nondepressed children. All possible sources of information can be used, i.e., additional information from the parent, child care worker, teacher or other sources. However, the emphasis is placed on information obtained from the child.

The initial items for the CDRS were selected on the basis of clinical experience, as there are not many well-developed objective methods for validating the diagnosis of depression in children. Drug response has been used in part with adults. Other measures, such as the Dexamethasone Suppression Test, are currently being developed for use in children, but are, as yet, less reliable than clinical diagnosis (Poznanski et al., 1983). Hence, the cardinal manifestations of childhood depression for the CDRS were by necessity derived from clinical experience.

The original CDRS had the following items: depressed mood, weeping, self-esteem and pathological

guilt, morbid ideation, suicidal ideation, schoolwork, social withdrawal, irritability, anhedonia, tempo of speech, appetite, sleep, hypoactivity, physical complaints and fatigue. In the CDRS-R, the items dealing with self-esteem and guilt have been split into separate categories and a verbal item for feelings of depression by the child was added. The original item of depressed mood in the CDRS is retained in the CDRS-R and is rated on the basis of nonverbal behavior. These changes were made for the following reasons. A verbal item of depressed mood is useful in order to distinguish clinically those children who relate feelings of unhappiness without showing depressive affect from children who deny feelings of unhappiness, despite manifesting depressive affect. Clinically, children in the first group, i.e., those who have only verbal dysphoria, are less depressed than children who show persistent depressive affect. A report of dysphoria by the parent is sometimes difficult to interpret. The parents' reports of depression in their child's behavior are frequently contaminated by feelings that the parents may have themselves, particularly if the parents are depressed. Guilt and self-esteem are separated so that the characteristics of each behavior could be analyzed separately. Hence the CDRS-R has 17 items, 14 of which are scored on the basis of verbal observation and three on nonverbal items: tempo of language, hypoactivity, and nonverbal expression of depressed affect.

The original CDRS had 15 items with a total score of 61 points. Since a rating of 1 = normal, the baseline is the total number of items, i.e., 15 for CDRS and 17 for the CDRS-R, rather than 0. The new CDRS-R has 17 items with a total of 113 points.

The range of possible points in each subcategory was 1–5 in the CDRS and has been increased from 1 to 7 points in the CDRS-R. The additional 2 points were added as clinicians were rating between numbers on the old scale, thus creating fractions. In addition, lengthening the pathological end of the scale increased the chances that slight lessening or worsening of symptomatology would be recorded. The lengthening of each subscale is shown in Table 1.

If the subcategory description does not seem to describe the child's behavior, the 1–7 scale can be used free of description with the following guidelines, 1 = normal, 2 = doubtful pathology, 3 = mild symptomatology, 5 = moderate symptomatology and 7 = severe symptomatology for the items.

All items have a description of normalcy and mild, moderate, and severe psychopathology. Whenever possible, the subcategory descriptions are meant to reflect increasing severity, both in terms of the *frequency* of the behavior and the intensity of such a behavior. Most of the time, the frequency and intensity of behavior increase together. However, occasionally one might encounter a child who shows a very intense behavior which occurs infrequently. The importance given to the frequency versus the intensity of behavior is ultimately dependent on clinical judgment. An example of subcategory description is shown in Table 2.

Conversion of the CDRS to the CDRS-R

The conversion formula for converting a CDRS score to a CDRS-R score was determined by linear regression. The following equation is satisfactory if the CDRS score is above 20:

$$\text{CDRS-R} = -12.1 + 1.6 \times \text{CDRS}$$

Method

Fifty-three children who were referred for possible depression were evaluated in two outpatient clinical-research units, first at the University of Michigan and later at the University of Illinois. The demographic

TABLE 1

Comparison of Scaling: CDRS and CDRS-R

CDRS		CDRS-R
0	Unable to rate	0
1	Normal	1
2	Doubtful	2
3	Mild	3
		4
4	Moderate	5
		6
5	Severe	7

TABLE 2

Description for CDRS-R Item of Anhedonia

CAPACITY TO HAVE FUN (0–7)

0 Unable to rate

1 Interest and activities realistically appropriate for age, personality, and social environment. Shows no appreciable change with present illness. Any feelings of boredom transient

2 Doubtful

3 Mild. Describes some activities realistically available several times a week but not on a daily basis. Shows interest but not enthusiasm. May express some episodes of boredom more than once a week

4 Mild to moderate

5 Moderate. Is easily bored. Complains of "nothing to do." Participates in structured activities with a "going through the motions" attitude

6 Moderate to severe. Shows no enthusiasm or real interest. Has difficulty naming activities. May express interest primarily in activities that are (realistically) *unavailable* on a daily or weekly basis

7 Severe. Has no initiative to become involved in any activities. Primarily passive. Watches others play or watches television but shows little interest in program. Requires coaxing and/or pushing to get involved in activity

characteristics of these two populations suggest it is reasonable to combine these two groups as shown in Table 3.

The age and socioeconomic status (SES) are similar in the two populations. The sex ratios show a predominance of males in both samples as reported by other researchers. The major difference in these two populations was an ethnically mixed population in the Chicago sample as compared to an entirely white population in Ann Arbor.

Children were referred for an outpatient psychiatric evaluation by a diverse group of professionals, agencies and clinics, both private and public. Children were accepted for evaluation in our clinic if they met our inclusion-exclusion criteria. For inclusion in our study, the child must have been between the ages of 6 and 12 years, not have a major physical illness, have an IQ over 70, and be off all mood altering drugs for 2 weeks prior to the evaluation. The child must also have had a reliable adult informant to give the child's past history. Legal consent to participate in our study was required.

In both the University of Michigan and the University of Illinois clinics, the diagnostic evaluation was carried out over 2 days, 2 weeks apart. During the entire evaluation, the child and parent(s) were interviewed independently by different clinicians. The research protocol included an unstructured interview of the child, the K-SADS, a clinical global rating of depression, and a Global Assessment Score (Endicott et al., 1976). The parent or parents were interviewed about the child simultaneously while the child was interviewed by a different clinician, using the same instruments in order to ensure independent data collection.

The majority of the children in the two samples were interviewed for the K-SADS and the CDRS-R by two different child psychiatrists. Also, in order to reduce rater bias effects, the CDRS-R obtained on the second visit was administered by the clinician who did not previously rate the child.

The results of the above interviews were not shared until a clinical conference was held following the second day of evaluation. Thus each child had two CDRS-R scores obtained by different raters 2 weeks apart. The purpose of the clinical conference is to share information, establish the diagnosis, and formulate the recommendations for treatment. A follow-up visit to the clinic was scheduled 6 weeks after the first visit, both to obtain a third CDRS-R and to give the parents an interpretation of our findings.

TABLE 3

Demographics of Two Clinical Populations

	Chicago	Ann Arbor	*p*
Age	$\bar{X}$ = 9.2	$\bar{X}$ = 9.8	NS
	S.D. = 2.2	S.D. = 1.10	
Sex	M = (60%)	M = (81%)	
	F = (40%)	F = (19%)	
SES	$\bar{X}$ = 4.00	$\bar{X}$ = 3.38	NS
	S.D. = 1.24	S.D. = 1.24	
Race	B 43%	W 100%	
	W 40%		
	H 17%		

Results

Relationship of CDRS-R to Diagnosis of Depression

Thirty-four of the 53 children qualified for a clinical depression by RDC criteria, combining the "Definite" and "Probable" groups (the "Definite" group by DSM-III criteria and by Poznanski criteria (Poznanski et al., 1979)). The mean CDRS-R of the RDC, DSM-III and Poznanski diagnostic groups of depressed children as previously described varied from 50 to 52, suggesting that group differences between depressed children using these diagnostic criteria were minor. Thirty-two children met all three sets of diagnostic criteria, while the additional two children varied with each set of diagnostic criteria. Poznanski criteria differ from RDC and DSM-III primarily in having a nonverbal as well as a verbal definition of dysphoria. Since there were minor changes in group composition with the different diagnostic criteria, Poznanski criteria have been used for consistency within our clinical research unit and have been used by our group since the beginning of systematic research data collection in childhood depression. Table 4 shows the relationship between a clinical diagnosis of depression using Poznanski's criteria and the mean CDRS-R.

The difference between the depressed and nondepressed CDRS-R means is probably greater in the general population than shown in the Table 4 because children are referred to our clinic for suspected dysphoria. Hence, the comparison sample probably has more borderline depressed children than a more typical outpatient psychiatric population.

Our clinical experience has been that a child with an initial CDRS-R score of 40 or more ultimately obtains a diagnosis of a clinical depression. The mean CDRS-R of 52 and 49 with a standard deviation of 10

TABLE 4

Comparison of CDRS-R with Clinical Diagnosis of Depression

Diagnosis	*N*	Mean CDRS-R	S.D.
Major depressive disorder:			
Definite group	28	52	10
"Definite" and "probable" groups	34	49	11
Nondepressed psychiatric disorder	19	29	4

and 11 fits with this clinical experience. Two children diagnosed as clinically depressed had scores below 40 and their scores were outside the range of one standard deviation of the remaining group of "Definite" and "Probable" depressed groups. Although it needs to be tested, it appears that some children with clinical depressions and low CDRS-R scores may deny depressive symptomatology if there is a stigma of depressive illness in their family.

Five children had sum scores over 60 and these children clinically appear to be severely depressed. Thus the group of children with CDRS-R scores between 40 and 60 points contain the majority of children with mild to moderate depression and a division into the two clinical subgroups of mild and moderate is purely arbitrary. In our experience, the duration of the depressive episode appears to be clinically more important than the exact CDRS-R score at the time of evaluation; however, this problem merits further study.

Correlation between a Global Rating of Depression and the CDRS-R

Prior to scoring the CDRS-R, the clinician gave the child a Global Rating of Depression based on an overall clinical impression. This rating, which is a 1–7-point scale, was then correlated with the total CDRS-R score. The correlation of the CDRS-R with the global rating was $r = 0.87$. Hence, an improvement of the CDRS-R over the CDRS is that it increases the correlation with Global Rating of Depression.

One way to study the correlation of the mean Global Rating of Depression with the mean sum of the CDRS-R scores is to assign somewhat arbitrary points to the global rating based on clinical experience. Table 5 shows the association between groups based on global ratings of depression and average CDRS-R scores.

The majority of children felt to be nondepressed clinically were given a global rating under 2.5 on a 7-point scale. Global ratings over 4 were rare for the nondepressed group, partially due to hesitancies on the part of clinicians to rate a child as moderately or severely depressed on clinical appearance alone.

The correlation of the initial global rating with the sum of the CDRS-R indicates that a wide range of scores are encountered, particularly with global ratings of 1 and 2. However, the sum of the CDRS-R at the first interview was found to be more predictive of the final clinical diagnosis of depression or a nondepressed psychiatric diagnosis after the total evaluation than the initial global rating. Hence, the value of a depression rating scale systematically to assess depressive symptomatology has some diagnostic value.

Content of the CDRS Items Relative to the Child's Age Function and Severity of Depression

The items on the CDRS-R were broken down into four groups based on clinical experience. These four groups were the following:

1. *Mood*
   Depressed feelings (verbal)
   Depressed feelings (nonverbal)
   Irritability
   Weeping
2. *Somatic*
   Appetite—either increase or decrease
   Sleep—initial, middle and/or terminal insomnia
   Excessive fatigue
   Psychomotor retardation—includes tempo of speech and hypoactivity
   Physical complaints (nonorganic).
3. *Subjective*
   Self-esteem
   Guilt
   Morbid ideation
   Suicide ideation
4. *Behavior*
   Anhedonia
   Social withdrawal
   Schoolwork

Correlation analyses (using Pearson product-moment correlation coefficient) were then carried out, to assess the strength of the relationship between each of these groups and the variables of age, Global Assessment Score (GAS), Global Rating Depression (Global) and the sum score of the CDRS-R. The correlations are shown in Table 6.

The highest correlations were obtained for each of the subgroups to items (i.e., mood, somatic, subjective and behavior) and both the global rating of depression

TABLE 5

Association between Global Ratings of Depression and CDRS-R

Mean Global	*N*	CDRS-R	S.D.
<2.4	31	33	9.1
2.5–3.5	10	45	6.5
3.5–4.5	4	60	6.5
>4.5	7	68	11

TABLE 6

Correlations between Groups of Items and Associated Variables[a]

	Age	GAS	Global	CDRS-R
Mood	−0.02	−0.30	0.86**	0.88**
Somatic	0.004	−0.10	0.75**	0.86**
Subjective	0.11	−0.42*	0.75**	0.84**
Behavior	0.17	−0.25	0.53**	0.68**

[a] $^{**}p < 0.02$, $^{**}p < 0.001$.

and the sum score of the CDRS-R. The correlations between each of the four groups and the CDRS-R score account for more of the variance than the correlations to the Global Rating, although both groups of scores are highly significant. These findings suggest that the scale is unidimensional and is tapping several symptom clusters which make up a depressive syndrome.

The three groups which had the highest correlation to sum scores on the CDRS-R and accounted for the greatest proportion of the variance, were the groups containing mood, somatic and subjective items. The highly significant correlation with mood items would be expected, since depression in children is both observable by trained clinicians and is verbalized by children when queried. The significant correlation between the somatic items and CDRS score suggests that the "vegetative" signs such as sleep and appetite disturbances, are as centrally important in childhood depression as they are in adult depression. The subjective items of self-esteem, guilt, morbid and suicidal ideation also had a significant correlation, suggesting that these are symptoms which can be assessed in children and which contribute to overall depressive symptomatology.

The group of behavioral items, i.e., anhedonia, social withdrawal and problems with schoolwork, are often items which depend on reports from multiple sources (e.g., parents, school 1 report) and by direct observation. While the correlation for these behavior items to sum score or the CDRS-R was still significant, it did not account for as much of the variance as the other three groups. It may be that items in this behavior grouping are not unique to depression, and this accounts for the slightly lower correlation.

The lack of correlation with age suggests that the ratings on the CDRS-R are not affected by age of the child in our psychiatric population. Therefore, children such as we see in the age range of 6–8 years can be evaluated using the CDRS-R, although it is unclear if more reliance is placed on clinical judgment when rating younger and less verbal children.

A modest significant correlation was obtained for the subjective group of items and the Global Assessment Score. It may be that symptoms such as lowered self-esteem, feelings of guilt and morbid or suicidal ideation impinge upon the child's overall level of functioning more so than mood, somatic, and behavioral items. However, further analyses which will allow us to assess the contribution of each of these items, as well as to investigate the factor structure of the CDRS-R, are clearly needed.

Test-Retest Reliability of the CDRS-R

The inter-rater reliability was determined by the correlation between the 0 and 2-week score in the Chicago sample as it is done by two different raters: $r = 0.86$ and $N = 32$.

TABLE 7

Mean CDRS-R Scores in Three Samples

Sample	*N*	Mean CDRS-R
Children's Medical Inpatient—random sample	30	30
Children's Psychiatric Inpatient—consecutive admissions	30	36
Children's Outpatient Population—referred to dysphoria:		
Ann Arbor	22	38
Chicago	31	44

The correlations between the 2-week and 6-week ratings ($r = 0.81$, $N = 36$) were also significant, indicating the stability of both the syndrome and the measure.

Discussion

The CDRS and the CDRS-R have been used in three different clinical populations: a pediatric unit in a medical hospital, a psychiatric inpatient unit, and psychiatric outpatient clinics. Our increasing knowledge of the clinical phenomenology of childhood depression undoubtedly influenced the clinicians' perception of depressive symptomatology and may thus affect the rating of the instrument. Nevertheless, the mean score of the CDRS-R in these populations goes in the expected direction. For example, the mean CDRS-R was lowest in a random sample of medically ill children, higher in consecutive admissions to a psychiatric inpatient unit, and highest in the groups of children specifically referred for possible depressions. Table 7 summarizes these findings.

Thus the CDRS-R has been shown to be useful in a variety of settings, and in diagnosing both primary and secondary depressions.

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Depression in Prepubertal Children: Dexamethasone Nonsuppression Predicts Differential Response to Imipramine vs. Placebo[1]

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Introduction

The target of this research was the question of whether or not depression in children exists. If so, what is the nature of the disorder, and is it responsive to treatment? Seven years ago, the prevailing opinion was that major depressive disorder could not occur in children. This opinion was based on theory. Presumably, children did not have sufficient superego development to permit the development of a major depressive syndrome.

The authors' findings are in significant disagreement with that earlier theoretical supposition. Their data indicate major depressive disorder does occur in children aged 6 to 12 years and is similar to major depressive disorder in adults in a variety of ways (Preskorn et al. 1982, 1983; Weller et al. 1984). First, it is phenomenologically similar in terms of the presence of a persistent and serious depressive mood and the presence of vegetative signs and symptoms including sleep disturbance, appetite disturbance, energy disturbance, impairment in concentration and attention, and loss of interest in usual activities. Moreover, suicidal ideation does occur in childhood depression leading to suicide attempts and successful suicides. Second, childhood affective disorder is similar to adult affective disorder in that there is heavy familial loading for affective illness in such patients. Third, the authors have also found that the rate of dexamethasone nonsuppression is approximately the same in children and adults with major depressive disorder. Based on these studies, over 40 percent of children aged 6 to 12 years having a major depressive syndrome will fail to suppress cortisol production when challenged with the exogenous administration of dexamethasone. An additional 20 to 30 percent will be so called "early escapers," meaning that while they will suppress at 8:00 a.m., their cortisol levels at 4:00 p.m. will be above the 5 μg/dL cutoff level.

Given the seriousness of this potentially life-threatening disorder, the authors have directed a significant effort toward treatment intervention, specifically with the tricyclic antidepressant imipramine. The studies with imipramine progressed in stages. The first study examined the interindividual variability in drug levels. The second study dealt with the relationship between plasma levels of imipramine and antidepressant response as well as adverse effects. The third study was the classic drug vs. placebo double-blind study.

Based on this work, the authors have reached the following conclusions: First, imipramine is effective in treating major affective disorder in children when compared with placebo. The drug response rate can approach 80 percent when plasma drug concentration is controlled. In contrast, the placebo response rate is under 20 percent. These figures are remarkably similar to those seen in well-designed and well-executed studies of tricyclic antidepressant response rates in adults with major affective disorder. Second, the time course for antidepressant response to imipramine is also similar to that observed in adults with major depressive disorder. Within 3 weeks of initiating drug treatment, response is observed, given that the plasma drug level obtained is within the therapeutic range. Third, the minimum plasma level necessary for antidepressant response in children is remarkably similar to that needed for adult depressed patients. Fourth, patients who are dexamethasone nonsuppressors show the best response to imipramine and the poorest response to placebo. This finding is in agreement with similar reports in adult major depressive disorder.

Based on these studies, the plasma drug concentration necessary for optimum antidepressant response in children is 125 to 250 ng/mL. Below 125 ng/mL, the drug response rate is reduced approaching that of the placebo response rate. Above 250 ng/mL, the response rate is also reduced and toxic side effects begin to occur: prolongation of intracardiac conduction, drug-induced changes in blood pressure and heart rate, and the development of a toxic confusional state. The

[1]This research was supported by USPHS Grants MH-00272 (RSDA to S.H.P.) and MH-36739 from the National Institute of Mental Health.

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last side effect is particularly important. The authors have seen several patients who at plasma drug levels above 400 ng/mL have developed a toxic confusional state that has been misinterpreted by experienced clinicians as a worsening of the underlying depressive disorder. In these cases, the clinicians, blind to the plasma drug level, wanted to increase the dose because of presumed deterioration in the depressive syndrome.

These studies have also shown that there is significant interindividual variability in plasma drug levels, such that 10- to 20-fold differences in steady-state plasma levels of imipramine and its active metabolites have been observed in similarly aged patients on the same dose of imipramine. This plasma level variability appears unrelated to age, height, weight, or sex, and can lead to different patients on the same dose having plasma drug levels ranging from subtherapeutic to toxic. In fact, the studies have shown that at the Food and Drug Administration's (FDA) maximum recommended dose, 65 percent of all children will be undertreated in terms of plasma drug level, while 15 percent will be overtreated. These findings mean that only 20 percent of children will be in the optimum range on 75 mg of imipramine daily. Finally, the authors have shown that the single-dose prediction test is applicable to children and can be used to titrate patients rapidly into the optimum range. The three major studies are summarized below.

Study 1: Variability in Plasma Levels of Imipramine and Its Active Metabolites

Two-hundred fifty hospitalized patients with major affective disorder ranging in age from 6 to 70 years were studied in terms of the variability in plasma concentrations of imipramine and its active metabolites. Of these 250 patients, 70 patients were between the ages of 6 and 14 years. The criteria for the study were that (a) all patients had to be hospitalized to ensure compliance with drug therapy; (b) there had to be repeat plasma level determinations, both on the same dose and on different doses; (c) all levels had to be at steady state, meaning a minimum of 7 days on a stable dose of the drug; and (d) all levels had to be trough levels drawn 10 to 12 hours after the last dose. All levels were run in the same laboratory, using the same high performance liquid chromatography methodology, and were run in split sample duplicates. Plasma levels of imipramine, desipramine, 2-hydroxyimipramine, and 2-hydroxydesipramine were quantitated (Table 1).

TABLE 1. Steady-State Plasma Levels (ng/mL) in 38 Depressed Children on 75-mg Imipramine Orally at Bedtime.

Metabolite	Mean (SEM)	Range	Interindividual Variability
IMI	50 (4)	15-110	7-fold
DMI	101 (14)	32-346	11-fold
2-OH-IMI	77 (30)	10-330	33-fold
2-OH-DMI	34 (2)	23-48	2-fold
Total[a]	151 (16)	58-400	7-fold
Aug. total[b]	275 (41)	121-573	5-fold

NOTE: IMI = imipramine; DMI = desipramine; 2-OH-IMI = 2-hydroxyimipramine; 2-OH-DMI = 2-hydroxydesipramine.
[a]Total = IMI + DMI.
[b]Aug. Total = IMI + DMI + 2-OH DMI + 2-OH-IMI.

Study 2: Relationship Between Plasma Levels of Imipramine and Its Active Metabolites and Antidepressant Response

This study was planned to precede a placebo-controlled, double-blind, random assignment study (Preskorn et al. 1982, 1983), and was designed to examine the question of whether or not a relationship exists between plasma levels of the drug and its metabolites and antidepressant response. If so, then plasma levels would be adjusted in the placebo-controlled study to maximize the likelihood of seeing a drug vs. placebo difference.

The inclusion and exclusion criteria were as follows: All patients had to be between the ages of 6 and 12 years and be prepubertal. All patients had to be hospitalized for a major depressive disorder. The diagnosis was established by an open clinical interview and by a structured interview, the Diagnostic Inventory for Children and Adolescents (DICA; see Orvaschel 1985; Reich et al. 1982). All children had to give informed consent, which had to be co-signed by their parents. In addition to meeting *DSM-III* criteria (American Psychiatric Association 1980) for a major depressive disorder, the children had to be symptomatically ill for at least 30 days prior to enrollment in the study. The severity of the depressive disorder had to be above 20 on the Children's Depressive Rating Scale-Revised (CDRS-R; Poznanski et al. 1985), which is comparable to the Hamilton Psychiatric Rating Scale for Depression (HAM-D; Hamilton 1960). A CDRS-R score of 20 is equivalent to a score of 20 on the 24-item HAM-D for adults. Thus, these children had to be moderately to severely depressed to be eligible for the study. Children were excluded if they had organic brain disease, attention

deficit disorder, an IQ less than 85 on the Wechsler Intelligence Scale for Children-Revised (Wechsler 1974), and/or psychotic symptoms. Children who were medically unstable were also excluded.

The design of the study involved three phases: First, patients were evaluated at baseline with the severity of the depression being quantitated using three independent measures: the Clinical Global Impressions (CGI) scale (Guy 1976), a researcher-administered CDRS-R, and a patient's self-report scale, the Children's Depression Inventory (CDI; Kovacs 1980-81). Children were then followed in the hospital without drug therapy for 2 weeks. For these 2 weeks, children were treated with daily individual psychotherapy (5 days/week), group psychotherapy (3 days/week), family therapy (2 sessions/week), and milieu therapy including 4 hours/day of school. After 2 weeks, children were re-evaluated in terms of the severity of the depressive syndrome using all three measures. If unchanged, children were treated with imipramine, 75 mg at bedtime. All children received the same dose of the same drug in the same fashion. Plasma levels of imipramine and its metabolites were allowed to vary as determined by underlying differences in drug metabolism. The treating team was blind to the plasma drug level achieved but not to the fact that the children were being treated with imipramine. In this sense, the study—while an open, uncontrolled trial—was blind with regard to plasma drug level. The objective was to determine whether or not there was a relationship between plasma drug concentration and antidepressant response and/or adverse effects. During this 3-week period of time, the severity of the depressive syndrome was rated on a weekly basis using all three measures. In addition, plasma levels were obtained at weekly intervals to monitor plasma levels of imipramine and its metabolites.

After 3 weeks of drug treatment, the treating team was allowed to make a single dose change based solely on clinical assessment. This adjustment allowed the study to mimic clinical practice and afforded an additional opportunity to examine the relationship between drug concentration and clinical response. These were the guidelines for this adjustment: If the children were improved, then the dose was maintained. If the children were not improved and were experiencing side effects, the dose was reduced to 50 mg at bedtime. If the children were not improved and not experiencing side effects, then the dose was increased to a maximum of 5 mg/kg/day. Once adjusted, the dose was maintained for an additional 3 weeks. During this second 3-week phase, severity of depression was measured and plasma drug levels were taken at weekly intervals.

Throughout the 6 weeks of drug treatment, the following repeat measures were also made: An adverse-event scale was used on a weekly basis to assess the development of side effects to imipramine, vital signs, and memory function. An electrocardiogram (EKG) was done at the end of the baseline period, of the first 3 weeks, and of the last 3 weeks of drug therapy. An electroencephalogram (EEG) was done at baseline and at any time during the courses of study when it was clinically determined to be necessary.

Over a 70 percent drug response was observed if the plasma concentration of imipramine plus its active metabolite, desipramine, was between 125 and 250 ng/mL (Table 2). Fifty percent of the variability in antidepressant response could be attributed to variability in plasma drug levels of imipramine and desipramine. Of this variability, over 70 percent was accounted for by desipramine plasma levels. In comparing the slope of the relationship between clinical improvement and plasma drug level, desipramine appeared to be 2 to 3 times more potent than imipramine in accounting for antidepressant response. Plasma levels of 2-hydroxyimipramine and 2-hydroxydesipramine were not found to significantly add to the correlation between plasma drug level and antidepressant response.

In this study, only 31 percent of children treated with 75 mg of imipramine were in the optimum range. The clinician, while blind to the plasma drug level, was able to successfully adjust the dose in an additional 40 percent of children. Hence, at the end of the second 3-week phase of drug treatment, 72 percent of children were in the optimum range.

This latter finding suggests that imipramine can be used successfully without monitoring plasma drug levels. This conclusion is not surprising since the tricyclic antidepressants were used for over 20 years

TABLE 2. Response Rate as a Function of Combined Imipramine + Desipramine Plasma Levels.

Phase I.	*Overall response rate*	42%
	Within therapeutic range	73%
	Outside therapeutic range	12%
Phase II.	Initially outside range but then adjusted	100%
	Initially outside range and maintained outside	40%[a]

DATA SOURCE: Preskorn et al. 1982.

[a]All patients who improved in this group had tricyclic antidepressant plasma levels just below the optimum range; whereas, none with levels above this range improved during the second 3 weeks of drug therapy.

without monitoring plasma drug levels. However, the study did demonstrate several limitations to dosage titration based on clinical response alone. First, it took an additional several weeks of treatment before the appropriate dosage adjustment could be made, possibly resulting in an unnecessary prolongation of the patient's illness. Second, the adjustment was in the correct direction virtually 100 percent of the time when the plasma levels were below 125 ng/mL; in contrast, it was in the correct direction only 50 percent of the time (i.e., an apparent random phenomenon) when the plasma levels were above 250 ng/mL. In half of these latter cases, the dose was adjusted upwards despite the fact that the drug plasma level was already above the optimum drug concentration range. Hence, these children developed drug plasma levels above 450 ng/mL. We found that these plasma levels were associated with a poor antidepressant response and in several cases with a deterioration in the clinical status due to the development of a toxic confusional syndrome. This syndrome was incorrectly interpreted in several instances as a worsening of the depressive disorder and led to the clinician's wanting to increase the dose further. We believe that this finding underscores the importance of plasma drug monitoring when an optimum drug concentration range has been empirically defined.

Study 3: Double-Blind Randomly Assigned Placebo-Controlled Trial of Imipramine

Inclusion and exclusion criteria for this study were identical to the preceding study. Children following hospitalization and baseline assessment were treated from 4 to 7 days with a placebo. They were then randomly assigned to receive either placebo or 100 mg of imipramine at bedtime. These conditions were given using three tablets containing 25-, 50-, and 75-mg each. The 50-mg tablet was given in the morning and the 25- and 75-mg tablets before bedtime. For the placebo-treated children, all tablets were placebo. For the imipramine-treated children, the 50-mg tablet was initially a placebo while the 25- and 75-mg tablets were active. The reason for this approach will become obvious.

During the 2 weeks of the initial treatment phase, plasma drug levels were drawn at 8 and 12 days. If the drug plasma level in the imipramine-treated children on these two occasions was outside the 125 to 250 ng/mL range previously found to be maximally therapeutic (Study 2), the laboratory was able to adjust the dose without the treatment team's knowledge by substituting either active or inactive tablets, such that the imipramine-treated children could be on a dose ranging from 25 to 150 mg for the next 4 weeks of the trial. This approach allowed us to eliminate most of the variability in plasma drug levels (Study 1) by adjusting the dose based on the drug plasma level. Once the dose was adjusted, it was maintained for the remaining 4 weeks.

The same severity scales (i.e., the CGI, CDRS-R, and CDI) and measurements of adverse events, (i.e., the side-effect scale, blood pressure and other vital signs, EKG, and mental status examination) were used in this study as in the fixed-dose study (Study 2). Similarly, the children's depressive syndrome was diagnosed by an open clinical interview and a structured diagnostic interview, the DICA.

In both Study 2 (fixed dose) and Study 3 (drug vs. placebo), the dexamethasone suppression test (DST) was also used to biologically characterize the affective syndrome. Prior to drug or placebo treatment, children were administered 0.5 mg of dexamethasone at 11:00 p.m. The next day, plasma levels for cortisol determinations were drawn at 8:00 a.m. and 4:00 p.m. Patients were defined as being dexamethasone nonsuppressors if both the 8:00 a.m. and 4:00 p.m. levels were above 5 μg/dL and dexamethasone suppressors if these levels were below 5 μg/dL.

In a separate but concomitant study, we also examined dexamethasone nonsuppression rate in normal and psychiatric controls (Weller et al. 1984). The children with other psychiatric disorders (principally conduct disorders) were hospitalized on the same unit as the depressed children. The normal controls, psychiatric controls, and depressed children were studied simultaneously or concomitantly and the same methodology was employed. To summarize, the authors found in the double-blind, imipramine vs. placebo study that over 40 percent of children with major depressive disorder were DST nonsuppressors and 40 percent were DST suppressors using the criteria that both the 8 a.m. and 4 p.m. serum cortisol levels had to be above 5 μg/mL to be classified as nonsuppressor. An additional 20 percent fell between these two categories (i.e., either the 8 a.m. or 4 p.m. serum cortisol level was above 5 μg/dL). The DST nonsuppression rates for the normal controls (n = 18) and psychiatric controls (n = 50) were 0 and 15 percent respectively by the same criteria.

The authors found that imipramine was effective in comparison with placebo and that the imipramine-placebo difference could be detected within 3 weeks of starting drug therapy (Table 3). The placebo-controlled study extended the findings of the fixed-dose study (Study 2) by being the first study to show

TABLE 3. Overall Imipramine vs. Placebo Antidepressant Response as Percent Change From Baseline.

	CDI		CDRS-R		CGI	
	D21	D42	D21	D42	D21	D42
Imipramine (n = 10)	59	40	41	43	28	38
Placebo (n = 12)	25	38	33	35	15	26
ANOVA	<.10		<.05		<.025	

NOTE: All values are the mean percent change from baseline and are representative of the entire data set for the duration of the study. Children's Depression Inventory (CDI) and Children's Depression Rating Scale-Revised (CDRS-R) were measured at baseline and on Days (D) 12, 21, and 42 on treatment. Clinical Global Impressions (CGI) was measured at baseline and on Days 12, 21, 28, 35, and 42. There was no difference in baseline scores for imipramine- vs. placebo-treated patients. ANOVA = Analysis of variance for each measure across the duration of the study.

that imipramine is superior to placebo in the treatment of major depression in children, given that therapeutic drug plasma levels (125 to 250 ng/mL) are achieved. Of interest, the drug vs. placebo difference was more pronounced in the DST nonsuppressors in comparison with the DST suppressors (Table 4). In other words, the DST nonsuppressors showed the best response to imipramine and the poorest response to the placebo. No serious side effects were experienced when plasma levels of imipramine and its active metabolite, desipramine, were in the 125 to 250 ng/mL range.

TABLE 4. Differential Response to Imipramine vs. Placebo in Dexamethasone Nonsuppressors vs. Suppressors as Percent Change From Baseline.

	Nonsuppressors			Suppressors		
Day	IMI	PI	p	IMI	PI	p
			Clinical Global Impressions			
21	49	9	<.01	26	10	NS
42	44	36		27	13	
			Children's Depressive Rating Scale-Revised			
21	44	19	<.01	35	34	NS
42	51	32		42	37	
			Childhood Depressive Inventory			
21	69	10	<.05	50	25	NS
42	65	32		31	50	

NOTE: Suppressors and nonsuppressors were determined by a dexamethasone suppression test. IMI = imipramine; PI = placebo. p is based on analysis of variance

Conclusions

This paper summarized 7 years of active investigation in the area of childhood depressive disorder. Three primary studies were done sequentially in a planned exploration of the usefulness of imipramine to treat this disorder. These three primary studies, along with two additional studies (i.e., the dexamethasone suppression studies and the phenomenologic and family studies) have been or will be reported independently in the literature by this research group.

The findings from these studies are important for several reasons. First, existence of childhood depression had been questioned by many. Until the mid-1970s, its existence was considered impossible based on theoretical suppositions. At the time these studies were started, the concept that children could experience a major depressive disorder was controversial. Data gathered by the authors indicate that indeed major depressive disorder in children does exist and is similar to major depressive disorder in adults on several levels: (a) phenomenology; (b) incidence of DST nonsuppression; (c) family history of affective disorder; and (d) response to imipramine chemotherapy including drug-vs.-placebo difference, minimum threshold necessary for antidepressant response, and the time course of antidepressant response to such chemotherapy. Of note, the responsiveness of major depressive disorder in children to imipramine chemotherapy in these studies has been demonstrated in controlled studies of cases where nonpharmacologic intervention, including hospitalization, had been shown to be ineffective.

The authors believe that their data show that there is an optimum therapeutic plasma concentration range for antidepressant response in children with major affective disorder. Below the 125 ng/mL threshold, a poor response was observed. Above 250 ng/mL, response rates were also reduced but additionally these levels put the children at increased risk for adverse effects without additional benefit. These studies demonstrate that if the FDA maximum dosage limitation for children as outlined in the *Physician's Desk Reference* is used, the majority of children with major depressive disorder will not be responsive because of the development of inappropriate plasma drug concentrations.

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Imipramine in Prepubertal Major Depressive Disorders

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• **The potential effectiveness of imipramine hydrochloride (up to 5 mg/kg/d) was investigated in 53 prepubertal children suffering from major depressive disorder. Two complementary strategies were used simultaneously: (1) a five-week, double-blind, placebo-controlled design (N=38), and (2) a plasma level/clinical response study (N=30). Fifteen of the 16 children randomly assigned to active drug in the first study also participated in the second. Subjects were assessed using the Schedule for Affective Disorders and Schizophrenia for School Age Children and diagnosed according to unmodified Research Diagnostic Criteria. Response rates in the double-blind study were similar in both groups (imipramine, 56%; placebo, 68%). In the plasma level study, total maintenance plasma level (imipramine plus desipramine) was found to positively and linearly predict clinical response of the depressive syndrome ($P<.003$). No evidence of a curvilinear relationship was found. Depressive hallucinations during the episode negatively predicted clinical response ($P<.05$). Weight-corrected imipramine dosage did not predict either clinical response or plasma level in the individual subject. No predictors of response were found in the placebo group. These results suggest that the mean imipramine dosage was too low, and that future double-blind, placebo-controlled studies of imipramine in prepubertal major depression should include plasma level titration to above 150 ng/mL and an initial placebo washout period.**

(*Arch Gen Psychiatry* 1987;44:81-89)

Thirty of 50 well-controlled, double-blind studies reported imipramine hydrochloride to be superior to placebo in major depressive disorder (MDD) in adults,[1] thereby establishing its efficacy. Four well-executed studies have shown a strong relationship between plasma levels of imipramine plus its major metabolite desipramine hydrochloride and clinical response in adult endogenous depressives.[2-5] These data suggest that inadequate plasma levels may account for at least some of the negative double-blind studies.

There is now a consensus among investigators regarding not only the existence of MDD in prepuberty, but also assessment methods,[6-11] diagnostic criteria,[6-10,12-14] as reflected in *DSM-III*,[15] and, recently, natural history.[16,17] Several open studies of antidepressant drugs in "childhood depression" were reported during the last 15 years[8,14,18-24]; approximately three fourths of the children were reported to have responded. Conclusions from such data are constrained because all studies were uncontrolled and because each of the following criticisms applied to a majority of them: the diagnosis was made in clinical fashion without structured interviews or specification of diagnostic criteria or of specific symptoms observed; the length of the trials varied (from a few weeks to several months); and dosages were variable and usually low.

Frommer[25] was the first to conduct a controlled study of tricyclic antidepressant (TCA) medication in children diagnosed as depressed. She studied 32 children in a double-blind crossover design, comparing the effects of a combination of phenelzine and chlordiazepoxide for two weeks vs phenobarbital for two weeks. Seventy-eight percent of the children improved with the combination, while only 50% improved with phenobarbital. Unfortunately, given the design, no firm conclusions are possible. The effect found may have been due to the therapeutic action of phenelzine alone, chlordiazepoxide alone, or the combination of the two drugs, or it may have been due to negative action of phenobarbital, or to withdrawal effects from either of the two treatments.[26] Due to the very small sample size, a recent double-blind crossover study of amitriptyline vs placebo in prepubertal major depression, which fell short of significance, is inconclusive.[27]

Three preliminary studies have reported evidence of a relationship between TCA plasma levels and clinical response in prepubertal major depression[28-30] and provided initial support for the effectiveness of these drugs in depressed children. Although methodologically sounder, they do not address the basic question of drug effectiveness compared with placebo, the traditional method of measuring drug efficacy.

In the study reported in this article, two research designs were combined and applied concurrently: (1) a five-week,

Accepted for publication Sept 9, 1985.

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Reprints not available.

double-blind, placebo-controlled imipramine trial, and (2) a study of the relationship between maintenance plasma levels of imipramine and desipramine and clinical response at five weeks in the subjects randomly assigned to the drug. From the earlier studies, it was not possible to determine the optimal imipramine dosage for prepubertal MDD. In addition, well-founded concerns about toxicity in this age group[31-34] made it necessary to use conservative safety limits to imipramine dosage increase. If the mean administered imipramine dosage proved to be too low, there would be enough plasma level and response variance to determine their relationship. Conversely, if the mean imipramine dosage were high enough, the double-blind study might give positive results, but the plasma level study would be uninformative. In this manner, the chances of finding some evidence of drug effectiveness if imipramine were actually effective were maximized, and were less dependent on dosage uncertainties.

Imipramine was chosen because there was considerably more experience with this drug in children than with any other TCA. Imipramine had been shown effective in controlled studies in nocturnal enuresis,[35-38] attention deficit disorder with hyperactivity,[39] and separation anxiety disorder (school phobia).[40] It was noteworthy that in the latter condition, latency of clinical response and weight-corrected dosage were similar to those in adult depression, while in the other two disorders, dosage was low and clinical response immediate. In addition, the pharmacokinetics of imipramine and desipramine in children were known.[41,42] The report of a death of one child treated with very high weight-corrected doses of imipramine (14.7 mg/kg/d)[31] was worrisome, but it was apparent that cardiotoxicity[32] was a characteristic of all TCAs,[33] and it was generally believed that proper electrocardiographic (ECG) monitoring with safety limits and dose restrictions[34] would ensure safety.

PATIENTS AND METHODS

Patients

Prepubertal children were referred to the Child and Adolescent Depression Clinic from the entire New York metropolitan area. The clinic personnel screened any child for the diagnostic protocol who was reported by at least one source (including himself or herself) to have at least one of these four referral criteria: persistently looks sad, frequently says he feels sad, suicidal statements or behavior, and/or school refusal.

Diagnostic Protocol.—All referred children were initially screened by the research coordinator. If judged likely to fit criteria for the study, the child entered a two-week diagnostic protocol. This included blind psychiatric, psychosocial, and pediatric assessments, as reported elsewhere,[43] several of which were not directly relevant to the study reported in this article. Psychiatric assessments were carried out by two of us (J.P.-A. and W.J.C.), using the Schedule for Affective Disorders and Schizophrenia for School Age Children (Kiddie [K]-SADS-P),[11] which is a semistructured interview schedule derived from the SADS part I.[44] To administer it, the rater first interviews the parent about the chronological structure and symptoms of the child's current episode. Then he or she interviews the child, following the same format. Symptoms are rated from each informant on semiquantitative scales that define each level of severity. As the child's interview proceeds, the rater integrates information from each source into a summary rating for each symptom, which is used later to determine if a child fits criteria for a particular diagnosis. Thus, the K-SADS-P synthesizes a wealth of clinical information from various sources. This procedure has been shown to be reliable for the assessment of depressive mood and the depressive syndrome.[11] Interrater reliability for the items in the depressive syndrome was obtained at the beginning of the study (mean intraclass $r = .86$). Test-retest reliability data on the same items (mean intraclass $r = .57$) and depressive scales (mean intraclass $r = .73$) have also been obtained by this group and support the reliability of the measures.[11]

Initially all subjects were assessed once, jointly by the two raters, with the K-SADS-P for the present episode. Ratings were also obtained for the week before the assessment. From the seventh accepted patient onward, all subjects were interviewed independently by each rater, also using the K-SADS-P, with a two-week interval between assessments. In the first K-SADS-P, the patient was assessed for the present episode and for the last week. The second K-SADS-P concerned the last week only. All assessors in the diagnostic protocol were blind to each other.

Criteria for Inclusion.—At the end of the two weeks, one of us (J.P.-A.) opened all information. Subjects were admitted into the study if both psychiatrists agreed that they fit Research Diagnostic (RDC) Criteria[45] for MDD (summary ratings), the pediatrician found no medical criteria for exclusion, and the parent signed informed consent for the study.

Inpatient status was not a precondition for the protocol. Although similar studies in adult depressives have been carried out in inpatients,[24,46,47] the clinical situation is quite different in child psychiatry. Inpatient psychiatric admission in adults is highly related to severity of psychopathology. In prepuberty, although psychopathology is also a variable, in most instances a key factor (besides geographical distance in rural areas) is the family's level of functioning, cohesiveness, and interest in the child.[48] In addition, a substantial proportion of prepubertal children with MDD present clinically significant separation anxiety.[26,49] In such children, the inevitable traumatic effects of a research hospitalization, otherwise not indicated on clinical grounds, on the child and the family were not deemed ethically justified. Thus, admission to and discharge from the child inpatient unit before and during the protocol were strictly based on clinical indication. Both diagnostic and psychopharmacological protocols were run identically regardless of patient status, except that if the child had been an inpatient for the week before an assessment, adult informant's ratings were obtained by interviewing the nurse instead of the parent.

Criteria for Exclusion.—Exclusion criteria were as follows: (1) taking medication that can produce depressivelike syndromes (eg, amphetamines, phenothiazines, and reserpine) (in such cases, a two-week washout period determined if the child's affective symptomatology was primary or secondary to drug intake); (2) significant medical illness, especially endocrinopathies and heart disease; (3) obesity (weight for height greater than 95th percentile on the National Center for Health Statistics curve) or severe chronic malnutrition (height or weight under third percentile); (4) seizures or other major neurological illness; (5) IQ less than 70; (6) anorexia nervosa *(DSM-III);* (7) autism; (8) schizophrenia; (9) Tanner III stage of either genital or breast development.[50,51] Children with inordinate fear of hypodermic needles were accepted into the double-blind study, but did not participate in the plasma level study (case 44).

Sample.—A total of 53 children with major depression completed at least one of the two protocols. Acceptances into the plasma level study were consecutive in completed cases 1 through 6 and 45 through 53. During the time period between completed subjects 7 through 44, the plasma level and the double-blind studies were run concomitantly. (A table detailing this information is available.) Thus, accepted cases during that period were randomly assigned to drug or placebo.

There were 38 completers in the double-blind study. Twenty-two children were accepted and randomly assigned to the placebo group. All of them completed the protocol. Twenty were assigned to the double-blind imipramine group. Sixteen completed the protocol and four dropped out: one failed to comply with study protocol, two refused to attend the clinic at midprotocol, and one child and his family suddenly moved away from the local area. Of the 16 imipramine double-blind completers, all but one (needle phobia) completed the plasma level protocol. Fifteen other children (cases 1 through 6 and 45 through 53) completed the plasma level protocol, but did not participate in the double-blind study. Among this second group, there were no dropouts. Altogether, there were 30 completers in the plasma level study.

As expected, there were no significant differences between imipramine ($N = 16$) and placebo ($N = 22$) groups in sex (62.5% vs

Table 1.—Prepubertal Major Depressive Disorder Imipramine Protocol

	Day								
	0*	3	6	9	12	19	26	33	35*
Electrocardiogram	X	X	X	X	X	X	X	X	...
Plasma level	...	...	...	...	X	X	X	X	...
Side effects scale	X	X	X	X	X	X	X	X	...
Blood pressure	X	X	X	X	X	X	X	X	...
Dosage started, mg/kg/d	1.5	3	4	5	5	5	5	5	...

*Days on which Schedule for Affective Disorders and Schizophrenia for School Age Children was administered.

59% male), age (9.03±1.58 vs 9.18±1.28 years), race (black-Hispanic-white ratios were 6/2/8 vs 8/6/8), socioeconomic status (31.4±13.7 vs 33.0±15.8) measured by the four-factor Hollingshead index,[32] body weight (31.6±7.6 vs 28.8±5.1 kg), or height (132.25±9.87 vs 132.33±8.44 cm).

Of the 30 children who completed the imipramine plasma level protocol, 18 were boys and 12 girls. Mean age was 9.56±1.46 years. Nine were black, 11 Hispanic, and ten white. Mean Hollingshead four-factor socioeconomic index was 33±15. Six subjects were inpatients during the protocol and 24 were outpatients.

Treatment

Imipramine Administration.—The drug regimen lasted 35 days (Table 1); it was preceded by a two-week drug-free intensive diagnostic workup period, without placebo administration. Approximately 20% of the patients who fit criteria in the first K-SADS-P spontaneously improved during that period, did not fit criteria for major depression any longer, and were excluded.

After baseline ECG and administration of imipramine side effects scale, the subject was given imipramine hydrochloride, 1.5 mg/kg/d divided in three daily, roughly equal doses, administered orally at 7 AM, 3 PM, and at bedtime. On day 3, ECG, blood pressure, imipramine side effect scale,[40] and a blood sample were obtained; if not contraindicated, the dosage was raised to 3 mg/kg/d. On day 6, the same procedure was followed and the dosage was raised to 4 mg/kg/d. On day 9, the monitoring was repeated; if not contraindicated, the dosage was raised to a maximum of 5 mg/kg/d.[34] On day 12, following the same procedure, the dosage was to be maintained constant, with weekly monitoring through day 35.

The pediatrician acted as the clinical monitor. He could deviate from this dosage schedule only if (1) heart rate exceeded 130 beats per minute; (2) PR interval exceeded 0.18 s; (3) QRS width exceeded baseline by more than 30%; (4) blood pressure exceeded 140/90 mm Hg; or (5) if there were any other severe side effects. As the upper limits of safety had not been established with certainty at the start of the protocol, the choice of limits needed to be conservative. They were determined in consultation with a pediatric cardiologist with experience in the use of imipramine in children. Except in patients in whom imipramine dosage had to be increased at a slower rate, this was a fixed dosage protocol by the end of the second week. Dosage was independent of the severity of the depressive picture. Although for the purposes of the plasma level study it would have been preferable to administer a fixed weight-corrected dose to maximize plasma level variance,[5] safety concerns about high-dosage imipramine treatment in prepubertal children[31-34] made the institution of cardiovascular safety limits necessary.

Mean imipramine hydrochloride dose in the group assigned to the drug (N=16) was 136.8±31.9 or 4.35±0.61 mg/kg/d, with a range of 3.25 to 5.0 mg/kg/d. All placebo-treated children reached a 5-mg/kg/d "dose." In the plasma level group (N=30), imipramine hydrochloride dose was 134.4±40.7 or 4.29±0.92 mg/kg/d. (A table detailing this information is available.)

From the seventh patient onward, accepted patients were randomly assigned to imipramine or placebo on the basis of a table of random permutations matching the two groups for age (6.0 to 7.99, 8.0 to 9.99, and 10.0 to 12.9 years), sex, and outpatient vs inpatient status. The double-dummy technique was used. All patients received the same number of identical-appearing tablets throughout the study, in three prepackaged envelopes per day, inscribed with date and time of administration, which in patients assigned to the drug group contained a mix of imipramine and placebo pills according to dose.

Everyone was blind to the nature of the pills (except the pharmacist) and to plasma levels (except the pharmacology laboratory). The clinical monitor and the research nurse collected side effect scales, ECGs, and blood pressure values. At the end of the imipramine protocol, the clinical monitor and the research nurse jointly guessed the patient's assignment to drug or placebo. Although they were not privy to group assignment, they were correct in all cases but one, because ECGs in the imipramine group practically always showed changes in resting heart rate and/or PR interval and/or QRS width. This eventuality had been anticipated before the start of the protocol. Thus, ECGs, blood pressure values, and side effect scales were kept from all clinical personnel except the clinical monitor and research nurse, who obtained such measurements and used them in monitoring dosage and systematically kept them to themselves.

All subjects randomly assigned to imipramine in the double-blind study participated simultaneously in the plasma level study. Children assigned to placebo had also blood sampling according to the plasma level protocol. There were only two exceptions: one boy in the placebo group and a girl in the imipramine group were accepted in the double-blind study, but received no venipunctures because of severe needle phobias.

Compliance was monitored by pill counts, the standard 12-lead resting ECG, and plasma levels. Parents were instructed to return any envelope they had missed at the next visit, and they were specifically asked about missed doses at every visit. It was established at the outset that any patient who missed more than six days of medication (consecutive or not) during the five-week protocol was dropped from the study.

Concurrent Treatments.—Neither other medications nor formal psychotherapy were administered during the protocol. Psychotherapeutic management[38] was routine. Emergency crisis intervention was permitted if clinically indicated. One child, a nonresponder with severe insomnia, had an episode of depersonalization in the fourth week of the imipramine protocol and was given a single oral dose of chloral hydrate, 500 mg at bedtime.

Side Effects.—"Nuisance" side effects were elicited by systematically interviewing parent and child together, and were recorded as present or absent in a standard form.[40] The most common (>30% of sample) side effects in the imipramine group were excitement, irritability, nightmares, insomnia, headache, muscle pains, increased appetite, abdominal cramps, constipation, vomiting, hiccups, dry mouth, bad taste, sweating, flushed face, drowsiness, dizziness, tiredness, and listlessness. In the placebo group, the side effects reported were very similar, although rates tended to be lower. Only the occurrence of flushed face on exercise was significantly more frequent in the imipramine group (two-tailed-Fisher's exact test, $P<.03$). No side effect was reported significantly more often in the placebo group.

Sitting blood pressure in the imipramine group increased slightly: for systolic pressure, a mean of +0.8 mm Hg (range, +12 to −16 mm Hg); for diastolic pressure, a mean of +3.0 mm Hg (range, +14 to −8 mm Hg). Nevertheless, blood pressure in the placebo group behaved similarly: mean change in systolic blood pressure was 0 mm Hg (range, +16 to −15 mm Hg), and mean diastolic blood pressure increased +3 mm Hg (range, +19 to −14 mm Hg). Between-group differences were not significant. On the basis of these data, it appears that neither blood pressure nor nuisance side effects are a good guide for either compliance or imipramine dosage titration in children with MDD.

Careful measurements of the standard 12-lead resting ECG proved to be very sensitive to imipramine administration and dosage changes. Practically every child receiving imipramine presented at least minor ECG changes when compared with baseline. Most frequently, these involved resting heart rate increase and PR-interval lengthening. In our experience, imipra-

mine-induced ECG changes are reversible with stoppage or decrease of medication, thereby their value in monitoring compliance. In contrast, the placebo-treated children showed no ECG changes whatsoever, which was the basis of the clinical monitor's correct guesses regarding drug assignment.

The weekly ECG data were analyzed by linearly regressing week number on the ECG measures. The regression coefficients were then used to test the hypothesis that there were linear changes as a function of time. In spite of the fact that ECG changes limited imipramine dose increase, small but highly significant changes in each of the four ECG parameters were found: PR interval increased on the average 0.003 s/wk ($P<.01$); QRS width also showed an average increase of 0.003 s/wk ($P<.001$); heart rate increased an average of 4.3 beats per week ($P<.001$); and QT interval corrected for heart rate increased an average of 0.01 s/wk ($P<.005$). These increases took place entirely during the first two weeks of the protocol, while the mean values remained constant for all ECG measures during the last three weeks. These data suggest good therapeutic compliance and are largely in agreement with those reported by others.[21,32,54,55]

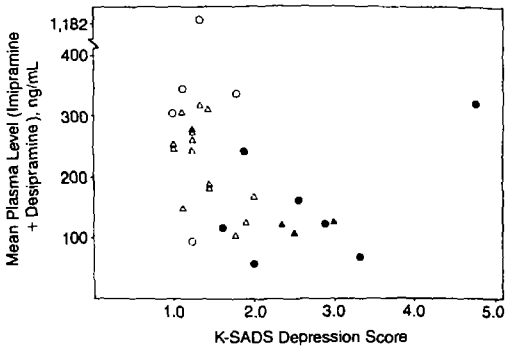
As we recorded clinical side effects with a form that provides only for binary answers,[40] the preceding group comparisons are deceptive. One way to determine severity and clinical significance of side effects is to focus on those that made dosage adjustments downward necessary, or barred any further dosage increase. Such did not occur in the placebo group. In contrast, in 17 of 30 children receiving imipramine, the dosage could not be raised to 5 mg/kg/d. (A table detailing this information is available.) In nine of these 17 children, imipramine dosage could not be raised further because their PR interval had lengthened to the safety limit. In one, heart rate had increased to 130 beats per minute at rest. Increases in QRS width and in systolic and/or diastolic blood pressure never reached preestablished safety limits. In the other seven children, clinical side effects were persistent and bothersome enough in the clinical monitor's judgment as to warrant no further dosage increases or a slight dosage adjustment downward. These were orthostatic hypotension (two subjects), marked irritability (two subjects), chest pain (one subject), and a behavioral syndrome of forgetfulness and perplexity (two subjects). All proved to be dose dependent, and none of these symptoms was part of the initial clinical picture. The only worrisome side effect occurred in a child with orthostatic hypotension. He had syncope with brief unconsciousness on getting up from bed in the morning, before micturition, at a dosage of 3.0 mg/kg/d. His dosage had to be lowered to 2 mg/kg/d for maintenance during the protocol.

Plasma Levels.—Blood samples were obtained at every clinic visit by the research nurse by venipuncture, transferred immediately to a lavender edetic acid tube without stopper,[66,67] and covered with a film of paraffin. Samples were centrifuged within an hour, and plasma was separated and frozen. Blood samples were obtained after school hours at least eight hours after the prior (7 AM) dose, so as not to interfere with school attendance.

The determination of imipramine and desipramine plasma levels was carried out by personnel blind to clinical picture and response. The method of assay was nitrogen-detection gas chromatography. This is a specific method that uses two internal standards, clomipramine and amitriptyline, without chemical derivatization, and has been validated by mass spectrometry.[68,69] Sensitivity of the assay is 1 to 5 ng/mL, accuracy is ±5%, intra-assay coefficient of variation is 5.8%, and interassay difference is 7.9% (the values being higher with gas chromatography).

Mean maintenance plasma levels of each compound were derived from the levels at the end of weeks 2, 3, 4, and 5, except in the cases where dosage titration continued past week 2, when a lower number of weekly levels was used. Mean maintenance plasma levels of imipramine ranged from 14 to 222 ng/mL (50 to 70 nmol/L) (mean, 87±56 ng/mL [310±200 nmol/L]). For desipramine, the values ranged from 29 to 1083 ng/mL (mean, 151±187 ng/mL). Mean total plasma levels ranged from 43 to 1182 ng/mL (mean, 238±199 ng/mL). (A table detailing this information is available.)

Most missing plasma level data on week 2 (43% of cases) were due to the fact that the dosage had not yet been stabilized. Missing data at weeks 3, 4, and 5 (16.6% of data points) were mostly due to the child's refusal of another venipuncture. Because of the research nature of the procedure, the child's will was respected, after psychological techniques to allay undue fear and anxiety were employed. To assess if missing data tended to aggregate within individuals, a κ statistic[69] was calculated for the last three weeks and the last four weeks of the protocol. In both cases, κ values were not significant ($\kappa = 0.001$ and $\kappa = 0.011$, respectively).



Relationship of nine-item depression score at five weeks on Schedule for Affective Disorders and Schizophrenia for School Age Children (Kiddie [K]-SADS) and mean maintenance plasma levels (imipramine and desipramine) in 30 prepubertal children with major depressive disorder treated with imipramine hydrochloride. Open circles indicate responder psychotics; open triangles, responder nonpsychotics; solid circles, nonresponder psychotics; and solid triangles, nonresponder nonpsychotics.

The half-life (β-phase) of imipramine and desipramine in children ranges from six to 15 hours, respectively[41]; therefore, plasma levels from these time points could theoretically be considered to be steady-state levels. To test this possibility, intraindividual variability of maintenance total plasma level (imipramine plus desipramine) was analyzed by means of an intraclass correlation coefficient ($r = .61$). Thus, stability of plasma levels, pill counts, and ECG data all suggest that families were generally compliant with drug administration. The within- and between-intrasubject variability of imipramine-desipramine ratios was found to be high, as in adult depressives.[5] Sources of pharmacokinetic variability may include hepatic metabolic variability, physical activity, food intake, and nonprescribed variation in the timing of drug ingestion as it related to blood sampling. Most of these factors are more likely to be operative in outpatients.

Imipramine Dosage and Pharmacokinetic Measures.—A Spearman ρ correlation matrix,[42] with the 30 children who received imipramine, including weight-corrected imipramine dosage, imipramine plasma levels, desipramine plasma levels, total plasma levels, and imipramine-desipramine ratios, showed, as expected, highly significant correlations between total plasma levels and its two summands, and also between imipramine-desipramine ratio and its two factors. Otherwise, only weak relationships were found between dosage and plasma imipramine level ($\rho = 0.28$, $P<.07$), dosage and imipramine plus desipramine plasma level ($\rho = 0.27$, $P<.08$), and imipramine vs desipramine plasma levels ($\rho = 0.25$, $P<.09$).

Outcome Measures.—The outcome measure was a K-SADS-P for the entire fifth week of treatment, integrating information from all sources. The rater was always blind to plasma levels. In the children in the double-blind study, he was also blind to the nature of the pills prescribed. All patients therefore were assessed with the K-SADS-P for the week before onset of imipramine administration and for the fifth week of treatment.

A K-SADS-P–derived qualitative measure of clinical response at week 5 described a child as a responder if scores in both depressed mood and anhedonia were 2 (slight, of questionable clinical significance) or less, and as a nonresponder if at least one of these two key

Table 2.—Before/After Treatment Analyses of Imipramine Double-blind Placebo-Controlled Study to Prepubertal Major Depressive Disorder

K-SADS* Depression Scales	Placebo (N=22) Before Treatment†	Placebo (N=22) After Treatment	Placebo (N=22) Pearson's r Correlation	Imipramine (n=16) Before Treatment†	Imipramine (n=16) After Treatment	Imipramine (n=16) Pearson's r Correlation	Analysis of Covariance F	Analysis of Covariance P
9-Item Mean	3.0	1.9	.11	3.1	1.9	.49	.03	NS
SD	0.66	0.86	NS	0.43	0.68	P<.06		
K-GAS* Mean	40.7	62.0	.18	39.9	62.6	.18	.02	NS
SD	7.15	16.7	NS	10.1	15.2	NS		

*K-SADS indicates Schedule for Affective Disorders and Schizophrenia for School Age Children; K-GAS, Kiddie Global Assessment Scale.
†No baseline significant differences between placebo and imipramine groups.

Table 3.—Pretreatment Clinical Characteristics*

	No. (%) of Cases		
		Imipramine Hydrochloride Group	
	Placebo Group (N=22)	Double-blind (N=16)	Plasma Level (N=30)
Endogenous subtype	11 (50)	9 (56)	14 (47)
Psychotic subtype	8 (36)	6 (38)	12 (40)
Separation anxiety	10 (45)	6 (38)	9 (30)
Phobia with avoidance	13 (59)	8 (50)	18 (62)
Obsessive-compulsive	2 (9)	2 (13)	2 (7)
Conduct disorder	3 (14)	4 (25)	5 (17)

*There was considerable overlap among subtypes and associated symptoms.

items was 3 (mild) or more. This method agrees closely with quantitative measures (Figure) and with the global rating.

Quantitative measures of clinical response have been defined elsewhere.[28] As the results were fundamentally the same from one scale to the other, only the analyses using the nine-item depressive scale are presented in this article. This scale is the mean score of the K-SADS-P summary ratings for the week preceding the assessment of the depressed mood items and eight of the 11 symptoms of the depressive syndrome. The three items excluded were anorexia, excessive appetite, and fatigue, which imipramine has been reported to produce as side effects in nondepressed children with other conditions.[29] This scale has a high degree of internal consistency (Cronbach's $\alpha = 0.774$).[11] In addition, the global rating on the Kiddie Global Assessment Scale (K-GAS) is also presented, as it involves a different kind of judgment.

Statistical Analyses.—The results of the double-blind study were analyzed using analysis of covariance.[62] The role of plasma levels and other clinical and pharmacological variables as possible predictors of clinical response was investigated by univariate analyses using χ^2 for discrete variables,[61] and logistic regression with maximum likelihood estimation[63] for continuous variables. Multivariate logistic regression[63] was also used to ascertain the main sources of variability.

RESULTS

Clinical Outcome: Double-blind Placebo-Controlled Study

Early Termination.—After the 38th subject of an expected 60, a midpoint analysis was carried out, using analysis of covariance. There were no significant differences between placebo and imipramine groups. The question was raised about the appropriateness of continuing the study. The decision to stop the double-blind study was reached on the basis of the following considerations: Even in the "best" of cases, if all 14 future imipramine-treated patients completing protocol were responders and all eight hypothetical future placebo-treated patients were nonresponders, we could not conclude that imipramine was more effective than placebo (Yates' corrected $\chi^2 = 3.52$, $P<.07$). The probability of this occurring, conditional on the observed response rates, was less than one in 10 million (3.3×10^{-8}).

Even in the event that the "true" response rate among imipramine-treated prepubertal major depressives were 75% and among placebo-treated subjects were 25%, the probability for the next 22 cases to be all responders to imipramine or nonresponders to placebo, calculated by the law of multiplicative probability,[64] would be $.75^{14} \times .75^{8} = .002$. It was concluded, therefore, that under any circumstances, completion of the projected sample would be extremely unlikely to alter the conclusions already reached. The decision was made to stop data collection in the double-blind study and to proceed with consecutive assignments to the plasma level/clinical response protocol until completing its projected sample size of 30.

Contrasts.—There were no significant differences in baseline severity between the imipramine group and the placebo group, regardless of the measure used (Table 2). Similarly, there were no statistically or clinically significant pretreatment differences between the two groups on patient status or on clinical characteristics such as rates of RDC endogenous or psychotic subtypes[65] or associated features (separation anxiety, phobia with avoidance, obsessive compulsive symptoms, or secondary conduct disorder) (Table 3). Neither before nor during the protocol did any subject have a manic or hypomanic episode.

There were no significant differences between the groups in clinical response, measured as before/after differences (Table 2) or as response/nonresponse. Clinical response rates were 56% (9/16) for the imipramine group and 68% (15/22) for the placebo group ($\chi^2 = 0.57$; not significant). In addition, the patterns of before/after depressive score correlations were similar in both groups. No significant correlations were found. (A table detailing this information is available.) There were no significant differences either within the subtypes of psychotic depressives (imipramine response rate, 33% [2/6]; placebo, 63% [5/8]; Fisher's exact test, $P = .29$) or endogenous depressives (imipramine response rate, 44% [4/9]; placebo, 75% [9/12]; Fisher's exact test, $P = .166$).

Clinical Outcome in the Imipramine Group: Relationship to Plasma Levels

The results of the analyses of predictors of clinical response to imipramine are quite similar among the 15 randomized plasma level completers in the double-blind study as in the extended (N = 30) sample. Because of the higher statistical power, only the second is presented. The clinical characteristics of that sample are summarized in Table 3. In the following analyses, clinical response was

Table 4.—Univariate Analyses of Possible Predictors of Clinical Response in 30 Prepubertal Children With Major Depressive Disorder Treated With Imipramine for Five Weeks

	Univariate Logistic Regression With Maximum Likelihood χ^2		
	B	χ^2 to Remove	P
(Log) mean maintenance imipramine and desipramine plasma levels	2.58	9.18	<.003
Pretreatment 9-item K-SADS* depression score	−2.32	7.23	<.008
Maintenance imipramine hydrochloride dosage, mg/kg/d	0.66	2.36	<.130
Missing plasma level data	−1.16	5.11	<.030

	χ^2			
	Nonresponder	Responder	χ^2	P
Psychotic subtype				
Nonpsychotic	3	15		
Psychotic	7	5	3.91	<.05
Endogenous subtype				
Nonendogenous	3	13		
Endogenous	7	7	2.03	NS
Separation anxiety				
Present	7	12		
Absent	3	8	0.02	NS

*K-SADS indicates Schedule of Affective Disorders and Schizophrenia for School Age Children.

Table 5.—Clinical Response as Function of Imipramine and Desipramine Plasma Level in 30 Prepubertal Major Depressive Children Treated With Imipramine*

	Mean Maintenance Plasma Level	
	Above Median (214 ng/mL)	Below Median (214 ng/mL)
Responders	13	7
Nonresponders	2	8

*Fisher's exact test, $P<.022$.

Table 6.—Multivariate Logistic Regression Analysis of Predictors of Clinical Response in 30 Prepubertal Major Depressive Children Treated With Imipramine for Five Weeks

	Model A (Saturated)			Model B (Less P>.30 Effects)		
Independent Variables	B	χ^2 to Remove	P	B	χ^2 to Remove	P
(Log) mean maintenance imipramine and desipramine plasma levels	2.8	7.59	<.006	2.5	7.10	<.008
Pretreatment 9-item K-SADS* depression score	−1.5	0.70	<.400	...	...	...
Psychotic subtype	−1.2	2.83	<.090	−1.5	7.20	<.008
Missing plasma level data	0.9	1.20	<.270	−1.3	3.82	<.060
Constant	−8.4	...	...	−11.1	...	...
Goodness of fit χ^2	...	18.48	...	...	19.18	...
df	...	25	...	...	26	...
P	...	<.82	...	...	<.83	...

*K-SADS indicates Schedule for Affective Disorders and Schizophrenia in School Age Children.

measured as a binary variable because of the higher stability of the results and the clinical meaningfulness of the response/nonresponse dichotomy. Logarithmic transformation of plasma levels and clinical ratings was used when their distributions differed significantly from the normal curve, as tested by the Shapiro-Wilk test.[66,67]

Univariate Analyses.—Log mean maintenance plasma level of imipramine and desipramine (Table 4) was found to be a strong predictor of clinical response (χ^2 to remove = 9.18, $P<.003$). Mean maintenance total plasma levels were significantly higher in responders (284 ± 225 ng/mL) than in nonresponders (145 ± 80 ng/mL) (Mann-Whitney *U* test, $P<.007$). The median maintenance plasma level was 214 ng/mL. Clinical response rates were 87% (13/15) for patients with plasma levels above the median and 47% (7/15) for those below the median (Fisher's exact test, $P<.022$, Table 5). A maintenance plasma level of 150 ng/mL was the most discriminating cutoff between responders and nonresponders. Values above this cutoff were associated with an 85% (17/20) response rate, while only 30% (3/10) of children with MDD and plasma levels under 150 ng/mL responded.

The Pearson correlation between log total plasma level and the log nine-item depression score for the fifth week of the protocol was significant ($r=-.40$; $P<.05$, two-tailed). The same was true between log plasma level and the fifth-week K-GAS score ($r=.41$; $P<.025$). Inspection of the scattergram in the Figure shows no evidence of response inhibition effects of "high" plasma levels. It also shows that the overall results are unduly influenced by patient 6, whose state worsened when plasma level was high, and who also was the only delusional depressive child in the imipramine sample. Given the data on low responsivity of adult delusional depression to TCAs,[4,68-80] the analysis was repeated with nondelusional subjects only ($N=29$). Among them, the correlation coefficient between log plasma level and nine-item depression score was much higher ($r=-.56$; $P<.005$), as well as that between log plasma level and K-GAS ($r=.51$; $P<.005$). As the exclusion of this outlier was not on statistical criteria, but on clinical grounds, no adjustment on significance levels was necessary. In contrast to plasma level, weight-corrected imipramine dosage showed no significant relationship to clinical response.

Pretreatment severity of depressive symptoms (K-SADS nine-item depressive score) was found to negatively and strongly predict clinical response ($P<.008$). Clinical response was significantly less likely to occur in children with MDD and RDC psychotic subtype (42%) than in nonpsychotic depressives (83%) ($P<.05$). In contrast, RDC endogenicity was not associated with clinical response at five weeks. In addition, presence or absence of associated separation anxiety showed no relationship to antidepressant response to imipramine in children with MDD.

Missing plasma level data, coded as the number of missing data points, was found to correlate negatively with clinical response ($P<.03$). Missing data were negatively correlated with imipramine maintenance dose ($r=-.39$) and total plasma level ($r=-.26$) and positively correlated with pretreatment severity (nine-item K-SADS depression score) ($r=.40$). This suggests that patients who were more ill refused more venipunctures, received lower dosages (due to clinical or ECG side effects), and had lower plasma levels. Thus, they were less likely to respond. It cannot be determined from the data what the causal sequence was to explain this correlational pattern. In addition, no significant relationships between age, sex, race, socioeconomic status, or body weight and clinical response during imipramine administration were found.

Multivariate Analyses.—To decipher the interrelationships between the four variables that reached significance, a multivariate logistic regression analysis (Table 6) was carried out. With the

Table 7.—Clinical Response Rate (%) in 30 Prepubertal Major Depressives as Function of Imipramine and Desipramine Mean Maintenance Plasma Levels Above or Below Their Medians

	Desipramine Plasma Level	
	Median or Below (110.5 ng/mL)	Above Median (110.5 ng/mL)
Imipramine plasma level		
Median or below (60.0 ng/mL)	27 (N = 11)	100 (N = 5)
Above median (60.0 ng/mL)	75 (N = 4)	90 (N = 10)

first saturated model, only imipramine plus desipramine plasma level reached significance ($P<.006$). Reanalysis with only three variables (cutoff at $P<.30$) yielded two significant findings—plasma level ($P<.008$) and psychotic subtype ($P<.008$)—and an almost significant trend, missing data ($P<.06$).

In summary, these data suggest that prepubertal major depressive children are more likely to respond, during the proper course of imipramine treatment, the higher their plasma concentration of imipramine and desipramine and the lower the severity of the depressive symptomatology. It cannot be fully ascertained from the results of this study if the negative prediction of clinical response is mainly due to the child having experienced depressive hallucinations and/or delusions during the episode or is simply a reflection of the overall severity of the depressive syndrome, because of the high correlation between these two variables (Pearson's $r=.53$) and also the strong effect of one delusional depressive child.

Other Exploratory Analyses

Compound Predominance in Plasma.—All analyses presented used the combined imipramine and desipramine plasma level as the pharmacokinetic variable. We explored whether the predominant compound in plasma made a difference from the point of view of clinical response. Table 7 addresses this point. It suggests that if at least one of the two compounds is above the median, the child's depression is likely to respond, regardless of which compound predominates. On the other hand, when both compounds are lower than their medians, the response rate is only 27%. Thus, there is little evidence to indicate that metabolite predominance in plasma has any effect on clinical response. There were no significant differences in imipramine-desipramine ratios between responders and nonresponders (0.93 ± 0.86 vs 0.73 ± 0.31; $t = -0.306$; not significant).

Outcome in Patients With 'Low' Plasma Levels.—To integrate the results from the double-blind and the plasma level/outcome studies, the imipramine group in the double-blind study was split into two subgroups according to the plasma level that had been found to be most discriminating in the larger sample: (1) "high" (>150 ng/mL [>530 nmol/L]) and (2) "low" (<150 ng/mL [<530 nmol/L]) mean maintenance imipramine and desipramine plasma level. Each subgroup was compared with the placebo group. The clinical response rate in the "high" plasma level group was 100% (6/6) (Fisher's exact test, $P<.15$). In the "low" plasma level group, the response rate was 22% (2/9), significantly different from the placebo response rate (Fisher's exact test, $P=.026$).

Unpredictability of Response in the Placebo Group.—Similar analyses, with the same nonpharmacological predictors of response, were conducted in the placebo group. No significant correlations were found. Neither severity nor psychotic subtype was associated with clinical response during placebo administration.

COMMENT

The design maximized the chances of finding some evidence of drug effectiveness if imipramine were indeed effective in prepubertal major depression. The lack of differences between imipramine and placebo at five weeks in this study does not support the effectiveness of the drug in this disorder, in spite of the clinically acceptable imipramine response rates in this and prior noncontrolled studies. However, the unexpectedly high placebo response made it almost impossible to find evidence of drug effectiveness. Even in the face of lack of drug/placebo differences, we can be legitimately concerned about plasma levels to assess if insufficient drug response rate may in fact be due to inadequate plasma levels. The finding of a positive linear relationship between total plasma level (imipramine and desipramine) and subsequent clinical response of the depressive syndrome is in line with similar data from adult endogenous depressives[2-5] and supports the idea of a specific drug effect that may be optimized in future studies by plasma level titration.

This study included a two-week diagnostic period, without active treatment or placebo washout. This eliminated some children who initially had fit criteria, but was not sufficient to eliminate enough placebo responders. The 68% clinical response rate during placebo administration should not necessarily be interpreted to mean lack of stability of the clinical picture of prepubertal depressive illness. Kovacs et al,[16,17] using very similar assessment methods and diagnostic criteria, found long duration and persistence of depressive episodes in prepuberty. Therefore, placebo responses may not be akin to spontaneous recoveries in a highly variable condition, and the possibility that depression in youth may be associated with higher predisposition to placebo response should be considered.[81] Future studies should include a placebo washout period and also a study of the stability and temporal pattern of clinical response to placebo in this age group, which may be helpful in differentiating nonspecific placebo effects from specific drug response, as recently reported in adult depressives.[82]

Unlike Preskorn et al,[29] we found no evidence of an inhibiting effect of high plasma levels on clinical response. Their case for a curvilinear relationship is based on only four cases. The short duration of the protocol, the reliance on self-report scales as outcome measures (which may not be sensitive enough to differentiate mood symptoms from side effects), and a different interpretation of psychotic subtype of major depression in children may explain this divergence between the two studies. Otherwise, they basically are in agreement.

It should be noted that interindividual variability in plasma protein binding was not taken into account, although their influence may be more important in children than in adults.[42] Similarly, hydroxymetabolites were not measured, although the latter have been reported to add very little to the prediction of clinical response in adult depressives.[83]

The results of the plasma level/clinical response study suggest that the imipramine dosage may have been too low, out of safety concerns that, in retrospect, were excessive. Our cumulative clinical experience indicates that the original ECG safety limits, especially the PR interval, were too conservative. A PR-interval limit of 0.21 s since has been quite safe in our hands. Similarly, the absolute 5-mg/kg/d dosage limit[34] has little biological meaning, as some children tolerate only lower dosages and others need dosages over 5 mg/kg/d to reach plasma levels in the range associated with response. Frequent monitoring appears to be much more important and practical than an absolute dosage limit. Thus, it is likely that imipramine response rates in prepubertal major depression can be optimized by plasma level titration to the range associated with therapeutic effect in this study, and with less restrictive safety limits for dosage. The incorporation of this information into the design of

future imipramine double-blind placebo-controlled studies in prepubertal major depression is likely to result in maximal responsivity of the imipramine group. It is important to emphasize that no predictors of plasma level were found. Dosage did not predict plasma levels.

The rate of response associated with "low" plasma imipramine and desipramine level was lower than placebo. As a post hoc unexpected observation in this study, it requires replication. This low response rate should not be confused with the presence of excessive side effects. Certain side effects did limit dosage increase, but dosage was not significantly correlated with plasma level or with clinical response, and plasma levels were allowed to vary (they were not titrated). In fact, of the 15 children with plasma levels below the median, seven received dosages of 4.5 or 5 mg/kg/d. There has been a similar observation in adult depressives.[84] If confirmed, this would suggest that "low"-level imipramine administration may actually inhibit the nonspecific (placebo) component of clinical response. In no other depression study, to our knowledge, has a double-blind placebo-controlled design been yoked to plasma level measurements that have been allowed to vary, without using them for titration purposes. Therefore, it is not known if "low" plasma levels in adult depressives treated with imipramine are less effective than placebo. This possibility should be kept in mind when interpreting the high proportion (40%) of negative imipramine double-blind placebo-controlled studies in the adult depression literature.[1] Although preliminary, this observation increases the advisability of titrating plasma level to the therapeutic range in future efficacy studies of imipramine in depressed children.

The RDC psychotic and endogenous subtypes have been described to be relatively frequent in prepubertal depressive disorders.[85] In adults, most of the available evidence indicates that psychotic depressives are more resistant or perhaps unresponsive to imipramine and other TCAs.[4,5,66-80] The results of our study seem to go in the same direction. But replication is required to disentangle fully the effects of pretreatment severity from those of psychotic subtype. In this study, the latter seems to play the predominant role. If this finding is replicated, similarity between child and adult data would occur in spite of profound developmental variations in the clinical expression of psychotic depression. In adults, depressive delusions are by far the most frequent manifestation of psychotic subtype, while in prepubertal depression, delusions are very rare, and the majority of psychotic subtypes in that age group present depressive hallucinations.[86]

The lack of effect of RDC endogenicity[45] is consistent with our view that prepubertal children with nonendogenous depression are likely to be endogenous by their next episode, and that in fact depressive disorders of such an early age of onset are highly likely to involve severe endogenous forms, even if they are not fully expressed at that early age.

In summary, the placebo comparison did not support the hypothesis that imipramine is effective in prepubertal depression. However, the high placebo response rate made any other finding almost impossible. On the other hand, imipramine and desipramine plasma levels were linearly associated with clinical response to the drug. These findings are not conclusive. They do suggest that future double-blind, placebo-controlled studies of imipramine in prepubertal major depression should include in their design an initial placebo washout period and that the drug effect in the index group should be optimized by plasma level titration to 150 ng/mL or higher according to the severity of the depressive syndrome or the presence of depressive hallucinations. Our experience also suggests that serial ECGs may be an excellent way to monitor safety and compliance in future studies.

This investigation was supported in part by grant MH-30838 (Dr Puig-Antich), and grants MH-0113-35171 and MH-07715-17 (Dr Chambers), and New York Psychiatric Institute Mental Health Cl Clinical Research Center grant MH-30906, from the National Institute of Mental Health; and grant 77-612 from the Foundations Fund for Research in Psychiatry, Ansonia, Conn (Dr Perel).

Valerio Nuccitelli, RPh, provided pharmaceutical assistance. Donald Klein, MD, Thomas Cooper, MA, and Joseph Fleiss, PhD, provided consultation and comments on the manuscript. Ciba-Geigy, Summit, NJ, supplied the imipramine and placebo used in this study.

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Childhood Depression and Risk of Suicide: A Preliminary Report of a Longitudinal Study

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Abstract. In the course of locating a sample of 427 adults who were assessed as children or adolescents with either major depressive disorder, mixed anxiety states, or no psychiatric disorder (normal controls), we found seven cases of suicide. Of the original sample, we located 159 of the 204 subjects with major depressive disorder (78%), 37 of the 66 subjects with anxiety disorders (56%), and 85 of the 177 normal controls (48%). All seven suicides occurred exclusively among the 159 children located from the major depressive disorder group, yielding a rate of 4.4% over approximately 10 years. Psychological autopsy was conducted in the seven suicide victims to assess the psychological status since the initial assessment and at the time of death. Although the onset of the first depressive episode in these victims was around puberty, the suicides usually did not occur until late adolescence or early adulthood. At least five of the seven subjects had recurrent depressive symptoms and were clinically depressed at the time of death. These preliminary findings suggest that major depressive disorder in childhood has significant mortality by suicide. *J. Am. Acad. Child Adolesc. Psychiatry*, 1993, 32, 1:21–27. **Key Words:** major depressive disorder, suicide, childhood.

In contrast to the debates two decades ago, it is now clear from epidemiological and clinical studies that major depressive disorder (MDD) does occur in children and that many cases first occur in adolescence and young adulthood (Christie et al., 1988). There is some agreement that the symptom patterns in children and adolescents are similar to those of adults as described in the *DSM-III* (American Psychiatric Association, 1980; Ryan et al., 1987; Strober et al., 1981), and that it is associated with substantial impairment in psychosocial functioning (Puig-Antich et al., 1985a & b) including substance abuse, school drop-outs, and suicide attempts (Brent et al., 1990; Fleming and Offord, 1990; Kandel and Davies, 1986). However, it is not certain if these symptoms persist into adulthood.

Despite the increasing prevalence of depression in children and adolescents, the associated familial aggregation, and the high risk for suicide attempts, we know little about the continuity between the childhood and adult forms (Klerman and Weissman, 1989). Information on the continuity between the childhood and adult forms of depression requires longitudinal studies of children into adulthood. Ideally, these studies should include (1) systematic psychiatric assessments of subjects both in childhood and in adulthood, (2) follow-up diagnoses conducted blindly with regard to the original childhood diagnoses, (3) at least two control groups assessed at both points, as children and as adults, including (a) normal controls who have no evidence of ever having a psychiatric disorder to determine the natural history, course, and incidence of disorders over time, and (b) a second control group with other psychiatric disorders, but not depression, to determine the specificity of the diagnostic outcome in adulthood.

There are no published studies, to date, that meet all these requirements. The study that comes closet to having the ideal design was recently published by Harrington and associates (1990). This study used a "catch-up longitudinal design" to assess adult psychiatric status and social adjustment of depressed children and adolescents compared with individually matched nondepressed psychiatric controls. The sample included 80 child and adolescent psychiatric patients who had a depressive syndrome operationally defined and retrospectively based on their symptoms recorded when they attended a psychiatric clinic. These children were individu-

Accepted March 24, 1992.

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This work derives directly from the ideas, imagination, and vision of Joaquim Puig-Antich, M.D. He undertook a study of depressed children at a time when there was little consensus about its existence or methods for its assessment. He entrusted the second author with their follow up. The initial and unexpected finding, a high suicide rate among the depressed children grown up, was discovered after his death.

The authors would like to thank David Shaffer, M.D., Jennifer Lish, Ph.D., Prudence Fisher, M.S., and Virginia Warner, M.P.H., for advice on the assessment. This work was supported by a grant from the John D. and Catherine T. MacArthur Foundation Network 1 5-34209 to David Kupfer, M.D., and by the NIMH Grant 903.JOO1B to the Child Psychiatry Clinical Research Center at the New York State Psychiatric Institute, New York, NY. Dr. Rao was supported by the NIMH Institutional Research Training Grant 5-38501 through the College of Physicians and Surgeons of Columbia University.

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ally matched with 80 nondepressive psychiatric controls on demographic variables and nondepressive childhood symptoms using a computer algorithm. Follow-up was done after an average of 18 years from the initial contact. The major findings were that the depressed group was at an increased risk for affective disorders in adult life as well as psychiatric hospitalizations and treatment. They were no more likely than was the control group to have nondepressive adult psychiatric disorders. These findings strongly suggested that there was a substantial specificity and continuity in affective disturbance between childhood and adult life. This study, albeit closest to the ideal design, had to rely on retrospective reconstruction from earlier notes for initial diagnoses.

There are other longitudinal studies of children and adolescents with major depression that do provide similar findings despite some methodological limitations, including small samples, short follow-up period, absence of diagnostic criteria, and absence of control groups. These studies suggest that the depressive episodes have prolonged course with recurrence (Chess et al., 1983; Garber et al., 1988; Kovacs et al., 1984a, b; Olsen, 1961; Strober and Carlson, 1982; Welner et al., 1979), persistence of depressive symptoms into adulthood (Chess et al., 1983; Garber et al., 1988; Kandel and Davies, 1986; Poznanski et al., 1976; Welner et al., 1979), increased rates of only affective illness when compared with controls, suggesting specificity of the disorder (Garber et al., 1988; Welner et al., 1979), poor social functioning in adulthood (Garber et al., 1988; Kandel and Davies, 1986; Olsen, 1961; Poznanski et al., 1976; Welner et al., 1979), and bipolar disorder in the future (Strober and Carlson, 1982; Welner et al., 1979). Some studies also have demonstrated increased prevalence of affective disorders among family members (Garber et al., 1988; King and Pittman, 1970; Strober and Carlson, 1982; Welner et al., 1979).

The paucity of longitudinal studies of depressed children into adulthood is, in part, because until recently the conventional belief was that depression did not occur in children, and if it did, it was thought to be masked. There were few instruments for systematic assessment of children and adolescents until the late 1970s. Joaquim Puig-Antich, M.D., was a pioneer in adapting diagnostic assessment for children and conducting comprehensive studies of depressed children. Between 1978 and 1984, he conducted comprehensive clinical and biological studies of children with either MDD, mixed anxiety states, or no psychiatric disorder (normal controls). The sample, now in adulthood, provides a unique opportunity to answer several questions regarding continuity and discontinuity between childhood and adult depression: Are they similar disorders? Are they developmentally linked? Is childhood depression a precursor of adult bipolar and other disorders? How are patterns of continuity or discontinuity affected by comorbidity, familial loading, and abnormalities in psychosocial functioning? The answers may suggest prevention strategies and treatment interventions for depressed children.

This article reports our initial findings on suicide during the course of efforts to locate Dr. Puig-Antich's sample in preparation for a follow-up study.

Method

Initial Sample

The sample included 204 child or adolescent patients diagnosed as having a major depressive disorder, 66 as having mixed anxiety disorders (separation anxiety disorder, phobias, obsessive-compulsive disorder, or overanxious disorder), and 177 normal subjects who had no current or past psychiatric history. A fourth group of 30 children with attention deficit disorder or conduct disorder (ADD-CD) were studied initially but are not included here because of the small sample size and unsuccessful efforts to locate the group. The total sample for this study consisted initially of 447 children.

Initial Assessments

Patients were accepted for an initial screening at New York State Psychiatric Institute (NYSPI) between 1978 and 1984 if they were between 6 and 17 years old and were reported to appear sad or said they were sad, or presented with suicidal ideation or behavior, school refusal, nervousness, fears, or rituals. Each case was screened for appropriateness during a 2-week diagnostic evaluation that included the Schedule for Affective Disorder and Schizophrenia for School Age Children (K-SADS) (Chambers et al., 1985), psychosocial assessment using a semistructured instrument, the Psycho Social Schedule (PSS) (Lukens et al., 1983), pediatric examination that included Tanner staging, IQ, and wide range achievement tests. A second K-SADS was conducted 10 to 16 days later to assess symptoms for the past week by another physician. The assessments were done independently, and both the child and the parent were interviewed. Adolescents also were administered the K-SADS, Epidemiologic version (K-SADS-E) (Orvaschel et al., 1982) to assess the nature of any previous episodes of psychiatric disorders.

Interrater reliability, test-retest reliability for symptoms and intraclass correlation coefficient reported elsewhere were high (Puig-Antich et al., 1985a, 1989b). The diagnosis of major depression was made using the unmodified adult Research Diagnostic Criteria (RDC) (Spitzer et al., 1978). The diagnoses of the various anxiety disorders conformed to the *DSM-III* criteria.

Normal controls were recruited by random sampling of the third, fourth, and fifth grade children at an urban school on the basis of having a student body whose ethnic and socioeconomic characteristics were similar to those of the first half of the depressed sample. Neither the children nor their parents were told that the study was connected with depression to avoid biased sampling. Two separate groups of interviewers assessed the child and collected the family data. The two groups were kept blind to each other's results. The K-SADS-E was used to interview the child and the parent. At no point were the interviewers certain of the proband having been accepted as normal. Only children who met none of the *DSM-III* criteria for psychiatric diagnoses during their lifetime were accepted into the normal group.

In addition to the above assessments, information on the family history of psychiatric illness was obtained from the

mother, using the Family History Method (FH-RDC) (Andreasen et al., 1977). Treatment with tricyclic antidepressants and psychosocial interventions, sleep, and neuroendocrine studies were conducted on a subgroup of children and adolescents (Chambers et al., 1982; Puig-Antich et al., 1981, 1982, 1983, 1984a, b, c, d, and e, 1985a, and b, 1987, 1989a and b; Ryan et al., 1986, 1987).

Follow-Up

Attempts were made to locate the original sample between 1989 and 1991 by using the old addresses of the patients and their neighbors, obtained from the clinic records and from files maintained by credit bureaus and public utilities. Psychological autopsy was conducted on the seven identified suicides.

The psychological autopsy was conducted by a child psychiatrist (U.R.). Psychiatric history since the initial assessment and the psychological status at the time of death were assessed using the K-SADS-E (Orvaschel et al., 1982). Modifications were made to obtain information on the number of depressive episodes, clinical symptoms and treatment during each episode, and the psychological status at the time of death. Psychosocial functioning, during the lifetime and within the last 6 months before death, was obtained by using a modified semistructured interview, the Social Adjustment Inventory for Children and Adolescents (SAICA) (John et al., 1987). Details of the suicide, including the precipitants of death, the method used, and the physical circumstances were assessed through a semistructured interview, the Completed Suicide Event Interview (Fisher et al., unpublished). Family history of psychiatric illness was obtained by using the Family History — Epidemiologic Version (FHE) (Lish et al., unpublished). The FHE is a screening instrument that was modified from the FH-RDC for epidemiological studies. The FHE was modified to obtain information on suicide among family members and friends. Significant family life events also were assessed using a modified version of the Coddington Life Events Questionnaire (Coddington, 1972). A parent was the informant in six cases and an aunt in the seventh case. The interviews were conducted between January and March of 1991 in six cases. The parents of one subject were interviewed within 3 months of death in another study using similar measures. Other informants were sought but consent was not obtained. Information also was obtained from the initial assessments done by Puig-Antich et al. between 1978 and 1984, the hospital records during and subsequent to the initial evaluation, and the medical examiner's reports.

Results

As of January 1991, the research staff had located 159 of the 204 depressed subjects (78%), 37 of the 66 subjects with anxiety disorders (56%), and 85 of the 177 normal controls (48%) (Table 1). Of the 281 subjects located thus far, there have been seven deaths by suicide. All seven suicides occurred exclusively in the depressed group, yielding a rate of 4.4% over 10 years, among the located depressed subjects. Efforts to locate the remaining sample continue.

Table 2 describes the characteristics of the seven suicide victims. There were four males and three females. No clear pattern was observed among the seven victims either in the demographic features, subtypes of MDD, comorbid diagnoses, treatment response, or method of suicide. The first depressive episode occurred before or around puberty in each case. The initial assessments by Dr. Puig-Antich were conducted during the late adolescent period in five subjects when they sought treatment. Two subjects were assessed around puberty. The timing of suicide in all but two cases was in late adolescence or early adulthood. Death occurred during the period of study in one subject and the remaining deaths occurred well after the initial assessment. A variety of methods were used, although tricyclic overdose was the most common cause of death (three of seven). Of the remaining four subjects, one died by the use of explosives, one by jumping, one by accidental fire after ingesting gasoline, and one by drowning. Among the three subjects with tricyclic overdose, two were on active treatment at the time of death. One subject saved the medication for almost a year after terminating treatment. Five subjects had met RDC criteria for a major depressive disorder around the time of death, and one of these subjects had psychotic symptoms in addition to depressive symptoms. One subject had depressive symptoms but did not meet criteria for a major depressive disorder. Adequate information was not available to make a diagnosis in one subject.

Information obtained from initial assessments, medical records, and interviews with parents indicated that all the subjects had a prolonged course of illness. They were usually isolated with few or no friends and had a history of suicidal ideation and/or attempts. Four subjects initially responded well to tricyclic antidepressants, two subjects showed partial improvement, and one subject showed very minimal improvement with tricyclics. Addition of other drugs, including lithium, did not cause any significant change. Two of the subjects with a poor response to antidepressants later developed psychotic symptoms and were treated with antipsychotic medication with no significant

TABLE 1. *Description of Sample, Percent Located, and Suicide Rate*

Diagnostic Group	Total Sample	*N* Located	% Located	Suicides	Suicide Rate/100 in Located Sample
Major depression	204	159	78	7	4.4
Anxiety disorders	66	37	56	0	0.0
Normal controls	177	85	48	0	0.0
Total	447	281	65	7	2.5

TABLE 2. *Characteristics of the Seven Suicides*

Case No.	Gender	Onset First MDD	Age at Initial Assessment	Age at Death	Suicide Method	Provisional Diagnoses at Death
1	M	13	17	26	Explosives	MDD
2	M	14	17	21	Tricyclic OD	MDD
3	M	14	16	23	Jumping	MDD, Psychosis
4	M	12	16	18	Gasoline ingestion	Bipolar, depressed
5	F	10	11	15	Drowning	Unknown
6	F	14	17	20	Tricyclic OD	MDD
7	F	12	13	14	Tricyclic OD	MDD (Possible)

Note: MDD = major depressive disorder; OD = overdose.

improvement. After the initial assessment at NYSPI, at least six subjects had recurrence of depressive symptoms with deterioration in psychosocial functioning. One subject later developed bipolar disorder. A second subject also developed manic symptoms. However, it was not clear whether this was induced by the various substances the subject abused. Five of the subjects had written letters to their parents about the intent of suicide, but the information was received after the death in all cases. All except one subject had a family history of affective illness and/or alcoholism among the first-degree relatives. Two subjects had relatives with a diagnosis of bipolar disorder. There was a history of suicide attempts among the relatives of three subjects.

A brief description of each of the seven subjects follows:

Subject 1 was a 17-year-old white young man initially assessed in 1980. He had a history of depressive symptoms for 4 years before assessment and had made three previous suicide attempts. He also had a history of alcohol abuse beginning at age 14. His peer relationships were impaired from early childhood. Treatment was started with an antidepressant medication after his initial assessment at NYSPI. He showed significant improvement in his depressive symptoms and school functioning but continued to abuse alcohol. Medication was discontinued in 1981, and he was discharged from the clinic. He did well for a year after discharge but became depressed again by the end of 1982. He started to have occupational difficulties and changed several jobs. He never sought treatment for these problems. His parents were divorced when he was 23, and his condition worsened. A 6-year heterosexual relationship was terminated by his partner one year before death. He became withdrawn and essentially nonfunctional except for brief periods of employment. Six days before death, he took an overdose of tranquilizers and alcohol. On the day of his death, he appeared to be his normal self. He picked up his paycheck and apparently purchased a gun and some explosives. He died at the age of 26 by detonating himself in a vacant house under construction.

Family history is significant for alcoholism and depression on both sides of the family.

Subject 2 was a 17-year-old white young man who was referred in 1984 by his school counselor with a history of depression for 2½ years and a decline in academic performance. He never had made a suicide attempt but had recurrent thoughts with rehearsed planning. He was quiet and had very few friends from early childhood. Treatment was started with an antidepressant after his initial assessment. He responded positively for 3 years but discontinued his medication in 1987. He became depressed again and dropped out of school, although he was performing well academically. He planned to join the military in 1988 but became anxious as the time approached. He was rejected by a girl friend 2 days before death. A week before joining the military, he took a lethal overdose of the antidepressant medication he had saved. He was 21 years old.

Family history was significant for alcoholism in the father and older brother and depression in two siblings, one of whom has been treated with antidepressants.

Subject 3 was a 16-year-old black male adolescent who was referred to the clinic in 1983 after a suicide attempt. At the age of 14, he began to show some signs of depression, which worsened progressively until his admission. He was started on an antidepressant after his assessment at NYSPI. Several changes were made in medication because of poor response and/or significant side effects.

He did not complete high school and never worked. He developed psychotic symptoms (delusional thinking and hallucinations) in addition to depressive symptoms in 1986 and terminated treatment at NYSPI. Subsequently, he had several hospitalizations for suicide attempts. One month before death, he became very depressed and developed psychotic symptoms. He died at the age of 23 by jumping out of a sixth floor window.

Family history is significant for depression and alcoholism in the father.

Subject 4 was a 16-year-old white male adolescent referred in 1983 for depressive symptoms and poor school performance of 4 years' duration. He was in treatment for 3 years before that with poor response to several medications. He was started on antidepressant medication after assessment at NYSPI. Several changes were made because of poor response to treatment. He had cyclic changes in mood along with psychotic symptoms and was hospitalized for more than a year. Difficulties continued after discharge. Two weeks before death, he became increasingly depressed and did not respond to lithium and antidepressants. He expressed hopelessness about his condition several times and ingested gasoline while his parents were away. He was later discovered alive. However, as he was being removed from the scene, the fumes from the gasoline he had ingested were

ignited by a furnace pilot light. He became engulfed in flames and subsequently died. He died at the age of 18 years.

The subject was adopted at 4 months of age. The natural father was thought to have been treated for bipolar disorder. No psychiatric problems were known in the adoptive family.

Subject 5 was an 11-year-old black girl referred in 1980 because of behavior problems at school, temper tantrums at home, impaired peer relationships, and suicidal threats. On evaluation, she had symptoms of behavior problems and depression with onset at the age of 10. She was started on an antidepressant medication after assessment and had good response. Since the age of 5 years, she had lived with her maternal grandmother after her mother's death. There were significant difficulties between her and her grandmother with frequent running away from home. She was placed in a residential school in 1983. Information was obtained from a great aunt who saw her on weekends. She could not swim but went into the deep end of a swimming pool and drowned at age 14. Autopsy report could not be obtained in this case because of the nonavailability of her legal guardian.

Her mother had behavior problems from the age of 8, was dependent on alcohol, and was killed by her boyfriend at the age of 23. Her maternal uncle had been incarcerated on charges of narcotic trafficking and weapon shooting. Along with substance abuse, two maternal aunts had behavior problems from childhood, one of the aunts had several psychiatric hospitalizations.

Subjects 6 was a 17-year-old white young woman who was referred in 1980 by her psychologist who had been treating her for 3 years, because of worsening depression, decline in academic performance, and dropping out of school. She was started on an antidepressant. There was some improvement in depressive symptoms, but she continued to have problems with family and peers. She began to abuse alcohol and several drugs. She never attained any gainful employment. After her father's death in 1982, her symptoms worsened. She developed some manic symptoms subsequent to her assessment at NYSPI. However, no formal diagnosis was made. She made several suicide attempts (sometimes making serious attempts) before and after her initial assessment at NYSPI. One attempt, insulin overdose, resulted in a coma and some memory deficits. Two months before death, she had an abortion and terminated the relationship with her boyfriend. She became more isolated and died by overdosing on her antidepressant. She was 20 years old at the time.

Family history is significant for depressive illness in the father. Both parents were holocaust survivors and several members of the family died in the holocaust, making it difficult to obtain adequate family history. Two second-degree relatives were given a diagnosis of bipolar disorder and were on lithium therapy.

Subject 7 was a 13-year-old white girl referred in 1979 with depressive symptoms and school refusal for 2 years. Symptoms worsened after parental separation and change in school. She was started on an antidepressant with a good response. Attempts were made in 1980 to decrease her medication resulting in recurrence of symptoms. Medication was reinstituted. Her mood improved, and she became more involved socially. She continued to have problems with school attendance, although there was mild improvement. One year after initial assessment, at age 14, she died by an overdose of her antidepressant medication.

There was no known psychiatric illness among any family members.

Discussion

The major finding in this study is the high rate of suicide in subjects with early onset MDD when compared with subjects with early onset anxiety disorders or normal controls. Although the first onset of depression often was around puberty or earlier, the suicides occurred in late adolescence or early adulthood.

The association between child or adolescent onset depression and suicide has been noted by other investigators. Welner and his associates (1979) conducted an 8- to 10-year follow-up of 77 adolescent psychiatric inpatients and found that four of the 28 subjects with affective disorder died of suicide, yielding a rate of 14.3% over 10 years. Harrington and associates (1990) assessed a sample of 80 children and adolescents with a diagnosis of major depressive disorder an average of 18 years after the initial contact and discovered two suicides, yielding a rate of 2.5% over 18 years. The discrepant rates of suicide in these two studies and the currently reported study may be as a result of varying degrees of severity of the disorder. Welner's study had an inpatient sample, whereas the sample in both Harrington's study and the present investigation were predominantly from outpatient populations.

Follow-up studies of adults with major depression also have shown increased risk of suicide associated with affective disorders. A lifetime incidence of 15% (3 or 4 times higher than that of the other psychiatric disorders and 30 times higher than the general population rate) has been reported (Guze and Robins, 1970; Miles, 1977). The relative risk for suicide in affective disorders is found to be higher during the early period of follow-up, and the rate drops during the succeeding years, probably suggesting an adjustment to their depressed status (Fawcett et al., 1987; Guze and Robins, 1970; Roy, 1982; Tsuang, 1978). Most deaths in the reported sample occurred well after the initial assessment. Suicide in children, adolescents, and young adults is rare despite recently increasing rates. The subjects in the present investigation are still young adults, and most have not passed through the risk period (25 to 40 years) typically found in adult studies. Only longitudinal studies of children and adolescents with major depression can empirically answer whether this group continues to have a risk of recurrent episodes of depression with increased morbidity and suicide into later adulthood.

Suicide by tricyclic overdose was the most common method in our sample (three of seven cases, 43%). Shaffer and Gould (personal communication) assessed the psychological status and the method of suicide in 170 consecutive suicides in New York. They found that the most common methods were through hanging (36%) and gunshots (29%). Only 8% died by means of ingestion. There is a suggestion that treatment with tricyclic antidepressants may be a poten-

tial hazard for suicide in adolescents and requires close supervision for compliance and suicidal ideation.

The findings of this study should be interpreted with certain limitations. We have not located the full original sample, resulting in an oversampling of the depressed group. However, similar efforts to find cases of suicide were made for all groups. We have little knowledge of the outcome in the ADD-CD sample, a group at high risk for suicide. The information obtained for the interval period and the psychological status at the time of death were done several years after death, leading to a possible retrospective recall bias. Effort was made to corroborate the information from hospital records. The provisional diagnoses at the time of death were not made blind to the original diagnoses of the subjects, probably leading to an overdiagnosis of MDD. Finally, we have only two control groups (anxiety disorders and normal controls). We are not certain whether the high suicide risk is specific to early onset depression. Other investigators have found high rates of suicide in subjects with early onset schizophrenia (Kupferman et al., 1988; Welner et al., 1979) and in adult subjects with schizophrenia (Miles, 1977; Tsuang, 1978).

The unique feature of this study is that these subjects were assessed as children with standardized instruments that provided detailed information before death. The findings suggest that early onset depression is associated with mortality by suicide in late adolescence or early adulthood. If an investigation were conducted to determine the rate of suicide in affective disorders by taking a sample of adult subjects, these subjects would have been lost for follow-up, possibly leading to an underestimation of the suicide rate in this population. In conclusion, we have described seven cases of completed suicide over a 10-year period in a sample of 157 subjects initially diagnosed and treated for MDD as children or adolescents. No cases of suicide were found in a control sample of children diagnosed as having an anxiety disorder or in the normal subjects. These findings suggest that MDD in children and adolescents is associated with increased risk for suicide and that this risk may be specific to MDD. These are preliminary findings, and we plan a comprehensive assessment of the full sample.

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Journal of Abnormal Child Psychology, Vol. 13, No. 4, 1985, pp. 513–526

Measuring Depression in Children: A Multimethod Assessment Investigation[1]

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The present investigation examined measures for the assessment of depressive symptomatology in children, as well as two related constructs (self-esteem and anxiety). The sample consisted of 166 elementary school children from grades 3 through 6. Two self-report depression measures, the Children's Depression Inventory (Kovacs, 1979) and the Child Depression Scale (Reynolds, in press), as well as anxiety and self-esteem scales, were completed by the children. Parents (mothers and fathers) evaluated their children on the depression and anxiety scales from the Personality Inventory for Children (Wirt, Lachar, Klinedinst, & Seat, 1977), and teachers provided global ratings of depression and academic performance. The results support the reliability and validity of both self-report children depression measures. Data obtained on the parent report measure do not recommend its use at this time for assessing depression in children, while results on teachers' global ratings of depression provide some evidence that teachers may be a good source of information regarding depression in children.

Depression as an affective characteristic in children has recently begun to generate empirical research interest (Reynolds, 1984, 1985). It is only within the past 6 years that researchers have begun to develop objective meas-

Manuscript received in final form September 28, 1984.
[1]The authors gratefully acknowledge the generous assistance provided by Al Holmquist, principal of Mazomanie Elementary School, and James Clark, principal of Oregon Elementary School, and their teachers. This research was funded in part by a Spencer Foundation Grant to the first author, through the School of Education, University of Wisconsin-Madison. The writing of this article was facilitated by a Wisconsin Alumni Research Foundation grant (135-1503) to the first author.
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0091-0627/85/1200-0513$04.50/0

urement scales for assessing depression in children. This lack of evaluation methodology may be one reason for the relative sparseness of empirical research on childhood depression prior to 1978. In addition to the lack of assessment measures, the conceptualization of childhood depression in the 1960s and early 1970s focused on masked depression as expressed by depressive equivalents (e.g., Cytryn & McKnew, 1972; Glaser, 1967; Rie, 1966) that were phenomenologically at variance with symptomatology associated with depression in adults. The utility of this view was limited at best, and research that focused on masked depression failed to validate this concept (Welner, 1978).

The currently held perspective is that depression in children is, for the most part, nosologically and phenomenologically similar to depression in adults, with minor modifications for developmental differences (Cytryn, McKnew, & Bunney, 1980; McKnew, Cytryn, & Yahraes, 1983; Puig-Antich, 1982). This view is buttressed by the American Psychiatric Association (1980) in the third edition of their *Diagnostic and Statistical Manual for Mental Disorders* (DSM-III). DSM-III views depression in children and adolescents as similar to that found in adults, with minor modifications of symptoms and their duration.

Kovacs and Beck (1977) suggest that the first step in bringing order to the study of depression in children is with standardized description and reliable measurement. In a recent review of evolving assessment methodology design to measure depression in children, Kazdin (1981) concludes: "Relatively few investigations have been designed to evaluate individual assessment devices. Although individual measures of childhood depression hold considerable promise, the overall areas of assessment are underdeveloped" (p. 372).

Within the past few years, research on the measurement of depression in children has appeared, the impetus provided in part by the development of several measures of childhood depression (e.g., Lefkowitz & Tesiny, 1980; Kovacs, 1979; Petti, 1978; Poznanski, Cook, & Carroll, 1979). At present, the most commonly used self-report measure of child depression appears to be the Children's Depression Inventory (CDI) developed by Kovacs (1979, 1981, 1983) as a downward extension and revision of the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). The general acceptance of the CDI as a measure of the depth or severity of depressive symptomatology in children is illustrated by its utilization by an ever-growing list of investigators (see Reynolds, 1985, for a review).

The research as well as clinical need to examine depressive affect in children (Reynolds, 1984) provides an impetus for the development of psychometrically sound and proven measures of depression in children. The current investigation examined the psychometric characteristics of a new

self-report measure of depressive symptomatology in children, the Child Depression Scale (Reynolds, in press), as well as several existing measures. Of primary concern in this study was both the reliability and the construct validity of these measures. Kazdin (1981) has suggested that the optimal procedure for examining construct validity of child depression measures is the utilization of the multitrait-multimethod technique postulated by Campbell and Fiske (1959). With this validation methodology, convergent and discriminant validity are examined and are optimized when measures from different sources (methods) are obtained.

In this investigation, measures of subjects' depression were obtained from three sources: the child (two self-report depression scales), parents (both mother and father), and teachers. In addition, measures of anxiety were obtained from child self-report and parents' ratings. Children also completed a measure of self-esteem. Measures of self-esteem and manifest anxiety were used in this investigation since these variables have been closely associated with depression in numerous theoretical, research, and review papers on childhood depression (Cytryn & McKnew, 1974; Cytryn et al., 1980; Kashani et al., 1981). In addition to the aforementioned measures, teachers were asked to provide global ratings of subjects' academic achievement. Reynolds (1979) has previously shown such ratings to be unrelated to teachers' ratings of hyperactivity, withdrawn, and acting-out behaviors (r's = .07, −.04, .09, respectively) and strongly related to IQ scores ($r = .68$, $p < .001$), thus providing analysis of discriminant validity.

METHOD

Subjects

Participants were 166 children from grades 3 through 6 from two elementary schools in southcentral Wisconsin. With respect to gender, the composition of the sample was 46% male and 54% female. The average age was 116.75 months, with a standard deviation of 13.27 months. Racially, the sample was 95% white and 5% nonwhite.

Procedure

Informed consent letters were sent to 196 pairs of parents, requesting the participation of their children as well as their own cooperation in the study. Parents were told that the purpose of the study was to find out how children feel about themselves, although the exact nature (e.g., to investigate child-

hood depression) was not specified. Consent was obtained for 166 children (87%). Most parents also indicated a willingness to participate in the study by completing rating scales on their children. Of these, 113 mothers and 78 fathers completed usable rating scales on their children. Children completed self-report measures in their classes. Self-report measures were orally administered by classroom teachers using instructions provided by the investigators. In order to control for reading ability, teachers read all items to students while they followed along on the protocols. When self-report measures were completed, teachers were instructed to collect the scales and enclose them in manila envelopes. This procedure assured that students' self-reports would not influence teachers' global depression ratings.

Copies of rating forms were sent to each parent who indicated a willingness to participate. Separate forms with individual preaddressed return envelopes were sent to mothers and fathers. Parents were asked not to collaborate on their ratings. All forms and scales collected from children, parents, and teachers were precoded with identification numbers to ensure anonymity. Subjects' names did not appear on any of the measures.

Instrumentation

Children's Depression Inventory. The CDI was developed by Kovacs (1979) as a downward revision and modification of the 21-item Beck Depression Inventory (Beck et al., 1961). The current version consists of 27 items and uses a three-alternative forced-choice format. Items sample a domain of "overt symptoms of childhood depression such as sadness, anhedonia, suicidal ideation, and sleep and appetite disturbance" (Kovacs, 1981). Kovacs reports an internal consistency reliability (coefficient alpha) of .86. She also reports a correlation of $r = .55$ ($p < .001$) between the CDI and clinicians' independent global ratings of depression. With self-report measures of anxiety and self-esteem, Kovacs (1983) reports correlations of .65 and −.59, respectively, with the CDI.

Child Depression Scale. The CDS was developed by Reynolds (in press) to measure self-reported depressive symptoms in children 8 through 13 years of age who are in regular school settings. The CDS consists of 30 items. Twenty-nine items relate to clinically identified (e.g., DSM-III and research literature) symptoms of depression in children, and use a 4-point "almost never" to "all the time" response format. Item 30 consists of five "smiley-type" faces ranging from sad to happy, where the child puts an X over the face that indicates how she or he feels. Item content was selected in order to enhance the fidelity (sensitivity) of the CDS as a measure of depression in nonclinic populations.

Personality Inventory for Children. The PIC (Wirt et al., 1977) is an objective personality inventory structured to be completed by the child's parent. It consists of 600 true/false items that provide information on 16 clinical scales and 17 supplemental scales. In this investigation only the Depression and Anxiety scales were used. The Depression scale consists of 46 items that were considered by a group of clinical psychologists as indicative of childhood depression. The Anxiety scale of the PIC consists of 30 items, 17 of which are also on the Depression scale. Wirt et al. (1977) report a correlation of .81 between the Anxiety and Depression scales. This correlation should be considered spurious as a function of the substantial overlap of items. The authors also report test-retest reliability coefficients of .80 for the Depression scale and .76 for the Anxiety scale, with a sample of 46 normal children.

Self-Esteem Inventory. The SEI, developed by Coopersmith (1967), was used to assess self-esteem. This instrument is operationally defined as a measure of "the evaluation which the individual makes and customarily maintains with regard to himself: it expresses an attitude of approval or disapproval, and indicates the extent to which the individual believes himself to be capable, significant, successful and worthy" (Coopersmith, 1967, pp. 4-5). For this investigation, SEI Form B (Coopersmith, 1975), which consists of 25 short statements requiring a "like me" or "unlike me" response, was used. The scale is keyed in a positive direction such that a high score is indicative of a positive self-concept.

Children's Manifest Anxiety Scale-Revised. The CMAS-R, by Reynolds and Richmond (1978), is a revised form of the Castaneda, McCandless, and Palermo (1956) Children's Manifest Anxiety Scale. The CMAS-R consists of 28 statements (items) and utilizes a yes/no response format. Reynolds and Richmond (1978) report an internal consistency (KR_{20}) reliability of .85. The scale is keyed so that a high score is associated with high anxiety.

Teacher Depression Rating. A modified form of the teacher rating form used by Lefkowitz and Tesiny (1980) was adapted for this investigation. Several changes were made in language in order to aid teacher comprehension (e.g., ebullience was changed to enthusiasm). Global ratings of depression were provided by teachers using the following definition and response format:

> A working definition, formulated from a review of the pertinent clinical literature, characterizes childhood depression as a state marked by a reduction both in enthusiasm and in the capacity for pleasurable experience. Four areas of functioning may be involved: (a) affective, by manifestations of anxiety and worry, (b) cognitive, by manifestations of self-deprecation, (c) motivational, by decreased performance and withdrawal, and (d) vegetative, by fatigue, sleep problems, and loss of appetite.
>
> Given this definition, please rate (circle) the level of this child's depression:

1	2	3	4	5
not at all depressed				extremely depressed

Teacher Academic Rating. Teachers provided global ratings of subjects' academic achievement by their response to the following item: "This student does better academically than (please circle) 80% 60% 40% 20% 1% of the class." As mentioned previously, Reynolds (1979) has found this teacher rating to be highly correlated with children's IQ scores and unrelated to several maladaptive children behaviors.

RESULTS

Descriptive Statistics

Table I shows the means and standard deviations of the study variables for females and males. Also included in Table I are t tests for differences between independent samples. As can be seen, a significant sex difference was observed on the CDS, with girls endorsing greater depressive symptomatology than boys. Although statistically significant, the strength of association, ω^2 (Hays, 1973), was only .04. A significant sex difference was also found on the SEI. In order to examine these variables for grade differences or possible grade-by-sex interactions, a grade(4) by sex(2) analysis of variance (ANOVA) was computed for all measures. With the excep-

Table I. Means and Standard Deviations of Study Variables by Subjects' Sex with Associated t Tests for Differences

Variable[a]	Female		Male		t	$p <$[b]
	Mean	*SD*	*Mean*	*SD*		
CDI	9.00	7.34	7.82	7.29	-1.02	n.s.
CDS	68.55	12.07	63.49	11.67	-2.71	.01
RCMAS	11.93	5.76	11.30	6.13	−.67	n.s.
SEI	14.10	4.52	15.87	4.88	2.42	.02
PIC-D mother	7.39	5.46	7.29	4.92	−.10	n.s.
PIC-D father	7.63	6.22	6.27	5.11	-1.05	n.s.
PIC-A mother	5.90	3.82	5.84	4.18	−.08	n.s.
PIC-A father	5.79	4.47	5.16	3.75	−.67	n.s.
Depression-teacher	1.89	.85	2.17	1.03	1.25	n.s.
Academic-teacher	4.03	.82	3.57	1.21	-1.88	n.s.

[a]CDI = Children's Depression Inventory (Kovacs, 1979); CDS = Child Depression Scale (Reynolds, in press); RCMAS = Revised Children's Manifest Anxiety Scale (Reynolds & Richmond, 1978); SEI = Self-Esteem Inventory (Coopersmith, 1975); PIC-D = Personality Inventory for Children, Depression Scale (Wirt, Lachar, Klinedinst, & Seat, 1977); PIC-A = Personality Inventory for Children, Anxiety Scale (Wirt et al., 1977); Depression-teacher = Global depression rating by teacher; Academic-teacher = Global academic achievement rating by teacher.

[b]Two-tailed probability.

tion of a significant main effect for sex with the CDS ($F = 4.66$, df 1,153, $p < .05$) all main effects and interaction terms were nonsignificant ($p > .05$).

Intercorrelations Among Child Self-Report Measures

The intercorrelations among measures for each method (child self-report, parents' ratings, and teacher ratings) are shown in Table II. Due to the large number of coefficients computed, an alpha level $\leq .01$ was utilized to test the significance of the correlations. An examination of the child self-report measures indicates that the strongest relationship was between the two depression rating scales ($r = .70$). When corrected for attenuation, the relationship increases to $r = .78$. The related constructs of self-esteem and anxiety also demonstrated significant correlations with the two depression measures (absolute r's ranging from .58 to .67). The negative relationship found between self-esteem scores and the depression and anxiety measures was expected since the SEI is scored in a positive direction while the other measures are keyed in a negative direction. It is also evident from Table II that both self-report measures of depression are highly reliable, as shown by the reliability coefficients (Coefficient alpha; Cronbach, 1951) of $r_{\alpha} = .90$ for both measures. Mean item with total score correlations, corrected for item redundance, ranged from .22 to .62 for the CDI and from .18 to .61 for the CDS. The mean interitem correlation was .23 for both depression scales. The anxiety and self-esteem measures also demonstrated satisfactory reliability.

Intercorrelations Among Parent Report Measures

Table II shows the intercorrelations among mothers' and fathers' reports of their child's level of depression and anxiety using the PIC. An examination of parents' ratings shows that while depression scale reliabilities are satisfactory, the correlation of .49 between mothers' and fathers' ratings was lower than expected. The correlation between parents' reports can be viewed, from a psychometric perspective, as constituting a measure of interrater reliability. When viewed as a reliability coefficient, the value of .49 indicates that a majority of score variance is due to error. Another interpretation of this modest correlation between mothers and fathers is that they may have validly different perspectives as to their child's expression of depression. The strongest relationships were found between each parent's depression and anxiety scale ratings, but these are spuriously high due to substantial item overlap in the scales.

Table II. Intercorrelations Among Child Self-Report, Parents' Ratings, and Teacher Ratings

Variable	1	2	3	4	5	6	7	8	9
Child self-report									
1. Children's Depression Inventory	(.90)[e]								
2. Child Depression Scale	.70[g]	(.90)							
3. Anxiety[a]	.58[g]	.67[g]	(.88)						
4. Self-esteem[b]	−.61[g]	−.67[g]	−.59[g]	(.81)					
Parents' report									
5. Depression[c]-mother	.26[f]	.26[f]	.18	−.22[f]	(.84)				
6. Depression[c]-father	.08	.18	.29[f]	−.18	.49[g]	(.82)			
7. Anxiety[d]-mother	.11	.11	.14	−.15	.71[g]	.49[g]	(.72)		
8. Anxiety[d]-father	.08	.12	.27[f]	−.15	.38[g]	.84[g]	.54[g]	(.74)	
Teacher report									
9. Depression rating	.38[g]	.33[g]	.30[f]	−.40[g]	.51[g]	.34[f]	.15	.22	
10. Academic rating	−.11	−.03	−.23	.14	.04	.05	.10	.05	.26

[a]Revised Children's Manifest Anxiety Scale.
[b]Self-Esteem Inventory.
[c]Personality Inventory for Children-Depression Scale.
[d]Personality Inventory for Children-Anxiety Scale.
[e]Values in parentheses are coefficient alpha (Cronbach, 1951) reliabilities.
[f]$p < .01$.
[g]$p < .001$.

Interrelationships Among Different Measurement Methods

An important consideration for examining validity is the relationship among measures of the same construct that differ in their method of assessment. Of interest here are the intercorrelations among all measures of childhood depression. An examination of parents' PIC Depression scale ratings shows that mothers' ratings correlated .26 ($p < .01$) with the CDI and the CDS, and somewhat lower with child self-report measures of anxiety and self-esteem. A moderate relationship ($r = .51$) was found between mothers' depression ratings and teachers' global depression rating.

Fathers' ratings on the PIC Depression scale did not correlate in the expected manner with the child self-report measures. Fathers' ratings of their child's depressive symptoms correlated $r = .29$ ($p < .01$) with the child self-report anxiety measure, as compared to correlations of $r = .08$ and $r = .18$ with the CDI and CDS, respectively. These low correlations with the child self-report depression measures argue against using fathers' reports on the PIC as a measure of child depression.

Teachers' global depression ratings correlated significantly ($p < .001$) with the two child depression self-report measures ($r = .38$ with the CDI and $r = .33$ with the CDS), as well as with mothers' depression ratings ($r = .51$). The correlation found between teachers' ratings and children's reported self-esteem ($r = -.40$, $p < .001$) suggests that teachers may be focusing on more cognitive affect symptomatology than behavioral-somatic manifestation of depression. Evidence for divergent validity of the depression measures can be seen in Table II by the nonsignificant correlations found between teachers' academic ratings and the child depression measures.

Regression Analyses

Table III shows the results of regression analyses with child self-report depression scales as the dependent variable and anxiety and self-esteem scales as independent variables. These analyses were conducted to determine the cumulative relationship between the child self-report depression measures and the major convergent validity variables. An examination of the beta weights (β) indicates that with the CDS as the dependent variable, anxiety and self-esteem relate in a similar and significant manner when each is partialed out. This is also shown by the substantial increment to the prediction equation ($\Delta R^2 = .11$) due to the addition of the second variable. The overall multiple correlation ($R = .74$) indicates a strong relationship between the CDS and the cumulative relationship of anxiety and self-esteem. While the overall R was somewhat lower for the CDI ($R = .66$), each independent variable

Table III. Summary of Regression Analyses with Child Self-Report Depression Scales as Dependent Variables

	R	R^2	Beta	F	df	$p <$
Child Depression Scale						
Anxiety[a]	.67	.44	.44	125.17	1/154	.001
Self-esteem[b]	.74	.55	-.40	94.33	2/153	.001
Children's Depression Inventory						
Self-esteem[a]	.61	.37	-.43	90.94	1/154	.001
Anxiety[b]	.66	.44	.32	59.50	2/153	.001

[a]Revised Children's Manifest Anxiety Scale.
[b]Self-Esteem Inventory.

demonstrated significant relationships with this depression measure when the other independent variable was partialed out (all β's $p < .001$).

In order to examine the relationship between child self-report depression measures in more depth, a multiple regression analysis with CDI as the dependent variable and CDS, anxiety, and self-esteem scales as independent variables was computed, the results of which are presented in Table IV. Of interest here was the relative contribution of each independent variable, as indicated by the beta weights, when the other independent variables were partialed out. As shown, the strong relationship ($\beta = .47$) between the CDI and the CDS when anxiety and self-esteem were partialed out provides support for the validity of these depression measures. The cumulative R was .73 ($R^2 = .53$), with an overall $F(3, 152) = 58.21$, $p < .001$. The addition of the anxiety and self-esteem measures added little variance to the prediction equation ($\Delta R^2 < .05$). When the CDS was analyzed as the dependent variable with the other three measures as independent variables, a multiple correlation of $R = .79$ ($R^2 = .63$) was obtained.

Finally, the relationship involving the CDI and the CDS, mothers' PIC Depression scale, and teachers' global depression rating was examined. Ta-

Table IV. Summary of Multiple Regression Analysis with Child Depression Inventory as Dependent Variable

Variable	b	Beta	SE_b	F	df	$p <$
Child Depression Scale	.260	.466	.046	31.73	1/154	.001
Self-esteem[a]	-.345	-.242	.107	10.35	2/153	.001
Anxiety[b]	.126	.110	.087	2.06	3/152	n.s.

[a]Self-Esteem Inventory.
[b]Revised Children's Manifest Anxiety Scale.

Table V. Summary of Multiple Regression Analysis with Children's Depression Inventory as Dependent Variable

Variable	R	R^2	Beta	F	df	$p <$
Child Depression Scale	.76	.58	.69	65.40	1/49	.001
Mother's PIC Depression Scale	.78	.61	.17	36.41	2/46	.001
Teachers' Global Depression Rating	.78	.61	.04	23.83	3/45	.001

ble V shows the results of the regression analysis with CDI as the dependent variable. Once again, a strong relationship between the child self-report depression measures was obtained. The β's associated with mothers' and teachers' ratings were nonsignificant.

DISCUSSION

This investigation examined childhood depression via three divergent measurement methods: child self-report, parent report, and teacher report. The results suggest the validity of the CDS as a self-report measure of childhood depression. The CDS also demonstrated high reliability, a prerequisite for validity. While the high correlation between the two self-report depression measures is not an absolute indication of validity, the correlations between these scales and the other self-report criterion measures (anxiety and self-esteem) adds validity information. The best evidence of this can be found in the beta coefficients shown in Table III. Further validation of the CDS should utilize structured clinical interviews as a criterion measure.

The results on the use of the Personality Inventory for Children for assessing depression in children need to be interpreted with caution. While mothers' reports showed significant although minimal correlations with childrens' self-reported depression, anxiety, and self-esteem, fathers' reports correlated very low witth child self-report depression measures (r's of .08 and .18). The correlation between CDI and mother's PIC Depression scale was similar to that reported by Leon, Kendall, and Garber (1980) in their study of 42 elementary school children. The PIC Depression scale consists of 46 items, yet the correlation between mothers' ratings and a single-item global depression rating by teachers was similar (based on Fisher's r to Z transformation) to that found between mothers and fathers on the same instrument. Significant, albeit low, correlations were found between mothers' ratings and

child self-report depression scores, and nonsignificant correlations between fathers' ratings and child self-reported depression were obtained. However, the opposite pattern of results were found when parents' anxiety ratings and children's scores on the CMAS-R were compared. It should be noted that Kazdin, French, and Unis (1983), using the CDI and several parent rating scales, also found very little correspondence between child and parent ratings of depression.

These findings suggest the need for research aimed at examining the viability of various sources of information for the evaluation of depression in children. For example, the potential utility of teachers' reports should not be dismissed. Lefkowitz and Tesiny (1980) found in their validation study of the Peer Nomination Inventory of Depression that teachers' ratings of depression provided the highest validity coefficient ($r = .41$) with their depression measure. Therefore, an important direction for further childhood depression scale development and research is with teachers as respondents. Teachers come in daily contact with many children. They, more than parents, are able to base their observations on a larger and more diverse set of norms. Teachers may also be more objective in their ratings, since they have less emotional involvement in the children than do parents. Parents' involvement in family dynamics and their own affective states may contribute to either an overdescription or a denial of depressive symptomatology in their children. Underendorsement is likely to be evidenced where the child's depression is a function of, or exacerbated by, family variables such as abuse, marital discord, and other stressors. Certainly further research is required to examine differential efficacy between parents and teachers as informants of children's depression.

The superior psychometric qualities demonstrated by the CDI and the CDS are not surprising given the construct under investigation. There is little doubt that most contemporary views concerning the diagnosis of depression include affective and cognitive components in addition to more behavioral symptoms (Dweck, Gittelman-Klein, McKinney, & Watson, 1977; Kovacs & Beck, 1977; Petti, 1978). Research suggests that young children can provide reliable and valid self-report information regarding such affective and cognitive characteristics as self-esteem (Coopersmith, 1967), anxiety (Reynolds & Richmond, 1978), and locus of control (Norwicki & Strickland, 1973). It therefore seems reasonable to expect children to be able to respond in a similarly accurate manner to self-report depression scales. As Kazdin (1981) notes with respect to self-report methodology, "It seems to be especially important in evaluating depression because affective states are likely to manifest in subjective evaluations of one's own experiences" (p. 359). It can be concluded, then, that if one wishes to know how a child feels, ask the child.

Although self-report measures have admittedly not achieved a state of perfection, they represent an extremely useful method for assessing the depth or severity of depressive symptomatology in children. The development of the Children's Depression Inventory and the Child Depression Scale provides researchers and clinicians with dependable instruments for the systematic investigation of depression in children.

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Fluoxetine Treatment of Children and Adolescents with Tourette's and Obsessive Compulsive Disorders: Preliminary Clinical Experience

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Abstract. Fluoxetine hydrochloride is the first selective serotonin uptake inhibitor introduced commercially in the United States. This report describes preliminary clinical experience with fluoxetine in 10 children and adolescents, aged 8 to 15 years, with primary obsessive compulsive disorder (OCD) or Tourette's syndrome (TS) plus OCD. In general, fluoxetine, which was administered from 4 to 20 weeks at a dosage of 10 or 40 mg per day, was well tolerated. Adverse effects included behavioral agitation/activation in four patients and mild gastrointestinal symptoms in two patients. No abnormalities were noted in the seven children who had follow-up EKGs. Five of the 10 patients (50%) were considered responders; their obsessive-compulsive symptoms decreased substantially during treatment with fluoxetine. Responder rates were similar in the primary OCD (two of four, 50%) and TS + OCD (three of six, 50%) groups. In conclusion, short-term fluoxetine administration appears to be safe in children and adolescents. Placebo-controlled trials are needed to further assess the efficacy of fluoxetine. *J. Am. Acad. Child Adolesc. Psychiatry*, 1990, 29, 1:45–48. **Key Words:** fluoxetine, psychopharmacology, obsessive compulsive disorder, Tourette's syndrome.

Fluoxetine, a relatively specific inhibitor of uptake of neuronal serotonin, may be useful in the treatment of adults with obsessive compulsive disorder (OCD) (Turner et al., 1985; Fontaine and Chouinard, 1986; Jenike et al., 1989) and the obsessive-compulsive symptoms associated with Tourette's syndrome (TS) (Riddle et al., 1988). This report describes preliminary clinical experience with fluoxetine in the treatment of children and adolescents with OCD and TS + OCD.

Method

Subjects

The 10 subjects (five boys, five girls; aged 8 to 15 years) represent a consecutive series of all patients under age 18 years who were treated for OCD with fluoxetine in either the Obsessive Compulsive Disorder or Tourette's Syndrome Clinics at the Yale Child Study Center or the Children's Psychiatric Inpatient Service (see Table 1). Subjects with pervasive developmental disorder, psychotic disorders, mental retardation, acute major medical illnesses, or abnormalities on clinical screening laboratory studies were excluded.

All subjects were extensively evaluated, medically and psychiatrically, by a child psychiatrist and clinical nurse specialist and met *DSM-III-R* diagnostic criteria for OCD. In addition, six of the subjects received a diagnosis of TS. Additional *DSM-III-R* diagnoses included: attention-deficit hyperactivity disorder (three subjects), chronic motor tics (two subjects), oppositional defiant disorder (two subjects), separation anxiety disorder (one subject), and overanxious disorder (one subject). In addition, one subject had a midbrain tumor characterized on magnetic resonance imaging scan by thickening of the quadrigeminal plate (see Table 1).

Four subjects had no prior history of treatment with psychotropic medications (TS-6, OCD-1, OCD-2, OCD-4). Four subjects had received imipramine (TS-1, OCD-3) or clomipramine (TS-4, TS-5) for the treatment of obsessions and compulsions. These medications had been discontinued at least 1 month prior to this study because of lack of efficacy or adverse effects. One subject (TS-2) had received haloperidol and clonidine in the past for treatment of tics. Four subjects were receiving medication concurrently for the treatment of tics (TS-1, TS-3, TS-4, TS-5), akathesia (TS-5), or past history of seizures (TS-3) (see Table 1).

Duration of Treatment

The design of the study was 20 weeks, open-label. For most subjects (see Table 2) the duration of treatment was shorter. Following 6 or more weeks of treatment, fluoxetine was discontinued in two outpatients (TS-1, OCD-3) and augmented with pimozide in one outpatient (OCD-1) because of lack of efficacy. Four inpatients (TS-2, TS-4, TS-5, OCD-2) were assessed following 4 or more weeks of

Accepted September 11, 1989.

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This research was supported in part by the following USPHS grants: Clinical Research Center Grant MH-30929 from the National Institute of Mental Health, Research Resources Grant RR-00125 from the National Institutes of Health, and Grant HD-03008 from the National Institute of Child Health and Human Development. Support was also received from the Leon Lowenstein Foundation.

The authors thank the staff and trainees of the Children's Psychiatric Inpatient Service, Yale-New Haven Hospital for skilled clinical care. The authors also thank Drs. Donald J. Cohen and James F. Leckman for their comments and support.

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TABLE 1. *Clinical Characteristics of Children and Adolescents Treated with Fluoxetine*

Subject Number	Primary Diagnosis	Age	Sex	Clinical Setting	Other Psychiatric Diagnoses	Concurrent Medication (mg/day)
TS-1	TS[a]	10	F	Outpatient	OCD	Clonidine (0.125)
TS-2	TS	13	M	Inpatient	OCD, ODD	–
TS-3	TS	13	M	Inpatient	OCD, ADHD	Haloperidol (4.5) Carbamazepine (1,300)
TS-4	TS	13	M	Inpatient	OCD	Pimozide (2)
TS-5	TS	13	M	Inpatient	OCD, ADHD[b]	Pimozide (3.5) Propranolol (40)
TS-6	TS	15	M	Outpatient	OCD	–
OCD-1	OCD	8	F	Outpatient	–	–
OCD-2	OCD	9	F	Inpatient	ODD, separation anxiety	–
OCD-3	OCD	14	F	Outpatient	ADHD	–
OCD-4	OCD	14	F	Outpatient	CMT, overanxious disorder	–

[a] *Abbreviations:* TS = Tourette's syndrome; CMT = chronic motor tics; OCD = obsessive compulsive disorder; ODD = oppositional defiant disorder; ADHD = attention-deficit hyperactivity disorder.

[b] *Note:* Subject number TS-5 also had a mid-brain tumor.

treatment in accordance with termination of their inpatient treatment.

Assessment

Prior to initiation of fluoxetine treatment, the research clinician conducted a semistructed clinical interview of the patient and primary caregiver and completed several rating scales. The clinician rated severity of obsessive-compulsive symptoms during the previous week by completing the Clinical Global Impression for Obsessive Compulsive Disorder (CGI-OCD) (Leckman et al., 1988) and the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Goodman et al., 1989a, b). Severity of tic symptoms was rated with the Clinical Global Impression for Tourette's Syndrome (CGI-TS) (Leckman et al., 1988). At the end of the treatment period, these measures were readministered and the Clinician's Change Rating for OCD was completed.

The CGI-OCD and CGI-TS are ordinal, clinician-rated scales with specifically defined anchor points modelled after the Clinical Global Impressions scale that is widely used in the assessment of depression in children and adolescents (Rapoport et al., 1985). Severity is rated on the CGI-OCD and CGI-TS as follows: 1 = normal, 2 = borderline, 3 = mild, 4 = moderate, 5 = marked, 6 = severe, and 7 = extreme.

The CY-BOCS consists of 16 anchored questions, each scored from 0 to 4 for none, mild, moderate, severe, and extreme. The first five questions assess time occupied by, interference due to, distress associated with, resistance against, and degree of control over obsessive thoughts. The next five questions assess identical dimensions of compulsive behaviors. The total score is the sum of the scores on questions 1 through 10 (range = 0–40).

The Clinician's Change Rating for OCD is a seven-point, ordinal scale designed to rate overall change in disorder since the initiation of treatment. Scores range from −3 (very much worse) through 0 (no change) to +3 (very much better).

Dosage of Fluoxetine

All subjects except one (TS-3) were started on 20 mg of fluoxetine each morning. Subject TS-3 received 20 mg of fluoxetine every other day. Dosage was maintained throughout the study for all subjects except one (TS-2), whose dosage was increased because of lack of improvement to 40 mg each morning after 3 weeks of treatment.

Monitoring Adverse Effects

All subjects had normal baseline electrocardiograms and routine clinical laboratory studies (blood count, urinalysis, and routine clinical chemistries). For the inpatients, sitting systolic and diastolic blood pressure and pulse were obtained daily at 08:00 for 2 weeks before initiation of fluoxetine and throughout the study. For the outpatients, hemodynamic monitoring was done before initiation of fluoxetine and again at the end of the study. In seven subjects, electrocardiograms and routine clinical laboratory studies were repeated at the end of the study. Weight was obtained at the beginning and end of the study.

Data Analyses

Responders were defined as those patients with a +2 (much better) or +3 (very much better) rating on the Clinician's Change Rating for OCD and a decrease of at least one point on the CGI-OCD.

Results

Adverse Effects

Four subjects developed mild-to-moderate behavioral agitation/activation (see Table 2). This symptom, which was not noticed by the subjects themselves, was observed by both parents and clinicians in all four subjects. The agitation/activation, which was characterized by increased motoric activity and pressured speech, generally started during the first few days of fluoxetine treatment, was most severe during the first 2 to 3 weeks, and persisted until the med-

TABLE 2. *Treatment Effects in Children and Adolescents Treated with Fluoxetine*

Subject Number	Fluoxetine Dose (mg/day)	Duration of Tx (weeks)	Side Effects	Clinician's Change Rating-OCD[a]	CGI-OCD		CY-BOCS Total		CGI-TS	
					Pre	Post	Pre	Post	Pre	Post
TS-1	20	8	Agitation/activation	0	4	4	26	25.5	4.5	4.5
TS-2	40	6	None	0	4	4	19.5	24.5	4	4
TS-3	10	20	Nausea	+1	5	4	–	–	3.5	3
TS-4	20	13	None	+2	5	3	23.5	20	5	5
TS-5	20	9	None	+2	6	4	–	–	4	4
TS-6	20	20	None	+2	5	3.5	25	14.5	4	4
OCD-1	20	8	Agitation/activation Epigastric distress	0	4	4	15.5	15.5	-	-
OCD-2	20	4	None	+2	4.5	3.5	15	10.5	–	–
OCD-3	20	6	Agitation/activation	0	4	4	21	21	–	–
OCD-4	20	20	Agitation/activation	+2	5	3	25.5	11	-	-

[a] See Methods section for description of rating instruments: Clinician's Change Rating-OCD, CGI-OCD, CY-BOCS, and CGI-TS.

ication was discontinued (subjects TS-1, OCD-4, OCD-5) or until another medication was added (pimozide in subject OCD-1).

One subject (TS-3) complained of persistent mild nausea. Another subject (OCD-1) complained of persistent mild epigastric distress.

There were no EKG changes or laboratory abnormalities in the seven subjects who had follow-up studies. No clinically meaningful changes in blood pressure or pulse were observed.

Weight changes were minimal and bi-directional. Five subjects gained weight, ranging from 2% to 6% of premedication weight; two subjects lost weight, ranging from 2% to 4%, and three subjects maintained their premedication weight.

Efficacy

Five of the ten subjects (50%) were considered responders to fluoxetine (see Table 2). Each of these subjects had a + 2 score (much improved) on the Clinician's Change Rating for OCD. Three of these subjects had a 2-point decrease in the CGI-OCD score, while the other two subjects had decreases of 1.5 and 1 points. In three of the five responders, the improvement in obsessive-compulsive symptoms was corroborated by substantial decreases in the CY-BOCS scores, ranging from 30% to 57%. One responder had only a 15% decrease in the CY-BOCS score (TS-4), while another (TS-5) did not have a CY-BOCS rating.

There did not appear to be a relationship between responder status and primary diagnosis, clinical setting or concurrent medication. Responder rates were similar in the primary OCD (two of four, 50%) and TS + OCD (three of six, 50%) groups. Three of the responders were inpatients, while two were outpatients. Two subjects who were receiving concurrent medications to treat tics were responders, while two were nonresponders.

No changes were observed in severity of tic symptoms as measured by the CGI-TS in the six patients with TS (see Table 2).

Discussion

The results of this preliminary clinical investigation suggest that short-term administration of fluoxetine in children and adolescents may be safe. No substantial changes in blood pressure, pulse, weight, clinical laboratory measures, or EKG were observed. These observations corroborate those in adults (Wernicke, 1985) and those in an adolescent who ingested a large amount of fluoxetine (Riddle et al., 1989). The long-term safety and adverse effect profile of fluoxetine in children and adolescents has not been studied.

The most common adverse effect was behavioral agitation/activation, observed in 40% of the children. This is a much higher rate than has been reported in adults treated for depression with comparable daily doses. This may reflect pharmacokinetic or underlying neuromaturational differences or may be a spurious finding in this small series of patients.

The data in this study must be interpreted with considerable caution because of lack of placebo control. Obsessive-compulsive symptoms in children and adolescents do not appear to respond to administration of placebo medication (Flament et al., 1985; Leonard et al., 1988); yet, placebo response in the patients in this study cannot be ruled out.

The authors do not have information regarding the minimal effective dose required to treat obsessions and compulsions in children and adolescents. The recommended daily dosage for depression in adults in 20 mg per day, the dosage given to most of the children in this study. Lower dosages might be as effective and result in fewer adverse effects. It is also possible that nonresponders in this study would have responded to higher doses. Yet, the one nonresponder whose dose was increased to 40 mg per day did not respond. The other four nonresponders had adverse effects that prohibited increasing their dosage.

The duration of treatment needed to elicit a clinical response to fluoxetine in children and adolescents is not known. Adults with depression generally respond following several weeks of treatment.

An important clinical question concerns length of treat-

ment before an attempt is made to discontinue medication. All five responders in this study are continuing to take fluoxetine. Fluoxetine was discontinued in one subject (OCD-2) after 8 months of treatment. Within 4 weeks, she experienced an exacerbation of obsessive-compulsive symptoms and fluoxetine was restarted with good improvement over the next few weeks.

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ADOLESCENTS AND SCHOOL PROBLEMS:

DEPRESSION, SUICIDE, AND LEARNING DISORDERS

Warren A. Weinberg and Graham J. Emslie

INTRODUCTION

Depression with or without learning disability is a common cause of school failure in normally intelligent young people (Weinberg, Rutman, Sullivan, et al., 1973; Weinberg & Rehmet, 1983; Livingston, 1985; Emslie, Weinberg, Rush, et al., 1987). Depression and suicide are major mental health problems in the adolescent age group, their epidemiologies being described elsewhere (Carlson & Cantwell, 1979; Chiles, Miller, & Cox, 1980; Holinger, 1981; Earls, 1984; Kaplan, Hong, & Weinhold 1984; Robbins & Alessi, 1985; Fine, McIntire, & Fain, 1986). In addition to school failure, school dropout is a significant prob-

Advances in Adolescent Mental Health,
Volume 3, pages 181–205.

ISBN: 0-89232-812-6

lem, particularly in Hispanic and other minority segments of urban school populations (Canino, Gould, Prupis, et al., 1986). The association between learning disabilities and depression is an area of continued confusion and controversy. Adverse adult sequelae of depressive symptoms in adolescents have been reported (Welner, Welner, & Fishman, 1979; Kandel & Davies, 1986), and learning disorders continue through adult years.

Because suicide is a leading cause of death in the adolescent age group (Fine, McIntire, & Fain, 1986), the impact on a school system and other students is substantial. Clearly, schools would be a logical target for the institution of preventive measures and yet the role of school personnel and other students is still uncertain. It appears that a completed suicide in an area can trigger a series of other suicides in susceptible individuals even if they do not directly know each other.

The focus of this chapter will be learning disabilities and affective illness (depression and manic depressive disease) in relationship to school problems and suicide.

The referred adolescent with school problems is either a chronic low achiever (with or without recent worsening), has had cyclical periods of success and failure, or is manifesting a first-time episode of doing poorly in school (Weinberg et at., 1973). Without expanded neurological study [electroencephalography (EEG); computerized axial tomography (CAT scan); nuclear magnetic resonance (NMR)], the history and usual office physical and fundamental neurologic findings will be unrevealing for classic, progressive neurologic disease or major static encephalopathy. However, behavior (cognitive, social, or emotional) represents active brain (cortex) function. These cortical functions must be evaluated in terms of disease processes in order to establish correct diagnosis with resultant successful treatment, and prevention of occurrence and recurrence.

Clinicians, depending upon their discipline, often assess only one aspect of higher cortical functioning. This can allow associated problems to be considered the cause of school failure with resultant inappropriate and unsuccessful treatment. When evaluating adolescents who are doing poorly in school, the clinician should answer the following questions: (1) What is the diagnosis, prognosis and treatment? (2) Is the disorder(s) primary, secondary, or a reflection of vulnerability, as alluded to by the Multiple Threshold Theorem, or is it situational? (3) Is the disorder(s) preventable from manifesting as a disease process either in occurrence or recurrence?

We have recently reported diagnostic criteria for learning disabilities, disorders of mood, depression and mania, and a primary disorder of vigilance (Weinberg & McLean, 1986). Utilizing these criteria the clinician should be able to correctly diagnose, treat, and prevent morbidity and mortality symptomatic of affective illness.

DEPRESSION AND SCHOOL PROBLEMS

School is one of the environments in which adolescents can manifest depression either in conjunction with or independent of problems at home and with free time (Livingston, 1985). In clinical populations, depressed adolescents manifest school problems in various ways: problems with school behavior, problems with learning and performance, and/or problems with school attendance. A common feature in identifying depression in adolescents is change from their usual self, particularly a significant deterioration in school performance with drop in grades, trouble completing work, inattention in class, and/or disruptive behavior. Many adolescents experiencing depression will start to fail in school and will stop attending school. Decreasing performance leads to less participation in activities previously enjoyed. The "no pass–no play" law further compounds the problems. Depressed adolescents often change to a peer group also doing poorly.

It is unknown how many adolescents who are not seen as having problems (i.e., who are personable, engaging, attentive, and respectful) have specific learning disabilities. Clearly, though, there is a link between learning disability, depression, school problems, and suicidal ideation. This interrelationship remains an enigma for the clinician, a puzzle for parents and teachers, and a process of disease and suffering for children and adolescents. Often parents move their adolescent from one school to another as the young person insists that it is the environment that causes him or her to feel badly. The youngster ends up taking the depressed state to the new environment, further compounding the isolation and failure.

Nonreferred School Populations

Depression as a cause for school problems can be studied in school populations, or in clinical populations referred for doing poorly in school. Recognition that affective illness is the cause of poor school performance requires systematic evaluation utilizing established criteria for depression. Several criteria are currently utilized: DSM-III (American Psychiatric Association, 1980), Research Diagnostic Criteria (RDC) (Spitzer, Endicott, & Robins, 1978), Weinberg (Weinberg et al., 1973), Poznanski (Poznanski, Mokros, Grossman, et al., 1985), and Feighner (Feighner, Robins, Guze, et al., 1972) (Table 1). The Weinberg and Poznanski criteria were developed specifically for school-age populations. The diagnostic assessment is based on clinical interviews of child/adolescent, parent historian, and, on occasion, peers and teachers. The Weinberg criteria dictate the use of a semistructured, closed-end interview technique. Useful adjuncts to clinical interviews are self-report measures (Birleson, 1981; Kazdin & Petti, 1982) assessing the range of depressive symptomatology,

Table 1. Comparison of Weinberg and Feighner Criteria for Primary Depression in Children and Adults

Childhood Depression	*Adult Depression*
A. The 10 symptoms and the characteristic behaviors for each symptom. Presence of both symptoms I and II and two or more of the remaining eight symptoms (III–X). I. *Dysphoric Mood* Statements of sadness, loneliness, unhappiness, hopelessness, and/or pessimism Mood swings, moodiness Irritable, easily annoyed Hypersensitive, cries easily Negative, difficult to please II. *Self-deprecatory Ideation* Feelings of being worthless, useless, dumb, stupid, ugly, guilty Beliefs of persecution Death wishes Suicidal thoughts Suicidal attempts III. *Agitation* Difficult to get along with Quarrelsome Disrespectful of authority Belligerent, hostile, agitated Excessive fighting or sudden anger IV. *Sleep Disturbance* Initial insomnia Interval insomnia Terminal insomnia Difficulty awakening in the morning V. *A Change in School Performance* Frequent complaints from teachers ("daydreaming," "poor concentration," "poor memory") Loss of usual work effort in school subjects Loss of usual interest in nonacademic school activities Many incomplete classroom assignments Much incomplete homework A drop in usual grades Finds homework difficult VI. *Diminished Socialization* Less group participation Less friendly; less outgoing	A. Presence of symptom one and five or more of the remaining eight symptoms (2–9). 1. Dysphoric mood (depressed, sad, blue, despondent, hopeless, "down in the dumps," irritable, fearful, worried, discouraged) (I, II)[a] 2. Poor appetite or weight loss (positive if 2 or more pounds a week or 10 pounds a year when not dieting (X) 3. Sleep difficulty (including insomnia or hypersomnia) (IV) 4. Loss of energy, e.g., fatigability, tiredness. (IX) 5. Agitation (III) or retardation (IX) 6. Loss of interest in usual activities (VI, VII) or decrease in sexual drive. 7. Feeling of self-reproach or guilt (may be delusional) (II) 8. Complaints of or actually diminished ability to think or concentrate, such as slowed thinking or mixed-up thoughts (V) 9. Recurrent thoughts of death or suicide, includes thoughts of "wishing to be dead" (II) B. Must be discrete psychiatric illness lasting at least one month with no preexisting psychiatric conditions.

Table 1. (continued)

Childhood Depression	*Adult Depression*
Socially withdrawing Loss of usual social interests VII. *Change in Attitude Toward School* Does not enjoy school activities Does not want or refuses to attend school VIII. *Somatic Complaints* Nonmigraine headaches Abdominal pain Muscle aches or pains Other somatic concerns or complaints IX. *Loss of Usual Energy* Loss of usual personal interests or pursuits (other than school, e.g., hobbies, sports) Decreased energy; mental and/or physical fatigue X. *Unusual Change in Appetite and/or Weight* Anorexia or polyphagia Unusual weight change in past 4 months	C. Patients with life-threatening or incapacitating medical illness preceding or paralleling the depression are excluded from the diagnosis of primary depression.
B. Interview of patient and historian(s) is conducted utilizing a *semistructured, closed-end technique.*	
C. A symptom is accepted as positive when at least one of the characteristic behaviors listed for the category is present.	
D. Symptoms I & II must be reported by the patient for it to be considered positive. Symptoms III–X can be reported by *either* patient or historian to be considered positive.	
E. Each symptom must be discrete change in usual self (a new behavior or worsening of an old behavior). The *symptom complex* must be present for more than one month *and* associated with a change to maladaptation.	

[a]Roman numerals correspond to respective symptoms of childhood depression.

Source: Weinberg & McLean (1986); reprinted with permission from *Journal of Child Neurology.*

which serve as screening measures to assess those needing further evaluation to prevent morbidity and mortality resulting from this disease.

We recently completed a study to determine depressive symptomatology in a large representative sample of nonreferred adolescents utilizing two self-report measures of depression. We will report selected findings and suggest a 15-item self-report form that could be used in screening for depression in adolescents with school problems (Appendix A).

In a large urban metropolitan school district, 3294 high school students attending health education classes were asked to complete two self-report measures of depressive symptoms: The Weinberg Screening Affective Scale (WSAS) and the Beck Depression inventory (BDI) (Beck, Ward, Mendelson, et al., 1961). The WSAS consists of 55 statements which require yes or no responses and a fourth-grade reading level. Fifty of the 55 questions directly relate to the Weinberg Criteria for Depression (Weinberg et al., 1973) and the Bellevue Index of Depression (BID) (Petti, 1978) and assess whether, by self-report, the child/adolescent fulfills an established criterion for depression. The BDI consists of 21 questions with four choices of answers giving scores of 0–3 for each item and a total score of 0–63. The BDI was established in adults and has been studied in adolescents (Strober, Green, & Carlson, 1981).

The Weinberg Criteria have 10 major symptom categories: two essential symptoms and eight auxiliary symptoms. For each symptom category, specific definitions and behaviors were delineated; these total 40 items. Subsequently, the original 40 items (symptoms and behaviors) were developed by Petti into the BID (Bellevue Index of Depression) and validated on hospitalized child patients (Petti, 1978). The Weinberg Criteria for Depression initially required the presence of the two essential symptoms plus two out of eight additional symptom categories (Table 1). Petti found that 20 positive responses of the original 40 items were diagnostic for depression. Comparisons of the original Weinberg Criteria and other criteria for depression have been made (Cytryn, McKnew, & Bunney, 1980; Carlson & Cantwell, 1982; Poznanski et al., 1985; Emslie et al., 1987). In clinical populations, a criterion of the two essential symptom categories plus four out of eight additional symptom categories correlates more with major depression by DSM-III criteria in child/adolescents (Emslie et al., 1987) than did the previous criterion only requiring two out of eight additional symptoms.

The subjects represented 89% of high school students enrolled in health classes by school district records; 99.2% of this large group of participating adolescents completed more than 90% of the WSAS and BDI questions. The sample is representative of the school population with regard to race and sex: 1825 (55.4%) black, 783 (23.8%) white, 598 (18.2%) Hispanic, and 86 (2.6%) other (Asian, American Indian, and Oriental); 50.7% were male. The mean age of the sample was 15.7 years (range: 14–20 years) with median and modal grade being tenth grade.

On the BDI, 743 subjects (22.6%) scored in the mild depression range

(10–15) and 597 (18.1%) of the students scored in the moderate to severe depressed range (score of 16+). The number of females in the moderate to severe range was 368 (22.7%) compared to 229 (13%) males. Hispanic females had the highest proportion in the moderate to severe range of the three major ethnic groups: 96/308 (31.2%); white males had the lowest: 36/418 (8.6%). On the WSAS, 440/3294 (13.4%) met criteria for depression by self-report. Hispanic females again had the highest percentage of depression by self-report: 69/308 (22.4%). Likewise, the lowest group was white males: 33/418 (7.9%).

With regard to suicidal ideation on the BDI, 101/3236 (3.1%) students responded positively to "I would like to kill myself", or "I would kill myself if I had the chance." Interestingly, 847/3283 (25.8%) answered "Yes" on the WSAS item: "Sometimes I wish I were dead" and 752/3236 (23.2%) answered positively to the BDI question: "I have thoughts of killing myself, but I would not carry them out".

In summary, adolescents in a large metropolitan school district reported a significant amount of depressive symptomatology, 13–18% showing evidence of depression by self-report. In addition, at a specific point in time, 3% of the population was experiencing significant suicidal ideation. It would appear that depressive symptoms are common and there is a significant pool of adolescents at risk for suicidal behavior.

For use as a screening instrument, a shorter form would have increased usefulness in school settings. Utilizing multiple regression analyses of the individual questions to the total score on the WSAS, it was found that 12 questions account for 85% of the variance in the total WSAS score. The scores on the modified form of the WSAS (Appendix A: WSAS-MF) correlate significantly with scores on the WSAS: $r = .92$, $p = .0001$. Ten percent (10%) of this sample scored seven or greater on the WSAS-MF and 25% scored 5 or above. The WSAS-MF should identify adolescents who warrant further evaluation for depression. A significant danger, however, is false negatives. Clearly, a low score does not preclude depression. Further study is needed to determine whether self-report of depressive symptomatology relates to actual pathology as evidenced by deterioration in functioning, i.e., does it identify disease?

Referred Populations

While 13–18% of nonreferred adolescents were depressed by self-report, 50–70% of referred children and adolescents doing poorly in school will be manifesting depression at the time of initial office visit (Weinberg et al., 1973; Weinberg & Rehmet, 1983). The depression can be a first episode, a recurrent episode, or a chronic, fluctuating condition that has persisted for more than one year (dysthymic disorder) (Kovacs, Feinberg, Crouse-Novak, et al., 1984) with or without recent worsening.

When the depression, with associated agitation and disruptiveness, is only

manifested at school, it is the school and/or a learning disability that is "blamed" by parents while the parents are often "blamed" by school personnel. If the dysphoric mood, depressive affect, and vegetative symptoms are only noted at home, parents often "blame" the school for maltreatment, with school personnel remaining unaware of the adolescent's illness. Depressed adolescents without a learning disability might continue to pass in school without major drop in grades. Those with mild, unrecognized learning/communication disorders may show a lowering in performance and those with significant learning disabilities will begin to fail. Delinquency in the lower social class adolescent, vandalism and drug abuse in the middle class, and boarding school "for wrong reasons" in the upper class adolescent might by considered resultant of depression. Fifty to eighty percent of suicides result from depression (Robins, 1981; Fine, McIntire, & Fain, 1986).

Suicidal ideation was manifested by 3% of the nonreferred population; 35% of referred depressed children and adolescents doing poorly in school manifest death wishes; 15% have suicidal ideation and plans; and 5% have attempted suicide prior to the initial office visit (Brumback, Dietz-Schmidt, & Weinberg, 1977b; Weinberg & Rehmet, 1983).

Overt actions of an adolescent during an episode of depression can be misleading and depression can go unrecognized unless the adolescent is systematically examined for affective illness. Primary communicative traits of an individual will dictate expressed behavior during depressive episodes. A quiet, passive, reserved, or introspective, hyposocial individual may become withdrawn, less communicative, hypoactive, and more "alone" during depression. An active, gregarious, more aggressive, and social adolescent may manifest unacceptable agitated, disruptive, nuisant, and argumentative behavior during periods of depression. The anxious, worrying, fearful young person will become incapacitated with excessive anxiety and fears. School phobia in adolescents is often symptomatic of depression. Depression can be manifest in variable and multiple somatic complaints which have no other physical basis and are a cause of frequent absences from school.

Differences in criteria compound the problem in recognizing depression as the disease process. The (RDC) developed by the Washington University School of Medicine's Department of Psychiatry (Feighner et al., 1972; Spitzer, Endicott, & Robins, 1978) precludes adolescents with depression from being given multiple primary psychiatric diagnoses (Hudgens, 1974; Robbins, Alessi, Cook, et al., 1982). However, when utilizing the DSM-III (American Psychiatric Association, 1980), it is common for adolescents to fulfill multiple concurrent diagnoses. Many adolescents doing poorly in school and fulfilling the criteria for Overanxious Disorder, Oppositional Disorder, and Attention Deficit Disorder with or without Hyperactivity only manifest such symptoms in significant degree when in a cycle of depression. There is a high prevalence of depression in hyperactive, attention-deficit young people (Zrull, McDermott, & Poznanski,

1970; Weinberg et al., 1973). Thirty to forty percent of hyperactive children/adolescents are only hyperactive when affectively ill, i.e., depressed or manic (Weinberg et al., 1973; Brumback & Weinberg, 1977b; Weinberg & Rehmet, 1983).

The recognition of manic moments or clearly defined cycles of mania must also be considered in the rubric of depression and suicide in children and adolescents (Feinstein & Wolpert, 1973; Hassanyeh & Davidson, 1980; Strober & Carlson, 1982; Esman, Hertziz, & Aarons, 1983), particularly in the context of problems for both school and the adolescent. It is difficult to conduct class with a manic adolescent present. Even though accepted and studied criteria for mania in young people have been reported, little attention is given to this symptom complex, either clinically or in the literature (Weinberg & Brumback, 1976; Brumback & Weinberg, 1977a; Delong, 1978; Strober & Carlson, 1982). The major symptom of mania is euphoria and it is expressed as denial of any problem or self concerns. Less commonly, euphoria is expressed as elated mood (appearance) and affect (feelings). The intrusiveness, silliness, and giddiness are obvious but often misinterpreted. Most important during the manic episode are the hostile anger and marked agitation that promote severe confrontation and conflicts with parents and teachers leading to expulsion from school and, on occasion, home. The hyperactivity, inattentiveness, distractibility, and disruptive behavior of a manic adolescent often leads to mislabeling and incorrect treatment.

Hyperactive, moody, demanding young children with excessive tantrums and chronic or intermittent sleep disturbances frequently qualify for the label *dysthymia*. As these children age to adolescence, prolonged and discrete cycles of affective illness, depression with or without prolonged manic periods, become evident and a cause of school failure. Some young children seem to be in a constant hypomanic state for months or years, and, with maturity, their bipolar affective illness becomes recognized.

Whether or not affective illness is a unified condition, i.e., manic-depressive disease as described by Kraepelin (1921), or multiple disease processes with different genetic mechanisms, penetrance, and expressions, remains debateable. Division of manic-depressive illness is arbitrary. The many labels for the mood, affective, and vegetative symptom complex that is cyclical with apparent maladaptation cannot be explained with the current level of knowledge. Even though biological correlates highly specific for depression occur in all age groups (Extein, Rosenberg, Pottash, et al., 1982; Puig-Antich, Goetz, Hanlon, et al., 1982; Livingston, Reis, & Ringdahl, 1984; Puig-Antich, Novacenko, Davies, et al., 1984; Emslie et al., 1987), the low selectivity of such correlates provides for possibly too many false negatives at the clinical level. However, the many environmental correlates of depression in adolescents may well be the result of the young person's affective illness, his family's biogeny, and primary (genetic) communicative traits rather than a cause of such illness.

DIAGNOSIS OF DEVELOPMENTAL SPECIFIC LEARNING DISORDERS AND PRIMARY COMMUNICATION TRAITS

Up to 60% of normally intelligent children/adolescents with readily apparent learning disabilities manifest depression at the time of initial office evaluation (Weinberg et al., 1973; Weinberg & Rehmet, 1983). However, it is often behavioral problems, a change in performance, failure, or dropping out of school that initiates referral for clinical evaluation rather than the chronic learning disorder. It is important for the clinician to be able to assess cognitive functioning as well as emotional and social behaviors. Recognizing communicative traits and specific cognitive deficits should provide for improved performance in the school environment and better interaction with parents at home during the depressive episode (Weinberg & Rehmet, 1983). The lack of recognition or inappropriate management of learning disabilities could be a cause of "reactive" depression in young people. A neurobiological basis for "reactive" depression is suggested (see below).

Anatomical, structural abnormalities have been reported for "developmental dyslexia" (Galaburda, Sherman, Rosen, et al., 1985) and neurological correlates of "learning disabilities" have been reviewed (Golden, 1982). However, these studies have not been based upon clearly defined criteria for the various types of learning disability. Utilizing a lexical paradigm, Developmental Specific Learning (and Communication) Disorders (DSLD) are presented as a continuum of deficits in select symbol language skills, their properties, and verbalization-communication functions (Weinberg, 1975; Weinberg, 1982; Weinberg & McLean, 1986). A clinically based taxonomy for DSLD in relationship to postulated cerebral localization and with specific criteria for each clinical syndrome is presented in Figure 1 (Weinberg & McLean, 1986). Table 2 offers localization of definable cognitive, emotional, attentional, and rational functions to right and left cerebral hemispheres (parietal and temporal cortex).

The Symbol Language Battery (SLB) (Table 3) may be used along with historical information and evaluation of verbalization functioning during the interview to establish DSLD diagnosis (Weinberg, 1975; Weinberg, 1982; Weinberg & McLean, 1986). The SLB can be administered in 15 to 30 minutes. Once established, the pattern remains constant within the individual over time even though improvement in each function continues.

Literacy for alphabetic or numeric language skills are 9½ to 12 year old behaviors. By definition, children and adolescents with DSLD are "delayed" in reaching that level of literary competence. Once past the literacy level it might be best *not* to consider the Symbol Deficits (reading, spelling, arithmetic, and graphic writing skill) of DSLD as a primary cause of school failure, if emotional or other significant behavioral abnormality is operative. In this context, Symbol Deficits of DSLD may be a by-product of school failure and not the significant

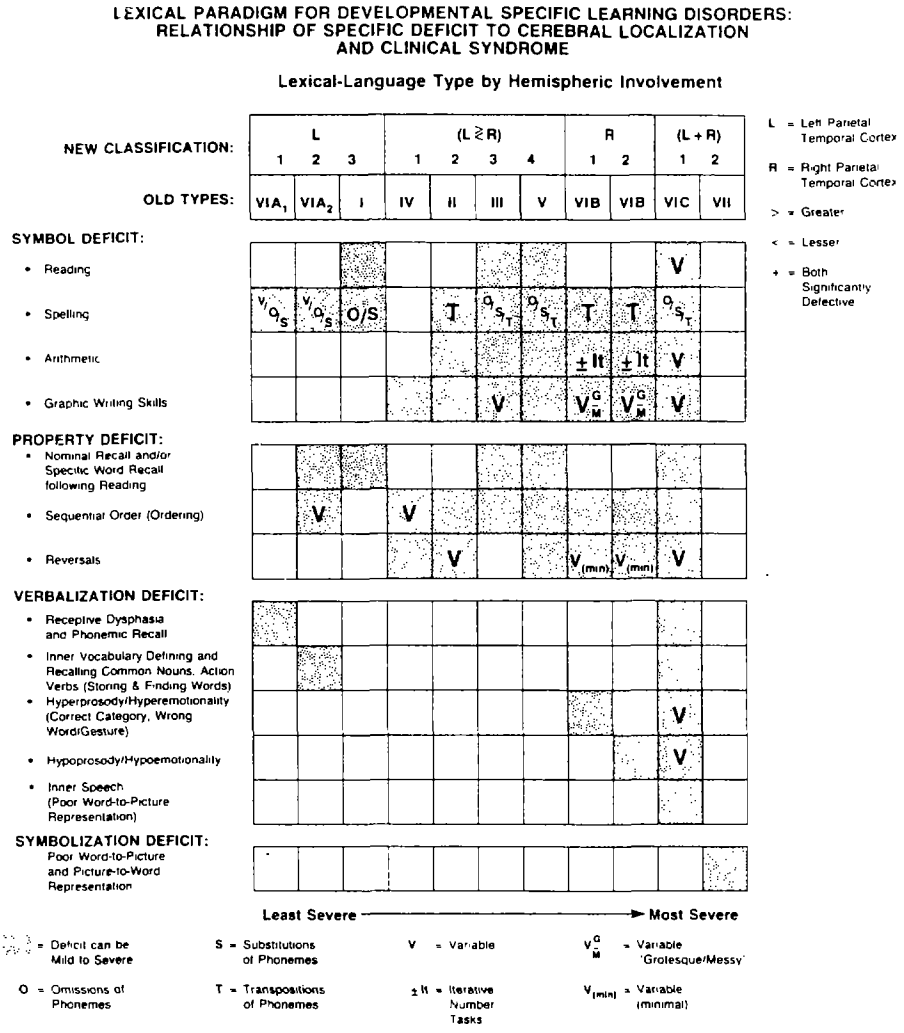

Figure 1. Lexical paradigm for developmental specific learning disorders: Relationship of specific deficit to cerebral localization and clinical syndrome. [Reprinted with permission from *Journal of Child Neurology* (Weinberg & McLean, 1986).]

condition. However, Property Deficits (sequential order, nominal recall, and specific word finding) (Figure 1 and Table 3) of DSLD remain overt problems at least through midadolescence and often through adulthood.

Verbalization Deficits (Figure 1) likewise remain defective through adolescent

Table 2.

Right Cerebral Hemisphere Functions (Parietal Temporal Cortex)	*Left Cerebral Hemisphere Functions (Parietal Temporal Cortex)*
Cognitive Functions:	*Cognitive Functions:*
Spatial orientation	Storage of basic symbols and recall of symbols and nominals: numbers, letters, colors, geometric shapes, and names
Spatial relations	Reading—spelling—writing
Order and sequencing	Comprehension and expression of spoken and written language
Timing and time perception	Rules of grammar and structure for verbal communication
Music appreciation	Storage/retrieval of words (inner vocabulary)
Recognition of objects and faces	
Geometric language	
Nonverbal communication	
"Coordination"	
Emotional Functions:	*Emotional Functions:*
Prosody	Denial and hostile anger (mania)
Primary emotionality	Obsessions and compulsions
Empathy and comprehension of emotionality	"Learned" pessimism and negativity
Affective behavior (depression)	
Attentional Functions:	*Rationality* (for consideration: a hypothesis):
Arousal—vigilance	Verborrhea and graphorrhea without a decent functioning right hemisphere: a "dumb valedictorian"
Attentiveness: right and left space	
Motor Persistence	
Rationality (for consideration: a hypothesis):	
Wit—humor—logic	
Summation:	
Picture-to-picture, word-to-picture, and picture-to-word storage and representation (primary visual imagery, inner speech, and symbolization)	

Source: Adapted from Brumback & Staton (1983) and Brumbeck et al. (1984).

years and evident through adult life in lessening degree. Even though these verbalization functions improve with aging and maturation, the deficits are still observable and often a problem when in a situation that demands the use of such functions. These are noted clinically in excessive need to lip read (receptive dysphasia), spelling errors characterized by phonemically correct mispellings (phonemic recall), and difficulty with nominal recall and word finding in conversation and writing. Communication style, exaggerated (hyperprosody/hyperemotionality), or underexaggerated (hypoprosody/hypoemotionality) must also be evaluated in every referred adolescent doing poorly in school.

In a different context, it is crucial to note the recent recognition of right brain being responsible for order, prosody, and nonverbal communication (primary emotionality) and thus, in major part, for social competence (Ross, 1981; Weinberg, 1982; Denckla, 1983; Weintraub & Mesulam, 1983; McConaughy, 1986) and the affective components of depression (Ross & Rush, 1981;

Brumback, Staton & Wilson, 1984; Freeman, Galaburda, Cabal, et al., 1985). Left brain is possibly responsible for the hostile anger and denial symptomatic of mania (Table 2). Fundamental neurological evaluation of adolescents commonly supports this understanding. Depressed adolescents often demonstrate left limb motor findings of tremor, hyperreflexia, spooning (hypotonia/weakness) of outstretched arm, hands, and fingers, and, on occasion, extensor toe sign (Babinski response) (Brumback & Staton, 1983). In our experience, the manic adolescent will show similar findings in the right limbs. Rapid cycling manic-depressive adolescents will show these motor signs in both right and left limbs.

It is uncommon to see pure left brain DSLD (Figure 1 and Table 2) on a referred basis. Almost all, if not all, referred adolescents have right brain dysfunctioning on a chronic basis, some very mild and others more clinically significant plus variable left brain learning disorder (Brumback & Staton, 1982). This observation is most evident in disorders of communication styles in affectively ill adolescents. Hypoprosodic and hypoemotional depressed adolescents will show a less depressed mood (appearance) in association with disturbing and often severe disorder of feelings (affect). They may indeed attempt or commit suicide without prior warning signs or suspicions of being so severely depressed. For these adolescents, routine screening for depression as a function of health care maintenance might be very important. On the other hand, the hyperprosodic, hyperemotional adolescent's mood (appearance) may be excessive in comparison to his or her feelings (affect). These adolescents may threaten suicide and homicide, act outrageously, and perform explosive, disruptive acts but with much less intense affect of depression. Recognition of this incongruency of mood and affect in affectively ill adolescents is of obvious importance to diagnosis, management, and prevention of destructive acts, either to self or others.

FAMILY HISTORY, "REACTIVE" DEPRESSION, AND SUICIDE IN ADOLESCENTS FAILING IN SCHOOL

The hallmark and dependent variable of biological psychiatry has been family history (Kraepelin, 1921; Winokur, Clayton, & Reich, 1969; Nurnberger & Gershon, 1982). Our findings and those of others continue to show that affectively ill adolescents come from biological families with similar disease (McKnew, Cytryn, Efron, et al., 1979; Weinberg & Rehmet, 1983; Akiskal, Down, Jordan, et al., 1985). Fifteen to twenty percent of our referrals are adoptees whose nonbiological families have a higher prevalence of affective illness than do nonreferred populations of adoptees. One might consider that adoptees are at risk both from their own biogeny and that of the adopters. Likewise, there is strong supporting evidence that DSLDs are genetic disorders and the sub-groups can be explained by an admixture of communicative traits inherited from one or both of the parents or their first-order relatives (Finucci,

Table 3. A Summary of Symbol Language Battery Items (SLB)[a]

Symbol Skill & Property Deficits	*Age of Emergence*
Reading	
Gilmore Oral Reading Test	
C-1, C-2: Monosyllabic words	6–8 years
C-3: Simple compound polysyllabic words	8-9.6 years
C-4: Phonetically nonspecific polysyllabic words	9–11 years
C-5, C-12: Quantitative efficiency	10+ years
Word labeling (from memory, given orally without visual input)	
dog-god	6 7 years
was-saw	7–8 years
tip-pit	7.6–8.6 years
not-ton	9-11 years
live-evil	9–11 years
dial-laid	9–11 years
Three pieces equal what fraction of the pie?	10.6–12 years
What is one fourth as a decimal?	10–11.6 years
What is three fourths as a decimal?	10–11.6 years
What is one fourth as a percent?	10.6–12 years
What is three fourths as a percent?	10.6–12 years
Nominal recall	
Birthday	
Month and day	6–7 years
Month, day, and year	8–9 years
Name recall	
Monosyllabic (Dill, Brill, Dietz)	6–8 years
Bisyllabic (Hertzberg, Rutman)	8–10 years
Trisyllabic (Hertzenberg, Ravenstein)	10–12 years
Four syllable name (Hertzenberger, Schwartzenheimer)	12+ years

Spelling	
Monosyllabic (it, is, the, stop, spot, look)	6–7 years
Monosyllabic (hit, hot, hat, hut)	7–8 years
Monosyllabic (work, talk, girl, went)	7–8 years
Monosyllabic, others (phone, should, could)	8–9.6 years
Polysyllabic (monkey, elephant, friend receive	9–10.6 years
Polysyllabic (purchase, ethics, delicious, delicate)	10–11.6 years
Arithmetic	
How many pennies in a nickel?	5–6 years
If you had six apples and two friends, how many apples could you give each friend?	6–7 years
If you had nine apples and three friends, how many apples could you give each friend?	6.6–7.6 years
How many quarters in two dollars?	7–8 years
How many half-dollars in five whole dollars?	8–9 years
If you had to walk 100 miles, and you could walk 10 miles an hour, how many hours would it take you to walk 100 miles?	9–10 years
Multiplication facts: 4×4, 6×7, 8×9	9–10.6 years
A whole pie is divided into four pieces	
One piece of pie equals what fraction of the pie?	10–11.6 years
Sequential order	
Counting from 0 to 10	
Forward (0–10)	4–5 years
Backward (10–0)	5–6 years
Letters of the alphabet	5.6–6.6 years
Days of the week	
Forward	6–7 years
Backward	7–8 years
Months of the year	
Forward	8–9 years
Backward	9.6–11 years
Reiteration	
$2+2+1-2$	6–8 years
$2\times3+2-1$	8–10 years
$4\times4+4-3$ (or $5\times5+5-4$)	10–11.6 years
Spatial orientation and graphic design	
Draw-a-person	5+ years
Print numbers (3, 5, 6, 7, 9)	5–6 years
Print lower case letters (b, d, p, q, w, z, m, n)	5.6–6.6 years
Draw-a-clock	
Appropriate size and placement	7–8 years
Correct time	7.6–8.6 years
Print or write three to seven lines telling me what you did last night.	7.6+ years

[a]Detailed instructions for administration and interpretation for SLB are available on request

Source: Reprinted with permission from *Journal of Child Neurology* (Weinberg & McLean, 1986)

Guthrie, Childs, et al., 1976; Foch, DeFries, McClearn, & Singer, 1977; Childs, Finucci & Preston, 1978; Defries, Singer, Foch, & Lewitter, 1978; Decker & Defries, 1981). We believe that separating family history, first and second order, into "pure familial" vs. "depressive spectrum biogeny" will be a productive avenue of study. "Pure familial" excludes first- and second-order relatives with alcoholism, schizophrenia, sociopathy, and hysteria. "Depressive spectrum biogeny" includes families with those conditions (Winokur, 1972; Winokur & Morrison, 1973; Schlesser & Altshuler, 1983; Hirschfeld, Klerman, Andreasen, et al., 1985; Winokur, 1985). Children and adolescents with dysthymia and secondary conduct disorders, drug and alcohol abuse, and oppositional disorders seem to come from families who have "depressive spectrum biogeny," whereas adolescents manifesting a discrete episode of depression or mania, either a first episode or recurrent cycle, seem to come from a "pure familial" history of affective illness.

The inductive cause of a depressed period remains unknown. Depression can follow viral illness, minor or major head trauma, and becomes evident with the use of certain prescribed medications. The remarkable prevalence and incidence of depression (and subsequent suicidal ideations) at the time of puberty and prolonged course of affective illness during adolescence suggest a hormonal basis for induction of this disease. A "genetic load" theorem might explain early manifestation of this disorder.

The concept of vulnerability based upon the "Multiple Threshold" phenomenon might be a simplistic explanation for an inducer effect in the high incidence of depression in learning disabled adolescents. Observations by Sherrington (1906) and Eccles (1977) and, in part, recent supportive case studies by others (Ferro, Matins, & Tavora, 1984; Eslinger & Damasio, 1985; Musiek, Reeves, & Baran, 1985; Williamson, Spencer, Spencer, et al., 1985) demonstrated that stimulation of an injured nervous system produces lowered functioning of that area but, more important in the context of depression and DSLD, impairment of that area's homologous part. We suggest, with vulnerability for affective illness and inappropriate demands on genetically defective areas of cortex (Galaburda et al., 1985), a "reactive" depression or manic state can be induced. The nature of the cycle, manic or depressed, might be determined by the area of defective brain that is being stimulated. Most adolescents with depression and DSLD have concomitant right parietal temporal cortex dysfunctioning (Table 2). If a youth is weak in numeric language skills and has a genetic vulnerability for depression, and the school demands more time on task, tutoring, and homework leading to course failure, one might anticipate an episode of depression. If a youth is weak in phonemic recall (spelling), a left brain function, and the school requires a heavy emphasis on spelling and spelling tests, a manic state could ensue. The young adolescent having difficulty with order and sequencing, who has heavy demands placed on "independent" planning and "study skills" plus hormonal influences of puberty, may manifest depression with but little vulnerability. Most

daily and classroom tests depend upon nominal recall and specific word finding. Emphasis on such "fill in the blank" testing for success and failure purposes could also lead to manic episodes in the vulnerable, since both are left brain functions (Table 2).

In summary, "genetic load" for depression may be so heavy that spontaneous episodes of affective illness may occur early in life, either chronic and fluctuating in intensity or in discrete cycles interspersed with variable periods of well states (cyclical in presentation), independent of inducers. For many young people with heavy "genetic load" of DSLD the school environment may be a prime cause for a less depressed vulnerable group to manifest depression (Weinberg & Rehmet, 1983).

A PRAGMATIC APPROACH TO MANAGEMENT

The following information has been written before and in detail (Silberberg & Silberberg, 1969, 1969b; Weinberg, Penick, Hammerman, et al., 1971; Weinberg et al., 1973; Weinberg, 1975; Yule, 1976; Brumback & Weinberg, 1977a; Delong, 1978; Hollister, 1978; Youngerman & Canino, 1978; Lena, 1979; Hewison, 1982; Weinberg, 1982; Petti, 1983a, 1983b; Weinberg & Rehmet, 1983; Weller, Weller, & Preskorn, 1983; Brumback & Staton, 1983; Geller, Cooper, Chestnut, et al., 1984; Puig-Antich, 1984; Weinberg & McLean, 1986). However, we believe it important to review the highlights of management for these suffering and failing adolescents. The above selected readings can be reviewed for more detailed information.

Adolescents manifesting school behavior problems, failing in school, or not attending school are frequently affectively ill and demonstrate clinical criteria for DSLD, right brain disorders with or without left brain deficits. Many of these adolescents are also having difficulty with vigilance, i.e., steady-state awakefulness, arousal, alertness (Weinberg & McLean, 1986). A multimodal approach to treatment is recommended for the depression (Petti, Bronstein, Delamater, et al., 1980) or manic depressive disorder (Table 4). Bypass strategies continue to be suggested toward management of the learning (and performance) and communication disorders.

Management of Learning Disorders (DSLD)

Symbol, verbal, and nonverbal communication skills are presented as genetically determined higher cortical functions, possibly as a genetic code that has its own rate of development (Belmont & Belmont, 1978). These skills may not depend upon drill, reiteration, or excessive "time on task" and may possibly develop with the same end result without formal, structured exposure (Weinberg, 1982). Adolescents, in comparison to prepubertal children, have some insight to

Table 4. Management of Adolescents with Affective Illness

I. *Individual, Family, and Environmental Counselling*
   1. Remove inappropriate stressors: bypass strategies; demands and tasks in keeping with the adolescent's facilities.
   2. Informative: emphasis on genetics, biology, and maturation with potential cycles.
   3. Educative: emphasis on what is known and not known; avoid rationalization and misinformation.
   4. Supportive: be a positive advocate
   5. Reassuring: a treatable and self-limiting condition with anticipation of long periods of well states.
   6. Assist with order and planning: toward school, work, play, and pursuit of assets and talents.
   7. Assist with decision making: "Continue usual pursuits"/"Do not drop-out."
   8. Cognitive coaching on a "mini" dayly basis: "Learn to think positive—act positive"/"Come to know that actions should dictate feelings"/"Intelligence should overrule emotions."

II. *Psychopharmacological Treatment*
   1. Tricyclic antidepressants (TCADs): amitriptyline, imipramine, desipramine, nortriptyline, protriptyline, doxepin.
   2. Thioridazine (and rarely haloperidol; other major tranquilizers are not presently being used).
   3. Carbamazepine (Tegretol).
   4. Lithium.

their deficits and by midadolescence will begin to implement (and request) bypass strategies on their own volition. Likewise, Property and Verbalization deficits begin to accelerate in improvement about midadolescence.

For those adolescents with alphabetic language problems (reading, spelling, and writing), we advise reading only abstracts, synopses, well-prepared teacher "handouts" and "fact sheets", lectures, tapes, and "talking books", and knowing what one is to learn prior to listening and/or reading. Spelling should not be penalized and spelling tests should be by multiple-choice technique. We encourage writing in the form of assisted outlines using memo/executive style, i.e., for content rather than quantity, syntax, or grammar. One can learn to dictate, possibly type, and use a word processor. A "poor speller" dictionary is also helpful. If defective in numeric language, use a calculator and "mini" desk computer, and test by multiple choice format. Multiple-choice untimed tests, either written or oral, which avoid "recall" and "naming" are advised for the adolescent having difficulty with nominal recall, specific word finding, and word-to-word definitions (Weinberg, 1975, 1982; Weinberg & McLean, 1986).

Assistance with order and planning, one-task-at-a-time approach, pictorial systems for self-reminding, and reminders offered by others in a positive and supportive manner are helpful. Avoiding overload is important to prevent willful neglect, excessive anxiety with resultant worsening in immediate recall, and less output of known material.

Adolescents manifesting incongruent mood and affect should be offered cognitive coaching on a "mini" daily basis by their parents and teachers. The emphasis is on awareness, self-control, and planned methods for expression.

These bypass strategies should be implemented within the regular classroom. The materials and information to be learned should be age appropriate, not "skill level." Special educational settings are to be avoided.

Management for Affective Illness

A multimodal therapy approach is recommended, i.e., concomitant management of the adolescent, the environment (home and school), biology, and family (Table 4). The adolescent, parents (or caretakers), and environmental others should all participate. The emphasis is cognitive training on a "mini" daily basis with support, reassurance, continued and reiterative education regarding depression, and assistance in order and planning about school, work, and play. Continuation of usual pursuits and avoiding "dropping out" are mandatory during depressed cycles. Rationalizations and misinformation are not acceptable either from the adolescent, parents, or teachers. Daily attendance at school; pursuit of extrascholastic activities; and comforting, nonconfronting, but well-disciplined home, school, and play environments are expected. Specific instructions are offered and implementation is encouraged on a continuous basis.

The hallmark of shortening the depressed cycle with anticipated lifting to well state within a 6- to 12-week time period is treatment with tricyclic antidepressants. Many referred young people either have been tried on the stimulants (methylphenidate, pemoline, dextro-amphetamine) or are on such drugs at the time of initial visit. These drugs improve vigilance (Weinberg & McLean, 1986) and have a mild antimanic effect but worsen the dysphoria, irritability, melancholy, and sleep disturbances of depression (Weinberg & Rehmet, 1983). However, a subgroup of adolescents with both primary affective illness (depression or manic-depressive disease) and either narcolepsy (Yoss & Daly, 1959) or primary disorder of vigilance (Weinberg & McLean, 1986) will require a combination of tricyclic antidepressants, lithium, and either methylphenidate or pemoline.

Thirty to fifty percent of depressed adolescents will have a parent who is affectively ill at the time of initial visit or during the treatment period. That parent will require concomitant recognition and treatment.

The great majority of depressed adolescents can be successfully treated as outpatients. Short-term hospitalization (three to eight weeks) is required for those who are acutely suicidal or homicidal, manic to the point of being "out-of-control," drug abusing, or when the home is either in need of respite from the adolescent or too unstable to offer appropriate care. Unstable homes of depressed adolescents are often due not only to the affective illness manifest by the adolescents, but also to depression in the parents or primary caretakers.

SUMMARY

In this chapter we state that Affective Illness (depression and bipolar disorder) is a major cause of school related problems. Most referred affectively ill adolescents will have concomitant specific learning disabilities, more right than left brain dysfunctioning. For some, the depressive illness or manic behavior might be "reactive" to inappropriate school demands. Criteria and treatment for Affective Illness and DSLD are presented.

Selected data from a recently completed study of a large school-based population of nonreferred adolescents is reported; 13.4% (440) of 3294 nonreferred adolescents fulfilled criteria for depression by self-report and 3% (101) expressed serious suicidal ideation. This suggests that a large pool of potentially suicidal adolescents exist in our society and that depressive symptomatology is not uncommon. An easily administered, nonthreatening self-report instrument (WSAS-MF) is offered to identify depression in adolescents. With recognition, and treatment as described, much morbidity (failure) and mortality (suicide and homicide) should be preventable.

APPENDIX: WEINBERG SCREENING AFFECTIVE SCALE*— MODIFIED FORM (WSAS-MF)

Instructions

We would like to ask you some serious and very important questions.
We want to know how you feel about yourself.
If you agree with the statement, circle yes.
If you do not agree with the statement, circle no.
We consider these questions and your answers very important.

1.	I will try to give my honest feelings on these questions.	yes	no
2.	I can't concentrate on my work. (V)†	yes	no
3.	I feel lonely too much of the time. (I)	yes	no
4.	I don't want to go to school anymore. (VII)	yes	no
5.	It seems like some part of my body always hurts me. (VIII)	yes	no
6.	People are always talking about me when I'm not there. (II)	yes	no
7.	I have too many bad moods. (I)	yes	no
8.	I don't have fun playing with my friends anymore. (VI)	yes	no
9.	It's hard to fall asleep and that bothers me. (IV)	yes	no
10.	I can't do anything right. (II)	yes	no
11.	I feel too tired to play. (IX)	yes	no
12.	I daydream too much in school. (V)	yes	no
13.	I wish I were dead. (II)	yes	no
14.	My answers are how I have been feeling most of the time.	yes	no
15.	These answers represent my honest feelings.	yes	no

*Complete (long form) WSAS available on request.

†Roman numerals represent the item in relationship to the Weinberg Criteria.

ACKNOWLEDGMENT

This work was supported in part by contributions from the Caleb C. and Julia W. Dula Educational and Charitable Foundation, Mr. and Mrs. Woody Hunt, Mr. Robert McBride, Mr. and Mrs. Morton Meyerson, and Mr. and Mrs. Michael Quigley; and Phi Delta Kappa.

A special note of appreciation and compliment is offered to Dr. Richard Adams, the high school principals and the health education teachers of the Dallas Independent School District, and their participating adolescents (students). Without Ms. Ann McLean's organizational and administrative excellence the Nonreferred Population study could not have been accomplished. The assistance with data analysis by Linda Parkin-Feigenbaum and Jeanie Rintelmann was invaluable. This manuscript could not be submitted without the patient and diligent typing of Ms. Sherri Gorman and Ms. India Davidson.

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ADVANCES IN ADOLESCENT MENTAL HEALTH

A Research-Practice Annual

DEPRESSION AND SUICIDE

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VOLUME 3 • 1988

JAI PRESS INC.

Greenwich, Connecticut *London, England*

55 Old Post Road, No. 2
Greenwich, Connecticut 06830

JAI PRESS LTD.
3 Henrietta Street
London WC2E 8LU
England

ISBN: 0-89232-812-6

Manufactured in the United States of America

Affective Disorders in Childhood and Adolescence--An Update. Edited by D.P. Cantwell and G.A. Carlson.

7

Childhood Affective Disorder and School Problems

Warren Weinberg and Anne Rehmet

The function of an educational evaluation center is to assess children who are having difficulties in school. Children are referred to these centers for evaluation of learning and behavior related to learning failure and classroom behavior problems. Often it is the classroom behavior of these children that accounts for their being referred by the teacher for evaluation and treatment. Parents frequently report a change in the child's mood, affect (feelings), sleep, interests, and homework effort concomitant with the negative comments being offered by the teacher to the parent. The referred child is described by parents and teachers as hyperactive, irritable, aggressive, agitated, inattentive, moody, lethargic, and generally disruptive. It is possible that a cycle of primary affective illness (depression or mania) accounts for the behavior of these children and their inability to behave and achieve in an acceptable manner similar to non-referred children with or without developmental severe learning disabilities.

RELATIONSHIP OF AFFECTIVE ILLNESS TO LEARNING DISABILITIES AND SCHOOL PERFORMANCE

Although affective illness in childhood has been infrequently discussed in medical literature as a cause of children's social, physical, or academic incapacitation, any of these symptoms can cause conflicts in school classroom situations and other social settings and can result in referral of the child to a physician for evaluation of school problems (Brumback and Weinberg, 1977b; Huessy and Cohen, 1976; Husain, 1979; Kovacs and Beck, 1977; Weinberg et al, 1973). It is apparent from previous investigations (Weinberg et al, 1973; Brumback et al, 1977) that childhood depression independent of learning disabilities might be a common condition in children who are doing poorly in school. In that study, all but one of 72 children manifested a learning disability as determined by the Symbol Language Battery (Weinberg, 1975) and psychometric test scores.

Children diagnosed as depressed did not differ from those diagnosed as nondepressed in respect to type of learning disability, age, sex, or IQ. Other publications discuss the relationship of hyperactivity and school problems to childhood emotional and learning disorders (Eisenberg, 1966; Fish, 1971; Kenney et al, 1971; Werry, 1968). However, these childhood "emotional" disorders have not been clearly defined.

Since poor school performance and school failure are part of the clinical picture of many depressed children, a possible relationship between depression and mental retardation (Rideau, 1971) or other intellectual disturbances has been suggested (Malmquist, 1977). Another study (Brumback et al, unpublished) found no difference in IQ and achievement test scores between the depressed and nondepressed group in learning disabled children. The results suggest that the poor school performance of depressed children neither results from nor produces a reduction in basic school skills. Indeed, poor school performance in learning disabled children might possibly be an expression of disinterest in participation and the defeatist self-depreciatory feelings related to primary depression. However, it is common for others to conclude that depression, frustration, and discouragement are secondary to learning disabilities and do not constitute a primary condition.

The relationship to school problems of affective illness, its cyclical nature of gradual worsening followed by improvement with recovery, was investigated at Winston School in Dallas, Texas. Do learning disabled children manifest depressive illness and is affective illness manifested by their families? Would children diagnosed as having affective illness still have school-related behavior problems while attending a school designed for children and young adolescents with developmental specific learning disabilities? Do children at Winston School manifest a cyclical behavioral disorder; if so, who are these children?

Winston School is a school for children, grades one through nine (chronological age six years, zero months through 14 years, 11 months), with developmental specific learning disabilities. The curriculum is designed to allow children to bypass the use of language and symbol skills which are developmentally delayed (Weinberg, 1975, 1979). Emphasis is on the acquisition and utilization of information through multimedia resources. The faculty is trained to pursue the child's learning and communicative assets. The student is not penalized for his/her limitations. There are no known inappropriate school stresses in this educational environment.

The mean physical growth, height, weight, and head circumference of the Winston School student population is at the 50th percentile for the general population and classic neurologic examination is normal in this group of developmental specific learning disorders. This student population is of normal intelligence, and the students are free of primary conduct problems or thought disturbance. Ninety-six percent manifest severe specific learning discrepancy with 80 percent having multiple severe specific learning discrepancies (Table 1).

Table 1 Percentage of New Winston School Students with Severe Learning Discrepancies as Defined by P.L. 94-142 (1975-1976 to 1978-1979)*

Number of Severe Discrepancy	n	%
No discrepancy	6	4
One discrepancy	27	16
Two discrepancies	46	28
Three discrepancies	36	22
Four discrepancies	25	15
Five discrepancies	16	10
Six discrepancies	6	4
Seven discrepancies	2	1
Total	164	100

Average number of discrepancies per student = 2.8

Symbol Language Skill Categories	n	Severe Discrepancies (%)
Oral Expression	106	65
Basic Reading Skills	98	60
Written Expression	97	60
Mathematical Calculation	53	33
Reading Comprehension	51	31
Listening Comprehension	37	23
Mathematical Reasoning	15	9

*1975-1976, n = 55; 1976-1977, n = 30; 1977-1978, n - 28; 1978-1979, n = 51.

A method of determining whether or not a child has a severe learning discrepancy has been provided through the New York Board of Regents–State Education Department, Office of Education of Children with Handicapping Conditions. The method was developed by the New York Child Service Demonstration Program, Title VI-G as a consideration for Public Law 94-142. The exact formula is: Chronologic age IQ/300 + .7 - 2.5 = Severe discrepancy level (in grade equivalents). This method provides a standard by which two percent of the population qualify as having a severe learning discrepancy between achievement and intellectual ability. A severe discrepancy exists when achievement "falls at or below 50 percent of an individual's expected achievement level when intellectural ability, age and previous educational experiences are considered" (Smith et al, 1977).

Using the seven criteria skills for specific learning disabilities as stated in PL 94-142, the performance of students at Winston School was analyzed for the following symbol language skills: (1) basic reading skills; (2) reading comprehension; (3) listening comprehension; (4) oral expression; (5) written expression; (6) mathematical calculations; and (7) mathematical reasoning. The categories of symbol language skills in which most Winston School students

had severe learning discrepancies were in oral expression, basic reading skills, and written expression--60 to 65 percent of Winston School students. The next grouping was mathematical calculations (33 percent) and reading comprehension (31 percent). This was followed by listening comprehension (23 percent) and mathematical reasoning (9 percent) (Table 1).

During and at the end of each school year, the headmaster and medical director of Winston School review each individual student with respect to behavior problems. The students are coded one of three ways for behavior problems observed during the time of the review: (1) clinically significant problem: a problem that persists for more than ten days. It may be persistent or recurrent through the school year. The problem is disruptive to classmates and teachers and limits the student's participation in the Winston School educational process. The problem is reported to the student's parents and clinical management for the student is requested; (2) "mini" problem: this problem is less severe than the clinically significant problem in duration and intensity. Typically, the problem lasts for only a few days, but is of sufficient severity for school faculty to note, report, and record the problem. This problem level may also be recurrent during the school year. Clinical management is discussed with the parents but not directly requested; and (3) no problems.

All 167 students enrolled in Winston School for the first four years of operation are included in this analysis. In addition to the above coding, all students at the initial clinical visit and before entrance into Winston School are clinically diagnosed using the following groupings: (1) no problem; (2) hyperactivity but no depression; (3) hyperactivity and depression; (4) depression; and (5) "mini" depressive syndrome. Children and adolescents with primary conduct disorder, thought disturbance, autism, and subnormal intelligence are not acceptable for admission to Winston School.

Tables 2 and 3 show the frequency and percentage of total Winston School student populations per year and new Winston School students per year in relationship to pre-entrance behavior diagnostic category. As noted in Table 2, the total Winston School student population for the year 1978-1979, 40 percent of the children manifest depression and 21 percent have depression plus hyperactivity. Table 4 shows the percentage per year of new Winston School students with a family history of affective illness. The percentage ranges from 68.6 to 95.8 percent per year of new Winston School students having a strongly positive family history for affective illness.

Data presented in Table 5 indicates that the percentage of students having no problem during the school year increases over a four-year prospection. It shows that the four-year population starts with a high level of problems and decreases over time, but problem periods of a cyclical nature continue.

The next question to answer is whether or not it is the same children who have behavior problems over time. Table 6 displays the frequency of problems

Table 2 Frequency Distribution for Total Winston School Populations by Behavior Diagnosis at Entrance

	1975-1976		1976-1977		1977-1978		1978-1979	
Diagnosis	n	%	n	%	n	%	n	%
No problem	10	18	16	22	18	21	19	16
Hyperactivity but No Depression	9	16	11	15	12	14	19	16
Hyperactivity and Depression	13	24	15	20	18	21	26	21
Depression	17	31	25	34	31	36	49	40
"Mini" Depressive Syndrome	7	11	6	08	7	08	9	07
Total	55	100	73	100	86	100	122	100

Table 3 Frequency Distributions and Percentages for New Winston School Students per Year by Behavior Diagnosis at Entrance

	1975-1976		1976-1977		1977-1978		1978-1979	
Diagnosis	n	%	n	%	n	%	n	%
No problem	10	18	8	27	3	11	5	09
Hyperactivity but No Depression	9	16	4	13	3	11	8	15
Hyperactivity and Depression	13	24	7	23	8	28	11	20
Depression	17	31	11	37	12	43	28	52
"Mini" Depressive Syndrome	6	11	0	0	2	07	2	04
Total	55	100	30	100	28	100	54	100

for the four-year population. Only 40 percent have no behavior problems over the four years. No students had only one problem period. The mean number of problem periods for this group is 2.7 over an eight-period time interval. It is evident there are no constant behavior problem students. There are some (seven of 25) with frequent (three to six) problem periods; and eight of 25 have two problem periods over four years. Most of the problems are manifested by the same students but most of the students are manifesting recurrent problems. Table 7 demonstrates two three-year prospections. The results show 1.5 and 1.4 problem periods per three-year follow-up, but with the addition of the fourth year (Table 6), the mean problem period increases to 2.7. Again, a cyclical or recurrent behavior disorder is suggested.

Table 4 Percentage of New Winston Students with a Family History of Depression, Mania, and/or Manic-Depressive Illness (Family History at Entrance)

	1975-1976 (n = 55; 4 adopted)		1976-1977 (n = 30; 4 adopted)		1977-1978 (n = 28; 4 adopted)		1978-1979 (n = 54; 4 adopted)	
Percent								
100								
95					95.8%			
90								
85			88.5%					
80							80%	
75								
70	68.6%							
65								
60								
55								
50								
45								
40								
35								
30		31.4%						
25								
20								20%
15								
10				11.5%		4.2%		
5								
0								
	n = 35	n = 16	n = 23	n = 3	n = 23	n = 1	n = 40	n = 10
	No affective illness				Affective illness			

The depression groups have increased in number and percentage whereas the most difficult problem groups, depression with hyperactivity, have demonstrated a mild decline in numbers by diagnosis before entering Winston School (Tables 2 and 3).

The next area to be addressed is the relationship of clinical diagnosis before entering Winston School to the occurrence of behavior problems during enrollment at Winston School. Table 8 through 12 display the data by each diagnosis. The children with both depression and hyperactivity present the greatest problem at Winston School. The next most problem-prone group is children with depression, followed by children with only hyperactivity. Very few children with a clinical diagnosis of no problem manifest problems while at Winston School.

Does the frequency and recurrence of behavior problems relate to the clinical diagnosis established before entrance to Winston School? Table 13

Table 5 Percentage of Winston School Students Over Time Having Behavior Problems at Winston School (Four-Year Prospection)

	1975-1976				1976-1977			
	During		End		During		End	
	%	n	%	n	%	n	%	n
CS	28.0	7	0.0	0	16.0	4	4.0	1
MP	24.0	6	4.0	1	24.0	6	12.0	3
NP	48.0	12	96.0	24	60.0	15	84.0	21
Total	100.0	25	100.0	25	100.0	25	100.0	25
	1977-1978				1978-1979			
	During		End		During		End	
	%	n	%	n	%	n	%	n
CS	20.0	5	4.0	1	4.0	1	4.0	1
MP	12.0	3	8.0	2	28.0	7	4.0	1
NP	68.0	17	88.0	22	68.0	17	92.0	23
Total	100.0	25	100.0	25	100.0	25	100.0	25

CS = clinically significant problem; MP = "mini" problem; NP = no problem.

Table 6 Frequency of Behavior Problems for Winston School's Four-Year Population (Four-Year Prospective Study: n = 25)

	n	Total Number of Problems
No problem	10	0
One problem period	0	0
Two problem periods	8	8 × 2 = 16
Three problem periods	1	1 × 3 = 16
Four problem periods	2	2 × 4 = 8
Five problem periods	2	2 × 5 = 10
Six problem periods	2	2 × 6 = 12
Seven problem periods	0	0
Eight problem periods	0	0
Total	25	52

Average number of problem periods = 2.7.

Table 7 Frequency of Behavior Problems for Winston School's Two Three-Year Populations (Two Three-Year Prospective Studies

	1976-1977–1978-1979 (Not here in 1975-1976) n	1976-1977–1978-1979 (Here in 1975-1976) n
No problem periods	8	10
On problem period	5	6
Two problem periods	2	3
Three problem periods	4	2
Four problem periods	0	3
Five problem periods	2	1
Six problem periods	0	0
Total	21	25
Average number of problem periods	1.5	1.4

Table 8 Percentage of Students with a Clinical Diagnosis of No Problem Having Behavior Problems at Winston Schools

Category of Problem	During School %	n	End of School %	n
		1975-1976		
Clinically significant	20.0	2	0.0	0
"Mini" problem	10.0	1	0.0	0
No problem	70.0	7	100.0	10
Total	100.0	10	100.0	10
		1976-1977		
Clinically significant	12.5	2	6.2	1
"Mini" problem	18.7	3	0.0	0
No problem	68.8	11	93.8	15
Total	100.0	16	100.0	16
		1977-1978		
Clinically significant	0.0	0	0.0	0
"Mini" problem	5.6	1	5.6	1
No problem	94.4	17	94.4	17
Total	100.0	18	100.0	18
		1978-1979		
Clinically significant	0.0	0	0.0	0
"Mini" problem	5.3	1	0.0	0
No problem	94.7	18	100.0	19
Total	100.0	19	100.0	19

Table 9 Percentage of Students with a Clinical Diagnosis of Hyperactivity (But No Depression) Having Behavior Problems at Winston Schools

	During School		End of School	
Category of Problem	%	n	%	n
		1975-1976		
Clinically significant	33.3	3	11.1	1
"Mini" problem	22.2	2	11.1	1
No problem	44.5	4	77.8	7
Total	100.0	9	100.0	9
		1976-1977		
Clinically significant	9.1	1	0.0	0
"Mini" problem	9.1	1	0.0	0
No problem	81.8	9	100.0	11
Total	100.0	11	100.0	11
		1977-1978		
Clinically significant	41.7	5	0.0	0
"Mini" problem	8.3	1	8.3	1
No problem	50.0	6	91.7	11
Total	100.0	12	100.0	12
		1978-1979		
Clinically significant	10.5	2	5.3	1
"Mini" problem	21.1	4	10.5	2
No problem	68.4	13	84.2	16
Total	100.0	19	100.0	19

displays the frequency and average number of problem periods by diagnosis during school years 1976-1977, 1977-1978, and 1978-1979 (three-year prospective study, n = 46). Students with the clinical diagnosis of hyperactivity *and* depression manifest the greatest number of problem periods (2.7), followed by children with only depression (1.4) before entrance into Winston School, and then by hyperactive children (1.1). The frequency for Winston School students with the diagnosis of no problem manifesting problem periods was minimal (0.6).

These findings support a relationship between clinical diagnosis before entering Winston School and manifestation of behavior problems during attendance at Winston School. The majority of the students fulfill criteria for a positive clinical behavior diagnosis of affective illness (depression) before entering Winston School. The family history of these children is strongly positive for the same condition. Winston School students manifesting no clinical behavior

Table 10 Percentage of Students with a Clinical Diagnosis of Hyperactivity and Depression) Having Behavior Problems at Winston Schools

Category of Problem	During School %	During School n	End of School %	End of School n
		1975-1976		
Clinically significant	76.9	10	23.1	3
"Mini" problem	15.4	2	15.4	2
No problem	7.7	1	61.5	8
Total	100.0	13	100.0	13
		1976-1977		
Clinically significant	40.0	6	6.7	1
"Mini" problem	33.3	5	20.0	3
No problem	26.7	4	73.3	11
Total	100.0	15	100.0	15
		1977-1978		
Clinically significant	55.6	10	16.7	3
"Mini" problem	11.1	2	5.5	1
No problem	33.3	6	77.8	14
Total	100.0	18	100.0	18
		1978-1979		
Clinically significant	30.8	8	7.7	2
"Mini" problem	34.6	9	23.1	6
No problem	34.6	9	69.2	18
Total	100.0	26	100.0	26

problem before entering Winston School continue free of behavior problems during their stay. Students fulfilling the criteria for both depression and hyperactivity have a prominent likelihood of manifesting behavior problems at Winston School; these problems are often recurrent over time. This observation strongly suggests a cyclical nature for the manifest clinical problem. Students with only depression or hyperactivity also seem to manifest cyclical problems but with less likelihood of occurrence. For the child who is hyperactive only, there are seemingly fewer problem periods.

The behavior of the general student population at Winston School seems to improve over time (Tables 8-12). It is difficult to define the variables that account for the improvement in the behavior of the students. It is noteworthy that the number of depressed students who are admitted has increased. There is a slight reduction in the number of students admitted who are both hyperactive

Table 11 Percentage of Students with a Clinical Diagnosis of Depression Having Behavior Problems at Winston Schools

	During School		End of School	
Category of Problem	%	n	%	n
		1975-1976		
Clinically significant	29.4	5	0.0	0
"Mini" problem	23.5	4	0.0	0
No problem	47.1	8	100.0	17
Total	100.0	17	100.0	17
		1976-1977		
Clinically significant	16.0	4	0.0	0
"Mini" problem	20.0	5	8.0	2
No problem	64.0	16	92.0	23
Total	100.0	25	100.0	25
		1977-1978		
Clinically significant	29.0	9	12.9	4
"Mini" problem	9.7	3	16.1	5
No problem	61.3	19	71.0	22
Total	100.0	31	100.0	31
		1978-1979		
Clinically significant	14.3	7	6.1	3
"Mini" problem	18.4	9	4.1	2
No problem	67.3	33	89.8	44
Total	100.0	49	100.0	49

and depressed (Tables 2 and 3). It is possible that depression without hyperactivity is less characterized by agitation, irritability, and "acting out" behaviors when compared to depression plus hyperactivity, a predicted antecedent of manic depressive illness. It is also possible that depression in some children is "reactive" or "masked" and not manifested in this education setting relatively "free" of certain stresses.

TREATMENT

Diagnosis of an affective disorder is requisite to initiating appropriate treatment. Empirically, the natural history by retrospective study is similar to that of adults. The average length of a depressive cycle persists from six to 18 months

Table 12 Percentage of Students with a Clinical Diagnosis of "Mini" Depressive Syndrome Having Behavior Problems at Winston Schools

Category of Problem	During School %	During School n	End of School %	End of School n
		1975-1976		
Clinically significant	0.0	0	0.0	0
"Mini" problem	33.3	2	0.0	0
No problem	66.7	4	100.0	6
Total	100.0	6	100.0	6
		1976-1977		
Clinically significant	33.3	2	0.0	0
"Mini" problem	0.0	0	0.0	0
No problem	66.7	4	100.0	6
Total	100.0	6	100.0	6
		1977-1978		
Clinically significant	28.6	2	14.3	1
"Mini" problem	0.0	0	0.0	0
No problem	71.4	5	85.7	6
Total	100.0	7	100.0	7
		1978-1979		
Clinically significant	22.2	2	0.0	0
"Mini" problem	0.0	0	0.0	0
No problem	77.8	7	100.0	9
Total	100.0	9	100.0	9

without drug management. Probably less than half of depressive episodes last longer than one year and, by history, some children have been and remain depressed for several years, if not longer.

Thereapy can involve alteration of the enviornment; offering protection and avoidance of inappropriate stresses (Brumback and Weinberg, 1977a; Krueger, 1979; Pearce, 1977); psychotherapy; and medical (drug) therapy. By educating the family to understand the nature of the child's depression, tension over the child's behavior can be reduced. A depressed child should neither be rejected nor punished but should receive increased affection, understanding, protection, supervision, and reassurance. That an exasperating child should receive extra understanding is probably the hardest concept for a family to accept. Teachers must try to reward the depressed child for his successes and not stress his difficulties. He should be allowed to stay in his regular classroom

Table 13 Frequency of Behavior Problems by Clinical Diagnosis for Winston School Years 1976-1977, 1977-1978, and 1978-1979 (Three-Year Prospective Study: n = 46)

	Clinical Diagnosis				
Problem Periods	Total	Problem	Hyperactivity Only	Depression Only	Hyperactivity and Depression
No problem periods	18	8	3	7	0
One problem period	11	1	2	6	2
Two problem periods	5	1	0	2	2
Three problem periods	6	0	2	1	3
Four problem periods	3	1	0	1	1
Five problem periods	3	0	0	2	1
Six problem periods	0	0	0	0	0
Total	46	11	7	19	9
Average number of problem periods	1.4	.6	1.1	1.4	2.7

pursuing his assets and avoiding social peer group isolation and unproven remedial, tutorial programs. Social workers, counselors, psychiatrists, and other physicians must be supportive of the depressed child. Medical therapy generally should avoid hospitalization, except occasionally for protection and for initiation of drug therapy. Hospitalization can result in isolation, emotional deprivation, and be viewed by the child as further punishment and rejection.

Proper management involves treatment, support, reassurance, protection, avoidance of confrontations, and supervision by parents, teachers, and friends, both at home and at school. Specific school curriculum should emphasize the developmental "bypass" strategies for success in classroom tasks (Weinberg, 1975, 1979). The children are encouraged to pursue their socially acceptable assets, skills, and interests. The children are reassured that they will recover and that parents, friends, teachers and physicians will offer the needed support through the recovery period. Since judgement is poor during a period of depression, supervision and protection while pursuing assets in the usual living environments are important. Punishment, often tried by parents and teachers in the past, is not successful and can be prevented through appropriate attitudes and proper environmental planning by parents and teachers.

Drug management for the treatment of depression in children remains controversial, as does the understanding that depression as a primary illness occurs in children. Medication, appropriately prescribed, can be very useful. Stimulants, frequently tried in "hyperactive" children and occasionally used as part of the treatment of adult depression, such as methylphenidate and

dextroamphetamine, have the advantage of an immediate positive effect in reducing the depression. However, the disadvantage of stimulants is that their effect is of relatively short duration and tolerance develops, requiring larger doses with less effectiveness (Beck, 1973; Freedman et al, 1975). In children, one positive effect of stimulants is to reduce hyperactivity; however, stimulants worsen the depressive symptoms of agitation, irritability, crying spells, insomnia, and poor appetite. The major tranquilizers (phenothiazines) reduce agitation and anxiety but have little effect on other aspects of the depression.

The best and most specific medications for depression at the present time are the tricyclic drugs of which imipramine and amitriptyline are the prototypes (Freedman et al, 1975; Rapoport, 1976). These drugs alleviate depressive symptoms in over 90 percent of children (Brumback and Weinberg, 1977a; Frommer, 1968; Ossofsky, 1974; Puig-Antich et al, 1975; Weinberg et al, 1973).

The tricyclic antidepressant medications have not been approved by the United States Food and Drug Administration (FDA) for use in children under 12 years of age, except for imipramine in enuresis. Yet, several empirical studies and observations (Brumback et al, 1977; Brumback and Weinberg, 1977c; DeLong, 1978; Frommer, 1968; Kuhn and Kuhn, 1972; Puig-Antich et al, 1978; Weinberg et al, 1973) have demonstrated significant benefit. Clinically, it has been observed that the tricyclic group of drugs is both safe and beneficial in the lifting of the child's depression and often in preventing further cycles.

This group of drugs is beneficial in alleviating dysphoric mood, self-deprecation, somatic complaints, sleep disturbances, and restoring energy and interest. Decreased aggressiveness follows later. In some children coincident administration of a major tranquilizer may reduce the aggressiveness and agitation more rapidly. Improvement is noted in three to 14 days as therapeutic dosage is achieved. A phenothiazine or haloperidol is sometimes needed for control of the irritability and agitation and for complete stabilization of mood.

The dosage range for the tricyclic antidepressant medications in children remains empirical. Generally, benefit is noted when dosage is 1 to 3 mg/kg per day and not exceeding 150 mg per day in the heavier, older adolescent. The FDA has recommended for experimental and research purposes not to exceed 5 mg/kg of body weight for 24-hour periods (Hayes et al, 1975). The FDA has also advised baseline and serial electrocardiograms when dosage approaches 5 mg/kg per day in order to prevent cardiac arrhythmias and cardiac conductive problems that are known to occur with high doses and overdosage of the tricyclics (Hayes et al, 1975; Martin and Zaug, 1975; Petit and Biggs, 1977; Winsberg et al, 1975).

The most commonly used tricyclics, amitriptyline, followed by imipramine and the desipramine, is offered on a trial-and-error basis as follows: (1) Two to five years of age: 20 to 50 mg per day with two-thirds to three-quarters of the total dose given at bedtime; (2) six to 11 years of age: 50 to 100 mg per day

with two-thirds to three-quarters of the total dose given at bedtime; and (3) 12 to 15 years of age (depending upon physical maturity and size: 50 to 150 mg per day with two-thirds to three-quarters of the total dose given at bedtime.

A trial dose of a small amount of tricyclic, for example 20 to 50 mg at bedtime depending upon age and size, is given during the first week with maximum dosage as stated above achieved within two to three weeks after the start of medication.

Dosage schedule for the commonly used phenothiazines, thioridazine or chlorpromazine, is 30 to 60 mg in three to four divided doses per day in the three- to six-year-old child. For older school age children and young adolescents the usual dosage is 50 to 150 mg per day in three to four divided doses. Haloperidol dosage ranges between 1 and 4 mg per day in three to four divided doses. Haloperidol is used if a phenothiazine is not successful in controlling the manic component or agitation.

Maximum dosage for a tricyclic (for example, imipramine) should be achieved within two to three weeks with improvement above the 50 percent level noted shortly thereafter with or without the addition of a phenothiazine. If improvement does not occur, a trial on the second tricyclic (for example, amitriptyline) is then offered using a similar schedule with the same expectations. If this is not successful within another two to four weeks, then desipramine or nortriptyline is offered. It is recommended that amitriptyline should be tried first, followed by imipramine, then desipramine, and finally nortriptyline. Of course, time is passing and depression in most possibly lifts without specific management in six to 18 months. In choosing a tricyclic to offer, it is helpful if another family member has been successfully managed with tricyclic drugs. It is statistically predictable, though not always clinically, that family members respond favorably to the same tricyclic (Baldessarini, 1975; Bielski and Friedel, 1976).

Fifty percent improvmeent is defined as the child is able to participate in his usual environments but still manifests symptoms of depression as observed by either or both parents, teachers, and friends. Sixty to 70 percent improvement is defined as when the child's performance is approaching his usual non-depressed self, functioning satisfactorily in his usual endeavors but still having "too many moments" of the depressive symptomatology. Eighty percent improvement is defined as complete restoration of the child to his usual pre-depressed state. By direct interview, though, the recovered child may continue to have depressed feelings, but they are "not too much" by the child's own estimation. A responder to a given tricyclic antidepressant medication with or without a phenothiazine should achieve an 80 percent level of improvement in one to three months.

Telephone calls from the parent at three to ten-day intervals during the initial treatment period are helpful to allow knowledge of response, change in

dosage or medication, and observation for adverse effects. It is the experience of the author that serious side effects are rare for the dosage listed above. A rash in one patient and hypertension in a second have been noted in a large cohort of tricyclic-treated children and young adolescents. Constipation, hesitancy and difficulty in voiding, dizziness suggesting orthostatic hypotension, and uncomfortable dry mouth are likewise rare in children and young adolescents. Acceptable adverse effects are a mild intentional tremor and a mild tachcardia.

Worsening behavior occurs with tricyclics in specific or general drug nonresponders. Increased dysphoria, agitation, and/or sedation are evident within several days. Also, tricyclics can worsen or trigger an episode of mania suggesting a bipolar illness, manic depressive disease.

Dyskinesias have not been noted in children and young adolescents with the above schedule of phenothiazines. Undue sedation, worsening of behavior, and even promotion of manic-like behavior have been observed in depressed children on phenothiazines. Rashes are uncommon (rare) as a hepatic toxicity.

Severe dyskinesia, as an idiosyncratic reaction, can occur within one to five days after beginning haloperidol. This reaction is an emergency and is alleviated with intravenous diphenhydramine, 25 to 50 mg.

Until the medication is discontinued, a depressed child is seen at monthly intervals for office examination with emphasis on the affective symptomatology and physical examination. Since depression is a recurrent illness, routine visits at six to 12-month intervals after full recovery are advised.

The beneficial drug regimen is continued until the child has been asymptomatic for a period of three to six months. The child is then weaned from the medication over a period of one to three months. There is a subgroup of depressed children who seemingly remain asymptomatic only if a maintenance dose of tricyclic is continued at bedtime for an indefinite period of time.

Treatment of the rarer manic syndrome often requires hospitalization for protection, supervision, and family relief. Youngerman and Canino (1978) have reviewed the literature on the use of lithium carbonate in treating mania in children and adolescents. Recent reports (Brumback and Weinberg, 1977c; DeLong, 1978; Frommer, 1968; Weinberg and Brumback, 1976; White and O'Shanick, 1977a) have suggested the benefit of lithium carbonate, but it has not been approved by the FDA for use in children under 12 years of age. Control of the mania with lithium is sometimes followed by a depressive cycle and the addition of a tricyclic antidepressant medication is helpful in that group of manic children, again suggesting a bipolar illness.

Phenothiazines and haloperidol, in the dosage schedule described above, are other drugs clinically beneficial in the control of manic behavior in some children. At this point in time, though, there remains an absence of controlled studies in the treatment and course of mania in children.

NEEDS FOR FUTURE STUDY

Further replication and refinement of the research cited in this chapter is essential to validate the diagnostic criteria for primary affective illness(es) in children.

Pursuit of physiological and biochemical correlates of primary affective illness should be encouraged. Epidemiological studies should be conducted in populations of school children to determine the percent variance of school problems that are represented by primary affective illness. Studies relating to the controversy of genetics versus environment need major emphasis in defining both its cause, natural course, and beneficial treatment. It is possible that developmental specific learning disorders are a genetic marker of affective illness and/or an epiphenomenon of "school problems." Longitudinal studies are needed to determine the natural history of the illness, its incidence, and prevalence.

Investigation of the response of this criteria-specific illness to antidepressant medication and other methods of treatment is urgently indicated. More specific differentiation of subgroups of children with primary and/or secondary depression, manic depressive illness, and hyperactivity might be possible thus allowing the most successful method for prevention and treatment to become known and implemented.

SUMMARY

Diagnosis and treatment of affective illness, possibly primary, in children has been reviewed in this chapter. Criteria for the diagnosis of this condition in children has been presented. This criteria, based upon the adult criteria with select modification, has been utilized in diagnosing affective illness in children and young adolescents referred to educational diagnostic centers because of school-related learning or behavior problems.

School skills of children with affective illness do not differ from other children in the referred population. Evaluation of intelligence and learning disabilities indicates no difference between groups with or without depression. It is evident that school behavior problems result, at least in part, from a cyclical behavior disturbance, possibly as a manifestation of primary affective illness.

Proper management of the child's environment and specific drug treatment are recommended. Results from a prospective study of children with developmental specific learning disorders attending school in an ideal environment indicate that, in a large subgroup, affective illness occurs and seems to be recurrent. Most at risk are children who manifest both hyperactivity and depression.

Clinically, hyperactive children whose behaviors, mood, and feelings are worsened by stimulant medication are probably only significantly hyperactive when depressed. This may be an antecedent of "bipolar" manic depressive disease. It may be that some children fulfilling the critiera for depression are depressed secondary to inappropriate schooling, or that appropriate schooling is "masking" their depression.

Affective illness, possibly primary, is a common cause of school-related behavior problems in children. The majority of children manifesting the disturbed behavior characteristic of affective illness are infrequently recognized and offered beneficial treatment. They are shunned by schools, families, and friends, often receiving inadequate education as social outcasts (Poznanski et al, 1976). From this group of chronically rejected, depressed children probably emerge the individuals who, during a further depressive (or manic) episode as young adults, are involved in self-destructive and antisocial acts. Early detection and appropriate treatment of children with affective illness will hopefully prevent their school and personal failure, social withdrawal, antisocial activity, and suicide (Brumback and Weinberg, 1977a, b).

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AFFECTIVE DISORDERS IN CHILDHOOD AND ADOLESCENCE

An Update

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SP MEDICAL & SCIENTIFIC BOOKS
a division of Spectrum Publications, Inc.
New York

To Susan

Suzi, Denny, Coleen, Erin, and Marianne

To Harold

Gregory and Jonathan

and

To Mr. and Mrs. Frederick W. Davis

SPECTRUM PUBLICATIONS, INC.
175-20 Wexford Terrace
Jamaica, NY 11432

Library of Congress Cataloging in Publication Data
Main entry under title:

Affective disorders in childhood and adolescence.
(Child Behavior and Development)
Bibliography: p.
Includes index.
1. Depression in children. 2. Affective disorders in children. 3. Adolescent psychopathology.
I. Cantwell, Dennis P. II. Carlson, Gabrielle A.
III. Series. [DNLM: 1. Affective disorders–In adolescence. 2. Affective disorders–In infancy and childhood.
W1 CH644M / WM 171 A25595]
RJ506.D4A38 1983 618.92'89 83-13672
ISBN 0-89335-189-X

Printed in the United States of America

Reliability, Validity, and Parent-Child Agreement Studies of the Diagnostic Interview for Children and Adolescents (DICA)

ZILA WELNER, M.D., WENDY REICH, PH.D., BARBARA HERJANIC, M.D., KENNETH G. JUNG, M.A., AND HENRY AMADO, M.D.

Abstract. The Diagnostic Interview for Children and Adolescents (DICA) is a structured interview for school-age children, patterned after the National Institute of Mental Health Diagnostic Interview Schedule (DIS) and based on the DSM-III criteria. An inter-interview reliability study of the child version (DICA-C) was determined by interviewing 27 psychiatric inpatients, 7 to 17 years of age. Using the kappa statistic for multiple major diagnostic categories, the results demonstrated high reliability. A comparison of the DICA-C diagnoses with the hospital discharge diagnoses for validation of the DICA-C showed that in 81.5% of the cases, the clinicians were in agreement with the DICA-C diagnoses. The DICA-C resulted in more diagnoses per child compared with the hospital discharge diagnoses. The results are discussed in view of the different methods of evaluation. Parent-child agreement based on the DICA-C and DICA-P interview in 84 outpatients, 7 to 17 years of age, and their mothers showed a good to moderate agreement in most DSM-III diagnostic categories. Taken together, these data suggest that the DICA-C is a reliable and valid instrument for either clinical or research purposes. *J. Amer. Acad. Child Adol. Psychiat.*, 1987, 26, 5:649–653. **Key Words:** psychopathology, interview, reliability, validity.

Structured and semistructured interviews for psychiatric assessment in clinical research are currently very popular both in child and adult psychiatry. The Diagnostic Interview for Children and Adolescents (DICA), for example, has been widely used in clinical research. Until recently, most of the published data on the reliability and validity of structured and semistructured interviews has involved studies with adults (Helzer et al., 1977; Helzer et al. 1981; Helzer, 1983; Robins et al., 1981). Only a few published studies for reliability and validity of the structured interview have been carried out with preadolescent and adolescent subjects (Chambers et al., 1985; Reich et al., 1982).

The following is a report on the reliability and validity of the DICA, using three different approaches: an inter-interview design, a comparison of the DICA interview diagnoses with the hospital chart discharge diagnoses, and a study of parent-child agreement.

The assumption that the clinician is the best yardstick for diagnoses can be easily challenged (Robins, 1985). However, it is not unreasonable to use the clinician as one source of information. The hospital discharge diagnoses that were used in this study to test the validity of the DICA-C diagnoses consisted of information that was gathered from different sources, including the child, his or her parents, the school, the hospital staff, and the attending child psychiatrist's clinical observation and clinical judgment. The chart discharge diagnoses were not based on a one-time clinical assessment but on a more comprehensive assessment during the period of the child's hospitalization in the psychiatric unit, and they were, therefore, considered an appropriate yardstick for testing the validity of the DICA-C diagnoses.

Previous studies of the DICA (Reich et al., 1982) have shown good agreement between mother-child pairs of some commonly used diagnoses as well as a number of individual symptoms. Some diagnoses and symptoms, however, were reported significantly more frequently by the mother, and others significantly more frequently by the child. This suggests that there are some areas in which parents are better reporters, and other areas in which the child is a better reporter about him or herself. Traditionally, the mother has been considered as the best source of information about the child; thus, a good mother-child agreement is accepted as a reassurance of the validity of the child interview. With the increasing use of the DICA and the resulting accumulation of data, it seems that the assumption that the parent is the best informant is not always correct. In this study, mother-child agreement will be analyzed again with the 1981 revised DICA, in order to have a better understanding of the areas in which children and their parents tend to agree or disagree.

It seems reasonable to assume that obtaining good results from all these tests would support the reliability and validity of the interview.

Method

Description of the Instrument

The DICA is a fully structured interview that was developed at Washington University in St. Louis, mainly for clinical and epidemiological research. The first version of the DICA came out in 1969, and was patterned after the Renard Diagnostic Interview (RDI) described by Helzer et al. (1981). The diagnoses in the DICA were originally based on the International Classification of Psychiatric Disorders in combination with the Feighner et al. (1972) criteria. A revised version of the DICA, patterned after the National Institute of Mental Health Diagnostic Interview Schedule (DIS) and based upon the DSM-III criteria, was developed in 1981. The DICA includes two separate interviews: DICA-C, a child interview, and DICA-P, a corresponding parent interview. The parent interview is a replica of the child interview in parent terminology. That is, the parent is questioned about the child. Each interview is divided according to 18 of the DSM-III diagnostic categories. Essentially, one or more questions has been designed to fulfill each symptom for each disorder, and a method of determining current and past symptomatology, as well as severity, is included in some diagnostic categories. Each diagnostic section is followed by instructions that list the specific DSM-III criteria for arriving at diagnoses in that section. The

Received Mar. 19, 1986; revised Feb. 2, 1987; accepted May 4, 1987.

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DICA-P also includes information about developmental and medical history.

Study Design

The study consisted of three different parts. The first part has an inter-interview reliability study of the DICA-C. The other two parts of the study were designed in order to test the validity of the child interview diagnoses. One approach consisted of a comparison of the DICA-C interview diagnoses with the hospital chart discharge diagnoses, and the other approach consisted of a parent-child agreement study.

The inter-interview study was conducted with psychiatric inpatients between ages 7 and 17. Informed consent was obtained from both parents and children. Twenty-seven consecutive children and their parents agreed to participate in the study. The only exclusion criteria was low intelligence as indicated by the admission history. Each child was interviewed by two different interviewers. The first interview was administered within 48 hours of admission, and the second took place within an interval of 1 to 7 days after the first interview. The interviews were administered by four lay interviewers (university students) who were trained by one of the developers of the DICA (B. H.). The training consisted of viewing and coding of child and parent videotaped interviews, practice interviews, and detailed checking of each practice interview. All the interviews administered for the inter-interview study were checked and edited by one of the developers of the DICA (B. H. and W. R.)

In the second phase of the study, 27 of the first DICA-C interview diagnoses were compared with the hospital chart diagnoses. The chart reviewers were blind to the diagnoses of the research interviews, and the physicians who made the chart diagnoses were blind to the research diagnoses. When comparing the DICA-C diagnoses to the hospital chart diagnoses, we used the discharge summary diagnoses that were dictated by the patient's psychiatrist at the end of the hospitalization.

The mother-child agreement study was carried out in the outpatient child psychiatry clinic at St. Louis Children's Hospital. Eighty-four consecutive patients and their mothers participated in the study. Forty-five subjects were being seen for evaluation or treatment, and 39 were former patients who came for a follow-up visit. After the informed consent was obtained from the mother and the child, they were both interviewed at the same time, but in separate rooms by different interviewers. The child was interviewed with the DICA-C and the mother was interviewed with the DICA-P.

Nine interviewers participated in this study: two child psychiatrists (B. H. and H. A.), an anthropologist (W. R.), and six lay interviewers (two medical students and four undergraduate university students). All the interviewers received training for the administration of the DICA as described above. The coding on all interviews was checked carefully by the two psychiatrists, and diagnoses were made using the coding guide prepared in the interview according to DSM-III criteria.

Results

Demographic variables are presented in Table 1. The mean age of the children was 12.4. Approximately half of the children were prepubertal, with more girls than boys. Based on information obtained from the first DICA-C interview, the 27 patients received a total number of 96 diagnoses. The number of diagnoses per child ranged from zero (no psychiatric diagnosis) to seven, with an average of 3.6 diagnoses. Two children received "no psychiatric disorder" and two other children received "undiagnosed psychiatric disorder." The total number of diagnoses obtained from the second DICA-C interview was 62 and ranged from zero to five with an average of 2.3 diagnoses per child. These findings are similar to the findings in the adult test-retest study by Helzer et al. (1977). The disorders that were typically missed in the second interview included overanxious disorder, separation anxiety disorder, and oppositional disorder. One can speculate that when the children adjusted to the unit and their general anxiety decreased, they reported fewer anxiety symptoms and less oppositional behavior. The frequency of the different diagnostic categories and the inter-interviews agreement of the different diagnostic categories are shown in Table 2. In general, we found an excellent inter-interview agreement. The highest agreement was achieved in the categories of attention deficit disorder, conduct disorder, and affective disorder. The lowest agreement was found in the anxiety disorders, $\kappa = 0.76$, which is still considered to be in the range of a good agreement.

TABLE 1. *Demographic Variables of Interviewed Inpatients*

Variable	Subjects	
	$N = 17$	%
Sex		
Female	17	63
Male	10	37
Race		
White	21	78
Nonwhite	5	19
Biracial	1	3
Age*		
7–12	13	48
13–17	14	52

* Mean age, 12.44; S.D., 2.95.

The second part of the study included a comparison of DICA-C first interviews with the hospital discharge diagnoses. The discharge diagnoses of 27 children were compared with the diagnoses arrived from the first DICA-C.

The total number of discharge diagnoses was 37, ranging from one to three per child with an average of 1.4 diagnoses.

The DICA-C interview reports a greater number of diagnoses per child than does the clinician in the discharge diagnoses. There are a number of reasons why this could be so. For one thing, the DICA reports all the diagnoses reported by the child and does not put them in any kind of hierarchy, whereas the clinician tends to have a hierarchy when arriving at diagnoses. For example, the chart diagnoses rarely included any of the anxiety disorders in the presence of major depression, whereas in the DICA-C these two diagnoses were often present in the same child. The discharge chart diagnoses also did not include disorders that the child experienced before the present episode. The highest agreement was achieved in the diagnostic category of affective disorders, $\kappa = 0.52$. There

TABLE 2. *Diagnostic Frequencies and Inter-Interviews Agreement[a] Based on DICA-C Interview*

Diagnostic Category[b]	Frequency of Diagnosis in First Interview		Frequency of Diagnosis in Second Interview		Inter-Interviews Specific Diagnosis Agreement[c] (%)	κ
	N	%	N	%		
Affective disorder	8	(30)	7	(26)	96	0.90
Attention deficit disorder	11	(41)	11	(41)	100	1.00
Conduct disorder	8	(30)	8	(30)	100	1.00
Oppositional disorder	8	(30)	6	(22)	92	0.79
Separation anxiety disorder/ phobic disorder/overanxious disorder	10	(37)	9	(33)	90	0.76
Adjustment disorder	3	(11)	4	(15)	96	0.83

[a] $N = 27$.
[b] Diagnoses not mutually exclusive.
[c] Agreement on presence or absence of diagnosis.

TABLE 3. *Agreement Between the First DICA Interview and Discharge Summary Diagnoses[a]*

Diagnostic Category[b]	Frequency of Diagnosis in First Interview		Frequency of Diagnosis in Chart		Agreement Between First Interview and Chart Diagnosis (%)	κ
	N	%	N	%		
Affective disorder	8	(30)	7	(26)	82	0.52
Attention deficit disorder	11	(41)	5	(19)	78	0.50
Conduct disorder	8	(30)	6	(22)	78	0.43
Separation anxiety disorder/phobic disorder/overanxious disorder	10	(37)	2	(7)	69	0.03
Adjustment disorder	3	(11)	6	(22)	67	−0.18

[a] $N = 27$.
[b] Diagnoses not mutually exclusive.

TABLE 4. *Cases in Which There Was No Agreement Between DICA-C Diagnoses and Hospital Discharge Summary Diagnoses*

	DICA-C	Hospital Chart
Case 1	Undiagnosed	Adjustment disorder with mixed disturbance of emotions and conduct Parent-child problems
Case 2	Socialized nonaggressive conduct disorder Adjustment disorder with depressed mood	Atypical psychosis
Case 3	No psychiatric disorder	Conduct disorder
Case 4	No psychiatric disorder	Separation anxiety disorder Parent-child problem
Case 5	Undiagnosed	Bipolar disorder, manic

was very poor agreement in the diagnoses of anxiety disorder. $\kappa = 0.03$, with much higher rates of these diagnoses made by the DICA than by the clinician. On the other hand, clinicians more often gave the diagnosis of adjustment disorder, $\kappa = -0.18$. The DICA-C interview was not as sensitive to environmental stresses that correlated with psychiatric symptoms as was the clinician. A comparison of DICA-C and the hospital discharge diagnoses is presented in Table 3. In five patients (18.5%) there was no agreement between the DICA-C diagnoses and the hospital discharge diagnoses. Details of the differences in diagnoses are presented in Table 4. The most common reason for the lack of agreement between the DICA-C diagnoses and the chart diagnoses was that the child did not report enough symptoms during the first interview and, therefore, was placed in the category of undiagnosed psychiatric disorder, or no psychiatric disorder, whereas the clinician was able to arrive at a diagnosis after a period of observation on the unit. In one case the DICA-C diagnoses were socialized nonaggressive conduct disorder, and adjustment disorder with depressed mood, whereas the chart discharge diagnosis was atypical psychosis. We concluded that the larger number of diagnoses from the DICA-C was not simply caused by overreporting, but also because (1) the DICA has no hierarchical system for diagnoses, and (2) clinicians tend to attribute different symptoms to one diagnostic category. In addition, the discharge diagnoses did not include syndromes that occurred in the past, whereas the DICA-C included past and present disorders. In 22 of the 27 (81.5%) patients who participated in the study, there was agreement between the clinicians' diagnoses and the DICA-C first interview diagnoses. With the DICA-C interview, however, the children were given additional diagnoses that were not recognized by the clinicians.

Mother-Child Agreement

Agreement on diagnoses between 84 child and parent interviews was compared using the kappa statistic, which measures positive agreement that exceeds chance. Diagnoses were compared in each category in which there were 10 or more subjects. Diagnoses were either definite, meaning all the DSM-III criteria were met, or probable, meaning one symptom was lacking or the duration was uncertain. Definite and probable diagnoses were counted as concordance; however, the majority of diagnoses were definite. Uncertainties about duration were found more frequently on the child interviews. For example, a child who met criteria for depression was counted as probable depression, even though he or she was uncertain as to its duration.

The agreement on the five DSM-III diagnoses for which there were 10 or more subjects is shown in Table 5. Compared with the previous study of 307 mother and child pairs (Reich et al., 1982), which were diagnosed using the prior version of the DICA, these results show much better agreement. The prior study diagnosed conduct disorder and antisocial personality separately, the latter indicating more severe cases of conduct disorder. The previous kappa for conduct disorder was only 0.37, and 0.58 for antisocial personality (12 subjects), compared with the present version of DICA with $k = 0.80$.

The present study also shows a much improved rate of agreement on the diagnosis of depression, with $k = 0.63$, compared to the previous $k = 0.36$.

Attention deficit disorder and oppositional disorder were not diagnosed as such on the previous interviews. Enuresis was the only diagnosis that showed a higher kappa on the previous study: 0.54 with 85 subjects previously, compared with 0.49 with 23 subjects at present.

Discussion

For those interested in the structured interviewing of children it is reassuring to find good inter-interview agreement in DICA-C, as well as good agreement among the DICA-C diagnoses, the hospital discharge summary, and the mother-child interviews. It is important however, to understand the the differences in the diagnostic process in the three sets of the study in order to analyze the data appropriately.

Helzer et al. (1977), in a test-retest study of adults with psychiatric illness, considered a kappa of 0.55 in the diagnosis of depression as acceptable when two interviewers independently rated the same patient 24 hours apart. Orvaschel (1981) concluded that kappa values of 0.75 to 0.80 indicated good reliability. In our inter-interview comparisons or, as previously mentioned, test-retest reliability study, the kappa ranged from 1 to 0.76 in the different diagnostic categories, indicating excellent to good agreement.

In the comparison study between the DICA-C diagnoses and the clinician diagnoses, one cannot expect the same high agreement as in the inter-interview study because the method of the diagnostic process is different and involves one source of information at a particular time, on one hand, and several sources of information during a period of several weeks, on the other hand. This study was conducted mainly to validate the DICA-C diagnoses. The results of this study indicate that in 81.5% of cases, the clinicians' diagnoses were also made by the DICA-C, but in addition, the children received other diagnoses by the DICA-C. This raises the question of whether or not the additional DICA-C diagnoses have a significant value in the course of the disorder or in the treatment consideration. Can clinicians benefit from the information that is derived from a structured interview? These questions can be answered only by a systematic follow-up study in which an attempt will be made to test the validity of the DICA-C diagnoses in a follow-up design where the course of the illness can be studied.

With respect to the mother-child study, the question of how to interpret the importance of the kappas is a matter of judgment. The kappas in the mother-child part of this study refer to interviewers independently rating two subjects. Adult studies that are more comparable in method to the mother-child study include those of Andreasen et al. (1977) and Winokur et al. (1969). These researchers used two separate interviewers, one to interview the patient and one to interview a first degree relative about the patient. Kappas calculated on the basis of data given in these studies on diagnoses ranged from 0.30 to 0.50 and showed poorer agreement on the whole than on the parent-child interviews described here. In view of the above studies, then, the kappa of 0.80 for the diagnosis of conduct disorder on DICA-C and DICA-P is remarkably high.

The inter-interview comparisons and the validity study were carried out in an inpatient population in which the symptomatology can be expected to be quite extreme. Thus, the results of the reliability test can be inflated because of the abundance of the symptomatology. However, taking into consideration the doubts that many clinicians expressed about the reliability of children, it is reassuring to find a good inter-interviews agreement based on a blind child interview alone. The severity of the psychopathology does not always correlate directly with high agreement of the diagnoses between clinicians. It was, therefore, reassuring to find a good agreement

TABLE 5. *Comparison of Parent-Child Diagnoses Using the Kappa Statistic*[a]

	Both DICA and DICA-P N	Diagnosis Made On		κ
		DICA-P Only N	DICA Only N	
Attention deficit disorder	29	12	2	0.66
Conduct disorder	29	3	5	0.80
Affective disorder	13	5	6	0.63
Enuresis	9	10	4	0.49
Oppositional disorder	37	8	12	0.52

[a] $N = 84$.

between DICA-C, based on a one-time structured interview with the child, and the chart diagnoses, which were based on a much more comprehensive evaluation. The sensitivity of the DICA to distinguish between normal children and disturbed children has not yet been studied. More studies on a large number of children from the general population and the outpatient population are needed.

Further studies must now be done on the instruments, including more work on the interview itself, such as rewording and possible developmental versions. The relative strengths and weaknesses of a computerized version of the interview should be assessed. Further studies of disagreements: mother versus child, child interview versus clinical diagnoses, and so forth, must be carried out in the hope of discovering the particular strengths and weaknesses of the different sources of information about the child.

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16.1.9.
Ethical Review Board Information and Protocol-Specific Informed Consent Document

Chairman of ERB: [redacted]

[redacted]

Assurance Number: [redacted]

[redacted]

[redacted]

September 10, 1990

[redacted]

RE: IRB FILE 0882 17000
Childhood Depression.- Biological Correlates

Dear [redacted]:

On September 10, 1990, [redacted] considered the above referenced study. The Board voted to update IRB approval of this protocol and consent form for one year. The [redacted] number for use of Fluoxetine in children should be transmitted to the Board when received from the FDA. Please use this approved consent form and destroy all other drafts or undated copies. Continuing review of this study is scheduled for September 1991.

University and Federal regulations require that written consent be obtained from all human subjects in your studies. The consent form should be kept on file for a period of three years past completion of the study. A copy of the consent form should be given to each participant in your study. Also, the University attorneys have asked us to remind investigators to put a copy of the consent form in the subject's medical record. Investigators should keep the original, executed copy of the consent form and file it with their records of the protocol.

The HHS regulations require you to submit annual and terminal progress reports to our Institutional Review Board and to receive continuing review of your activity annually by this Board. You are also required to report to the Board any death or serious reactions resulting from your study. Failure to submit the above reports may result in severe sanctions being placed on the [redacted] Furthermore, if you require a modification to this protocol contact me in order that appropriate review and approval can be made prior to implementing the change. If you have any questions related to the [redacted] please contact me at extension [redacted] or [redacted]

Sincerely,

[redacted]

[redacted] [redacted] [redacted]

[redacted]

SUBJECT CONSENT TO PARTICIPATE IN RESEARCH

TITLE OF STUDY: CHILDHOOD DEPRESSION BIOLOGICAL CORRELATES

SPONSOR:

INVESTIGATORS: OFFICE PHONE # NIGHT & WEEKEND

1. [redacted]
2.
3.
4.
5.
6.

You are being asked to participate in a research study. Persons who participate in research are entitled to certain rights. These rights include but are not limited to the subject's right to:

1. Be informed of the nature and purpose of the research;

2. Be given an explanation of the procedures to be followed in the research, and any drug or device to be utilized;

3. Be given a description of any attendant discomforts and risks reasonable to be expected.

4. Be given a disclosure of any benefits to the subject reasonable to be expected, if applicable;

5. Be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, their relative risks and benefits;

6. Be informed of the alternatives of medical treatment, if any, available to the subject during or after the experiment if complications arise;

7. Be given an opportunity to ask any questions concerning the research and the procedures involved;

8. Be instructed that consent to participate in the research may be withdrawn at any time, and the subject may discontinue participation without prejudice;

9. Be given a copy of the signed and dated consent form;

10. And be given the opportunity to decide to consent or not to consent to participate in research without the intervention of any element of force, fraud, deceit, duress. coercion, or undue influence on the subject's decision.

[redacted]

[redacted]

TITLE OF THE STUDY: CHILDHOOD DEPRESSION BIOLOGICAL CORRELATES

You have the right to privacy. All information that is obtained in connection with this study that can be identified with you will remain confidential within the limits of State Law. Information gained from this study that can be identified with you will be released only to the investigators, and if appropriate, to your physician and the sponsors of the study. For studies regulated by the Food and Drug Administration (FDA), there is a possibility that the FDA may inspect your records. The results of this study may be published in scientific journals without identifying you by name.

In addition, the records of your participation in this study may be reviewed by members and staff of the Institutional Review Board, and you may be contacted by a representative of the Board for information about your experience with this study. If you wish, you may refuse to answer any questions the Board may ask of you. We also would like for you to understand that your record may be selected at random (as by drawing straws) for examination by the Board to insure that this research project is being conducted properly.

We will make every effort at preventing physical injury that could result from this research. Compensation for physical injuries incurred as a result of participating in the research is not available. The investigators are prepared to advise you about medical treatment in case of adverse effects of these procedures, which you should report to them promptly. Phone numbers where the investigators may be reached are listed in the heading of this form.

If you have any questions about the research or about your rights as a subject, we want you to ask us. If you have any questions later, or if you wish to report a research-related injury (in addition to notifying the investigator), you may call the [redacted] during office hours at [redacted]

Participation in this research study is entirely voluntary. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without affecting your status (as a patient, student, employee, etc.), or the medical care that you will receive.

Any significant new findings developed during the course of the research which may relate to your willingness to continue participation in this study will be provided to you.

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP

[redacted] Page 2 out of 5 pages

TITLE OF STUDY: CHILDHOOD DEPRESSION BIOLOGICAL CORRELATES

DESCRIPTION OF RESEARCH IN LAY TERMS

PURPOSE: You and your child are invited to take part in a research study of Fluoxetine (a medicine that has proven effective in the treatment of depression in adults) in the treatment of depression in children and adolescents. To measure the effectiveness of this medication half of the subjects will receive a placebo (a pill with inactive ingredients). Neither you nor your treating psychiatrist will know which of these substances your child is taking. This "double-blind" procedure is necessary to ensure unbiased observations and ratings both by your child and your psychiatrist. Whether your child receives Fluoxetine or placebo will be determined by randomization (similar to the flip of the coin). The treatment phase of the study will last approximately 10 weeks. If you wish, your child may continue the medication after the study has been completed.

EXPERIMENTAL PROCEDURES: Your child was selected as a possible participant in this study by referral from your earlier evaluation and the recommendation to be treated with medication in the first part of the study. If you choose to have your child participate your child will be involved in a weekly evaluation which includes: a) an interview to address any problems or questions and to assess progress. b) filling out several questionnaires relating to (your child's) feelings and moods. c) vital signs, two electrocardiogram (EKG) and a 4 p.m. blood level in order to monitor and relate the level of medication in your child's system to response to the medication. At each visit you will be given a one week supply (plus 2 days) of medication. There will be no cost to you for any treatment provided in this study.

In summary, you and your child's participation in this study is voluntary. Should you decide to participate, you and your child will be involved for a period of approximately 10 weeks. If your child does not respond to the treatment, your child will be discontinued from the medication and will be treated as medically indicated.

POSSIBLE RISKS: The risk of obtaining a blood specimen is minimal. A small bruise may form around the needle hole, but is unlikely. This will resolve in several days and should cause little or no discomfort. Fluoxetine may cause some side effects in some patients. These side effects include anxiety, nervousness, and insomnia; drowsiness and fatigue or asthenia; tremor; sweating; weight loss, nausea, and diarrhea; and dizziness or lightheaded. Each week your child will be carefully monitored for side effects.

TITLE OF STUDY: CHILDHOOD DEPRESSION BIOLOGICAL CORRELATES

Ability to perform hazardous tasks such as driving or operating heavy machinery may be impaired, and ones response to central nervous system depressants such as alcohol and barbiturates may be increased.

Because drowsiness can be a side effect with Fluoxetine, your child should not drive or operate complicated machinery if drowsiness is present.

Safe use of Fluoxetine during pregnancy has not been established; Woman of childbearing potential who wish to participate in this study must use a medically acceptable form of birth control. If your child is a woman of childbearing potential, tell your psychiatrist which method of birth control your child will employ.

POSSIBLE BENEFITS: The study medication may improve your child's depression and your child may experience relief of many of the symptoms associated with this condition. Patients in this study will receive the benefit of free medication, full evaluation of symptoms, careful monitoring of treatment and general health discussions with the physician, the health information derived from laboratory tests, and finally, the chance to contribute to a scientific investigation. If Fluoxetine is found to as effective with children and adolescents as with adults, an important treatment for depression in children and adolescents will be validated.

ALTERNATIVES TO PARTICIPATION: If you do not choose to participate in this study, you have the options of your child continuing with the present service, being followed in the psychopharmacology clinic, or referred to other clinicians for treatment.

CONFIDENTIALITY: Your child's medical records will be confidential. No reports of this study will include patient names.

Your participation in this study is purely voluntary, and you may withdraw your consent and discontinue your participation in this study at any time. Should you wish to withdraw your consent, please notify your study psychiatrist. Such a decision on your part, will not influence the medical care to which you are otherwise entitled.

Your participation in this study will be discontinued if in your psychiatrist's clinical judgment, discontinuation is in your child's best interest, or if your child fails to comply with study procedures.

TITLE OF STUDY: CHILDHOOD DEPRESSION BIOLOGICAL CORRELATES

If your child has any adverse reactions, or any questions about the study, or any additional concerns or questions as to rights, please ask the following persons:

[redacted]

We have tried to explain all the important details about the study to you. If you have any questions that are not answered here, your psychiatrist will be happy to give you further information.

Information regarding your child's participation in this study may be released to the sponsor and the FDA; and the sponsor and the FDA may inspect the medical records if it is necessary to do so.

YOU ARE MAKING A DECISION WHETHER OR NOT YOUR CHILD PARTICIPATES IN THIS STUDY. YOU SHOULD NOT SIGN UNTIL YOU UNDERSTAND ALL THE INFORMATION PRESENTED IN THE PREVIOUS PAGES AND UNTIL YOUR QUESTIONS ABOUT THE RESEARCH HAVE BEEN ANSWERED TO YOUR SATISFACTION. YOUR SIGNATURE INDICATES THAT YOU HAVE DECIDED FOR YOUR CHILD TO PARTICIPATE HAVING READ (OR BEEN READ) THE INFORMATION PROVIDED ABOVE.

_____ _____ _____ _____
Signature of Subject Age Date Time

_____ _____
Signature of Parent/Guardian Signature of Witness

_____ _____
Relationship to Subject Signature of Investigator

Subject's Name (Typed or Printed):_____

Daytime Telephone No:_____

16.1.10.
Listing of Patients Receiving Test Drug(s) or Investigational Product(s) From Specific Batches

From April 1991 to August 1993, the pharmacy at [redacted] at [redacted] prepared and provided blinded study drug medication for the patients in this study. The pharmacy used marketed Prozac® capsules, which have an opaque green cap and off-white body. The cap is imprinted with DISTA 3105 and the body is imprinted with Prozac 20 mg. Active study drug was dispensed and appeared as the marketed product (green and white capsules). Placebo medication was prepared by emptying Prozac capsules completely and refilling them with lactose powder. The pharmacy made sure that the printing on the capsules was lined up before dispensing to the patient. Fifty-four patients (25 fluoxetine-treated, 29 placebo-treated) received study medication prepared in this manner.

From September 1993 to February 1995, Lilly supplied blinded clinical trials material for this study. Active and placebo study medication were identical in appearance as solid white capsules. Fluoxetine 20 mg capsules were provided from lots CT02768 and CT01678. Placebo capsules were provided from lots CT02769 and CT01679. All 4 lots had an expiration date of 1 May 1995 and an extension expiration date of 1 May 1996. Forty-two patients (23 fluoxetine-treated, 19 placebo-treated) received study medication supplied by Lilly.

No patient received study medication prepared in both ways (site-prepared and Lilly-provided). Lilly does not believe that the change from the site's preparation of study medication to Lilly's supply of medication compromised the blinding or conduct of this study. Patients and study site personnel were blinded to study drug assignment before and after this change occurred. It is possible that the change from the marketed product (green and white capsules) to the clinical trials materials supplied by Lilly (white capsules) may have had an indirect effect on study results; however, this effect would have been consistent for the two treatment groups. To determine if this change was associated with any effect on the study results, subgroup analyses were performed for key efficacy and safety endpoints and are presented in Sections 11.4.3 and 12.7, respectively.

16.1.11.
Audit Certificates

ELI LILLY AND COMPANY

[redacted]

AUDIT CERTIFICATE

Compound: LY 110140 Fluoxetine **Protocol:** B1Y-MC-X065

Study Title: A Double-Blind, Randomized Placebo-Controlled Trial of Fluoxetine in Depressed Children and Adolescents.

This study was subject to independent audit by staff of the Medical Quality Assurance Department or its contractors.

Audit Subject	Date of Audit	Auditor/s
[redacted]	19/June/1997	[redacted]

Signed [redacted] **Date** 15 MAR 2000

Medical Quality Assurance Representative

16.1.12.
Documentation of Inter-Laboratory Standardization Methods and Quality Assurance Procedures if Used

Inter-Laboratory Standardization Methods

Whenever possible, a central laboratory was used to maintain consistency of methods and to combine laboratory data across study sites and/or across studies. When using multiple local laboratories with different methodologies, the data were normalized, that is, laboratory results were expressed as a percentage of the upper and/or lower limits of each laboratory's reference range.

Laboratory analysis of blood and urine samples were performed at:

[redacted]

Quality Assurance Procedures

During the Study

The study site managed the data collected during the study. The data were managed using a screen and menu-guided automated system. Throughout the study, quality control procedures, such as double-data entry and edit checks, were used to assure the accuracy and completeness of the data.

The data entry system was developed by the study coordinator/systems analyst. Requirements for the data entry system were derived from the study binder, located at the site. After the system was created, test data were entered into all screens to test data input and online editing.

Source data was data entered directly into the automated system by site personnel. The data were initially entered from patient records. The data were spot-checked by comparing the database to source documents. The data were reentered (double-data entry) by a different individual into a second blank copy of the database. The two databases were compared and discrepancies were identified. The discrepancies were resolved by comparing to source documents and the first database was corrected. The efficacy data for randomized patients used in the site's analysis went through a final source data verification process. In addition, the univariate features of the data, such as deviations from symmetry or heteroscedasticity, were checked.

It should be noted that site personnel only entered selected variables into the database. Data were not electronically entered into the site database for non-solicited adverse events, pill counts, laboratory data, concomitant medications, ECGs, vital signs, and some inclusion/exclusion criteria. These data were available in source documents.

During the Data Import by Lilly

As the data from this trial were collected from an investigative site that was not monitored by Lilly while the trial was conducted (1991-1995), the following measures were taken to ensure the integrity of the data:

- a detailed plan to maintain the study blind at the patient level was developed (see Appendix 16.1.14)
- an extensive audit of the source documents and study files was conducted
- affirmation statements from the Investigator and Study Coordinators were obtained (see Appendix 16.1.15)
- an audit trail for the Lilly study database was initiated and maintained

- 100% source data verification of all data points for every patient at every visit (captured in the Lilly database) during the acute treatment phase of the study was conducted (see Appendices 16.1.16 and 16.1.17)
- a 100% data quality review of all data that had been entered into the Lilly database was performed
- a detailed statistical analysis plan was developed prior to reanalyzing any unblinded statistical summary data (see Appendix 16.1.6)
- a data validation plan was developed to document the data collection procedures (see Appendix 16.1.17).

Lilly acknowledges that [redacted] had published a manuscript detailing the results from this study prior to Lilly's decision to import the data from this investigator-initiated trial. This manuscript is presented in Appendix 16.1.7. A timeline of events following completion of the study at the site is presented in Section 9.1.1.3. The project team at Lilly developed a detailed blinding plan, presented in Appendix 16.1.14, to address how personnel would handle data during the data import process. This blinding plan has been followed throughout the preparation of this clinical study report.

Lilly Clinical Research Associates (CRAs) conducted an extensive medical audit of the site to determine the feasibility of importing the data from this study for inclusion in a submission. The purpose of the audit was to assess basic study data and documentation integrity, patient safety, and the qualifications of the investigator and site. As part of this audit, Lilly CRAs began collecting all essential regulatory documents, including copies of the protocol, informed consent documents, and ethical review board approvals. Patient files were reviewed; the information collected from these files was used to enable assessment of site decisions regarding patient safety and study inclusion/exclusion criteria and adherence to the protocol. Using the information obtained during this audit, a risk analysis profile was completed by Lilly area representatives from Regulatory, Medical Quality Assurance, Medical, and Statistics. This group decided to move ahead with the data importation process as the integrity of the data was sound and the site was found to be compliant with Good Clinical Practice standards.

Some of the data for this study had previously been entered into an electronic database by site personnel (as described in Section 9.6.1). The site database was obtained from the Investigator and converted into a Lilly database. Site personnel captured the following additional data through use of electronic case report forms developed by Lilly: non-solicited adverse events, pill counts, laboratory data, concomitant medications, ECGs, vital signs, and some inclusion/exclusion criteria. These data were collected from study files for each patient, source documents, and also through verbatim transcription of progress notes without interpretation of the data, and were entered into the Lilly database. Site personnel signed affirmation statements indicating that they would not alter source documents as they completed the electronic case report forms (see Appendix 16.1.15).

All data points captured in the Lilly database for all visits that occurred during the single-blind placebo phase and the double-blind acute treatment phase (Visits 1 to 10) were verified from source data during subsequent monitoring visits. In addition, all data points from all unscheduled visits that occurred during both the single-blind placebo phase and the double-blind acute treatment phase were source data verified.

Verification and validation of the data were performed by Lilly clinical personnel and an independent contract monitor (see Appendix 16.1.17). Throughout the process, selected Lilly CRAs had access to randomization codes (from source files). These CRAs had a primary role in data validation, including the following: development and approval of edits, assessment of edits, assessment of the completeness of data captured in comparison to medical audit records, and review of the data according to the monitoring plan. However, these CRAs were unable to make changes to the Lilly study database. Data entry, query generation and resolution, and corrections to the Lilly study database were made only by eligible blinded Lilly personnel. An automated audit trail was put into place to track all changes made to the database in response to Lilly queries. All changes were authorized in advance by the investigative site. The Lilly Clinical Research Physician (CRP) remained blinded until data lock. Ascription of COSTART terminology to all adverse events captured during the data collection, source data validation, and verification processes were performed by blinded Lilly personnel and approved by the CRP.

A statistical analysis plan, distinct from the one used by [redacted] and colleagues in publications, was developed by Lilly personnel prior to the final validation and unblinding of the reporting database (see Appendix 16.1.6). Treatment group assignments in the database were masked using a dummy randomization code to maintain blinding during the process of data validation and development of statistical summary tables. Lilly study data were formally unblinded to treatment group assignment at data lock.

16.1.13.
Errors to the Locked Database

Date 1/11/2000

Note to File, Re: 2119
Product or Compound Number: LY110140
Project Id: B1Y-MC-X065 Inv: [redacted] **Patient No: 2119**
Indication: Child Depression
File in: Project
Info from: GCP noncompliance/monitoring issue? No

Date (dd/mm/yy)	Participants Names	Position
1/11/2000	[redacted]	Medical Writer
		CRA

Description of the Issue: Patient 2119 reported hypomania on 2/16/93 at Visit 5, but patient was not discontinued from study until 2/23/93, also in database as Visit 5.

How Resolved: Patient 2119 actually had a Visit 6 on 2/23/93, which was the patient discontinuation visit. Patient 2119 Summary Visit was captured incorrectly in the database. The Summary Visit should be Visit 6, not Visit 5. Therefore, the number of days in therapy for the stop date of hypomania is correctly reflected as 20 days (report AEL1EM01) and the number of days in therapy until discontinuation of 27 days is correct (report RDL1EM01).

Note to File Generated by: [redacted]
Signature:
Lilly CRP signature may be required (see Medical Global Policy #16, Protocol Variations).
Note: If violation is likely to or has recurred, consider whether a protocol amendment is appropriate.
cc:

Date : 3/16/2000

Note to File, Re: Height for patients 2252 2249 2210
Product or Compound Number: LY110140
Project Id: B1Y-MC-X065 Inv: [redacted] **Patient No: 2252 2249 2210**
Indication: Child Depression
File in: Patient File and Protocol Binder
Info from: GCP noncompliance/monitoring issue?

Date (dd/mm/yy)	Participants Names	Position
16/3/2000	[redacted]	CRA
		Team Leader

Description of the Issue: Upon the locking of the database, several heights were found to be in error. The site was queried and the heights were corrected. These errors will not cause Lilly to unlock the database. Each of the heights between visits 2-10 does not affect the analysis already completed for the study. The analysis used was change from baseline of height between groups. Patient 2210 with a corrected height at V10 did not have a baseline height, so the patient was never used in the analysis.
2252 V3 height was 134.6, correct height is 136.7.
2249 V8 height was 134.6, correct height is 133.4.
2210 V6 height was 165.1, correct height is 163.8
2210 V8 height was 162.6, correct height is 162.1.
2210 V10 height was 167.8, correct height is 166.4.

How Resolved: These errors will be described in the Clinical Study Report.

Note to File Generated by:
Signature: [redacted]
Lilly CRP signature may be required (see Medical Global Policy #16, Protocol Variations).
Note: If violation is likely to or has recurred, consider whether a protocol amendment is appropriate.
cc:

Date : 3/9/2000

Note to File, Re: Missing Labs
Product or Compound Number: LY110140
Project Id: B1Y-MC-X065 Inv: [redacted] **Patient No: 2162 2179 2180 2212 2213 2231**
Indication: Child Depression
File in: Patient File and Protocol Binder
Info from: GCP noncompliance/monitoring issue?

Date (dd/mm/yy)	Participants Names	Position
9/3/2000	[redacted]	CRA Team Leader

Description of the Issue: Upon second review of the sites files, labs reports for specific visits were found for 6 patients, which were not entered into the Lilly Database. Patient 2162 V10, 2179 V6 (Cortisol result), 2180 V3 and V6, 2212 V1, 2213 V8, 2231 V1.

How Resolved: The CSR will indicate that an error to the database has occurred. The labs will also be included in the Appendix to the CSR.

Note to File Generated by:
Signature: [redacted]
Lilly CRP signature may be required (see Medical Global Policy #16, Protocol Variations).
Note: If violation is likely to or has recurred, consider whether a protocol amendment is appropriate.
cc:

Patient	Visit	Lab/ECG	Reference range	Result
2162	10	Albumin	3.7-5.6	4.4
		Alk Phos	175-420	181
		LDH	420-750	491
		AST	16-46	31
		ALT	10-35	14
		WBC	4.5-13.5	8.8
		RBC	4.40-5.30	4.38
		Hemoglobin	12.7-14.9	12.1
		Hematocrit	38.0-44.0	34.4
		MCV	79.0-89.0	78.7
		MCH	26.0-31.0	27.7
		MCHC	32.0-36.0	35.2
		RDW	11.5-14.5	12.1
		Plt	150-475	236
		MPV		9.7
		Segs	40-76	66
		Eosino	0-5	7
		Mono	0-12	6
		Lymphs	30-50	21
		Morph		NL
2179	6	Cortisol		4.6
2180	3	Albumin	3.7-5.6	4.2
		Alk Phos	135-520	90
		LDH	4232-700	573
		AST	16-46	15
		ALT	10-35	19
		T4	4.0-12.0	8.1
		TSH	0.4-6.2	3.2
		WBC	4.5-13.0	9.4
		RBC	4.40-5.30	4.75
		Hemoglobin	12.8-15.6	13.1
		Hematocrit	38.0-46.0	38.7
		MCV	80.0-90.0	81.4
		MCH	26.0-31.0	27.6
		MCHC	32.0-36.0	33.9
		RDW	11.5-14.5	12.6
		Plt	150-450	283
		MPV		8.7
		Segs	40-76	38
		Bands	0-6	1
		Eosino	0-5	4
		Mono	0-12	13
		Lymphs	24-45	44
		Morph		NL
		UA-Color		YELLOW
		appear		CLEAR
		spec grav	1.00-1.036	1.022

		Ph	5.0-8.0	5.0
		Protein	NEG	NEG
		Glucose	NEG	NEG
		Ketones	NEG	NEG
		Blood	NEG	NEG
		Bilirubin	NEG	NEG
		Urobilirubin	1	0.2
		Nitrite	NEG	NEG
		Leukocyte Ester	NEG	NEG
		WBC/HPF		RARE
		RBC/HPF		NONE
		Squamous		FEW
		Casts		NONE
2212	1	Albumin	3.7-5.6	4.0
		Alk Phos	135-520	33.5
		LDH	432-700	626
		AST	16-46	42
		ALT	10-35	29
		T4	4.0-12.0	7.3
		TSH	0.4-6.2	0.6
		WBC	4.5-12.0	6.8
		RBC	4.40-5.30	4.82
		Hemoglobin	12.8-15.6	13.8
		Hematocrit	38.0-46.0	39.3
		MCV	80.0-90.	81.5
		MCH	26.0-31.0	28.6
		MCHC	32.0-36.0	35.1
		RDW	11.5-14.5	12.2
		Plt	150-400	260
		MPV		9.5
		Morph		ABN
		Acantho/Echino		1+
2213	8	Albumin	3.7-5.6	4.2
		Alk Phos	105-420	105
		LDH	380-640	422
		AST	16.46	28
		ALT	10-30	14
		WBC	4.5-11.0	7.1
		RBC	4.50-5.20	4.45
		Hemoglobin	12.6-14.8	12.9
		Hematocrit	37.0-44.0	37.7
		MCV	80.0-90.0	84.8
		MCH	26.0-31.0	29.0
		MCHC	32.0-36.0	34..2
		RDW	11.5-14.5	11.5
		Plt	150-450	273
		MPV		7.7
		Neutrophil	40.0-76.0	61.5
		Eosino	0.0-5.0	1.8

		Baso	0.0-2.0	0.2
		Mono	0.0-12.0	7.3
		Lymph	24.0-45.0	29.2
		Morph		NL
2231	1	Albumin	3.7-5.6	4.4
		Alk Phos	135-520	208
		LDH	432-700	791
		AST	16-46	44
		ALT	10-35	41
		T4	4.0-12.0	7.8
		TSH	0.4-6.2	2.0
		WBC	4.5-13.0	7.0
		RBC	4.40-5.30	5.22
		Hemoglobin	12.8-15.6	13.6
		Hematocrit	38.0-46.0	41.3
		MCV	80.0-90.0	79.0
		MCH	26.0-31.0	26.1
		MCHC	32.0-36.0	33.1
		Plt	150-450	120
		Segs	40-76	51
		Bands	0-6	6
		Mono	0-12	5
		Lymphs	24-45	38
		Morph		ABN
		Polychromasia		1+

Date : 2-8-2000

Note to File, Re: 2212 Dosing Regiemen
Product or Compound Number: LY110140
Project Id: B1Y-MC-X065 Inv: [redacted] **Patient No: 2212**
Indication: Child Depression
File in: Patient File and Protocol Binder
Info from: GCP noncompliance/monitoring issue? No

Date (dd/mm/yy)	Participants Names	Position
2-8-2000	[redacted]	CRA Statistician Medical Writer Study Coordinator

Description of the Issue: It was recently determined that the X065 COMMENTS dataset and COMPLNCE dataset were not consistent with each other regarding the drug regimen for patient 2212. Please refer to the attached SAS output for these two datasets. The COMMENTS dataset shows that the patient started every other day dosing per direction of the physician at visit 7. The COMPLNCE dataset shows the patient on daily dosing throughout the study (DRGREG=1). [redacted] recently contacted [redacted] from the [redacted] site and confirmed that the patient actually started every other day dosing at visit 7.

How Resolved: The X065 data will not be unlocked and corrected. However, if a correction were to be made to the data, the attached SAS output shows the correction that would be made for the COMPLNCE data. At visits 7, 8, and 9 the DRGREG would be changed from DRGREG=1 (daily dosing) to DRGREG=2 (every other day dosing). The SD_COMPL variable would then be recalculated per the PETS loading program and would change from SD_COMPL=2 (not compliant) to SD_COMPL=1 (compliant) at visits 7, 8, and 9.

Note to File Generated by:
Signature: [redacted]
Lilly CRP signature may be required (see Medical Global Policy #16, Protocol Variations).
Note: If violation is likely to or has recurred, consider whether a protocol amendment is appropriate.
cc:

16.1.14.
Blinding Plan

Blinding Plan for Study B1Y-MC-X065

This study was initiated by the investigator [redacted] in 1991. The protocol was conducted as an exempt from IND study. Lilly decided to import the data from this study and submit it as clinical data for the evaluation of fluoxetine use in depressed pediatric and adolescent patients late in 1997 in response to FDA's request for pediatric data. The results of this study were published by the investigator [redacted] Consequently, Lilly personnel were unblinded to the results as interpreted by [redacted] and colleagues. As Lilly began electronically importing the [redacted] data for evaluation, the statistician reviewed efficacy and patient treatment group data; however, these data were not merged at the time. Efficacy data was reviewed for overall organization and completeness.

The following strategies are proposed in order to minimize bias while preparing the Clinical Study Report (CSR):

- A statistical analysis plan, distinct from the one used by [redacted] and colleagues, will be developed by Lilly personnel prior to viewing any unblinded statistical summary data in order to prepare a complete clinical study report.
- Treatment group assignments in the data will be masked using a dummy randomization code to maintain blinding during the process of data cleaning and development of statistical summary tables. Lilly study data, which is comprised of the electronically imported [redacted] data and the remaining data collected by site personnel onto CRFs, will become the complete Lilly data set. The Lilly data set will be formally unblinded to treatment group assignment at data lock.
- Data collection of required variables not captured electronically by the investigator will be captured on CRFs by site personnel, if possible. Otherwise, this data will be collected by non-Lilly personnel.
- Verification and validation of the data will be performed by Lilly Clinical Research Associates (CRAs). Throughout the process, the Lilly CRAs will have access to randomization codes (from source files). These CRAs will have a primary role in data validation, including development and approval of edits, assessment of edits, assessment of the completeness of data captured in comparison to medical audit records, and review of data according to the monitoring plan; however, they will be ineligible to make changes to the Lilly study database.
- Data entry, query generation and resolution, and corrections to the Lilly study database will be made by blinded Lilly personnel. An audit trail will be put into place to track all changes, which must be authorized by the investigative site, made to the database in response to queries.

- The Lilly Clinical Research Physician (CRP) will remain blinded until data lock. Ascription of COSTART terminology to all adverse events captured during the data collection, source data validation, and verification processes will be performed by blinded Lilly personnel and approved by the CRP.

The Blinding Plan, version 1.0, was developed to ensure data integrity. The data for this study were imported from an investigational site well after the study was completed. In addition, the results of this study were published in manuscript form by the investigator and his colleagues in 1997. Lilly has decided to import this data and create a formal integrated clinical and statistical report for submission to the FDA per its request for pediatric data. Since it is possible that Lilly personnel involved in this study have been exposed to this data, the following plan was developed prior to complete importation and analysis of the data. Your signature on this document indicates your understanding of the blinding procedures that will be utilized in this study and your commitment to preserving the integrity of the data for this study.

[redacted]

3/24/99
Date

[redacted]

3/22/99
Date

[redacted]

Date

[redacted]

3/23/99
Date

[redacted]

3/17/99
Date

[redacted]

3/17/99
Date

[redacted]

3/17/99
Date

[redacted]

Date

- The Lilly Clinical Research Physician (CRP) will remain blinded until data lock. Ascription of COSTART terminology to all adverse events captured during the data collection, source data validation, and verification processes will be performed by blinded Lilly personnel and approved by the CRP.

The Blinding Plan, version 1.0, was developed to ensure data integrity. The data for this study were imported from an investigational site well after the study was completed. In addition, the results of this study were published in manuscript form by the investigator and his colleagues in 1997. Lilly has decided to import this data and create a formal integrated clinical and statistical report for submission to the [redacted]per its request for pediatric data. Since it is possible that Lilly personnel involved in this study have been exposed to this data, the following plan was developed prior to complete importation and analysis of the data. Your signature on this document indicates your understanding of the blinding procedures that will be utilized in this study and your commitment to preserving the integrity of the data for this study.

[redacted]

Date

[redacted]

Date

[redacted]

3/18/99
Date

[redacted]

Date

[redacted]

3/17/99
Date

3/17/99
Date

Date

3/17/99
Date

16.1.15.
Affirmation Statements from the Study Site

[redacted]

[redacted]

[redacted]

[redacted]

Re: B1Y-MC-X065

Dear [redacted]

This memo is to acknowledge that all staff including [redacted] were not unblind to patient therapy code until June 1995, when all patients completed the study and all databases were cleaned and checked.

If you have any further questions or concerns please feel free to call me at [redacted]

Sincerely,

[redacted]

[redacted]

[redacted]

[redacted]

February 4, 2000

[redacted]

Memo regarding [redacted] research study: Childhood Depression: Biological Correlates, completed 1991 - 1995.

The pharmacists at [redacted] completed randomization to either Fluoxetine or placebo. This randomization was completed according to a computer generated randomization table and included four cells: males, females, 12 years and under, 13 years and over. As a validation of the randomization schedule, I kept a duplicate record of the randomization table. I did not complete any of the post randomization ratings in the study except for the following: subject 2013 visit T2, and subject 2014 visit T1 (see attached). These ratings were completed prior to my knowing what medication these subjects had been assigned to.

[redacted]

Date (ddmmmyy): 9/2/99

Note to File, Re: Drug Accountability and Compliance
Country and/or IND or NDA No.:
Product or Compound Number: LY110140
Project Id: B1Y-MC-X065 Inv: Patient No:
Indication:
File in: Inv File: ☐ Patient File: ☐ Protocol File: X Project File: X
Info from: Meeting: Phone call: X CRFs: ☐ Other:
GCP noncompliance/monitoring issue? Yes: No: ☐ Maybe: X

Date (dd/mm/yy)	Participants Names	Position
9/2/99	[redacted]	Study Coordinator CRA

Description of the Issue: The compliance captured on the Progress notes and drug log may differ in the information captured on the Drug Accountability log, according the study coordinator. The information captured on the progress notes and the drug log are not from the week before, which is what is captured on the CRF.
How Resolved: If the progress note, or the drug log differ from the Drug Accountability log, the information on the Drug Accountability log will be taken as the correct information.

Note to File Generated by: [redacted]

Signature: [redacted]
Lilly CRP signature may be required (see Medical Global Policy #16, Protocol Variations).
Note: If violation is likely to or has recurred, consider whether a protocol amendment is appropriate.
cc:

Date (mmmddyy): 11/3/99

Note to File, Re: Drug Accountability Log
Country and/or IND or NDA No.:
Product or Compound Number: LY110140
Project Id: B1Y-MC-X065 Inv: Patient No:
Indication:
File in: Inv File: ☐ Patient File: ☐ Protocol File: X Project File: X
Info from: Meeting: X Phone call: CRFs: ☐ Other:
GCP noncompliance/monitoring issue? Yes: No: ☐ Maybe: X

Date (mm/dd/yy)	Participants Names	Position
11/3/99	[redacted]	CRA
		CRA

Description of the Issue: The site documentation reflects that the Master Clinical Drug Accountability Log is the accurate source of information for all patients drug accountability throughout the study. This was not established until after queries and CRFs had been generated.

How Resolved: The site has been queried (JN 26) to send the drug accountability log to Lilly so that all patient compliance records can be updated appropriately.

Note to File Generated by: [redacted]

Signature: [redacted]
Lilly CRP signature may be required (see Medical Global Policy #16, Protocol Variations).
Note: If violation is likely to or has recurred, consider whether a protocol amendment is appropriate.
cc:

Eli Lilly and Company B1Y-MC-X065

Source Affirmation Statement

As a result of my collaboration with Eli Lilly and Company on B1Y-MC-X065, I agree not to alter any source document (where data was originally captured) for this study. This includes source documentation for the data that was originally entered into the electronic database, as well as source documentation for additional data that will be entered into the Lilly electronic database.

[redacted] 5/27/99
Date

[redacted] 6/7/99
Date

[redacted] 6-7-99
Date

Eli Lilly and Company B1Y-MC-X065

Transcription Affirmation Statement

By my signature below, I agree that the dictation of each progress note for each patient who participated in B1Y-MC-X065 has been read verbatim from the source document.

[redacted]

5/27/99
Date

16.1.16.
Monitoring Plan

Please note that [redacted] referred to his study by the name of "Fluoxetine in Depression with Biological Correlates." As discussed in detail in Section 9.1.1 of the clinical study report, when Lilly decided to import the data from this study, Lilly only focused on the acute treatment phase of [redacted] study. Lilly gave this portion of the study the name "Fluoxetine Versus Placebo in the Acute Treatment of Major Depressive Disorder in Children and Adolescents" (B1Y-MC-X065).

Monitoring Plan for LY110140
Protocol B1Y-MC-X065

Introduction

Outlined below is the process Lilly has established to address verification of non-Lilly clinical trial data. This process addresses the evaluation of all major areas of concern, including medical quality assurance, medical /regulatory issues, and study outcomes. This Plan will therefore be used while monitoring at a previously completed non-Lilly clinical trial site. The following outlines the minimum process for doing so.

Study

"Fluoxetine in Depression with Biological Correlates"

Phase I: Initial Audit Process

A Medical Audit of the study site will be conducted by Lilly MQA and Medical personnel to assess basic study data and documentation integrity, patient safety, and site and investigator qualifications. The following study documentation will be requested from the study site by Lilly, and sent to Lilly for review either prior to this visit, or as a result of this visit. In addition, patient files will be reviewed, and data collected to enable assessment of site decisions based on patient safety and study inclusion/exclusion criteria. Based on information collected during the audit, a risk analysis profile will be completed by Lilly area representatives (Regulatory, MQA, Medical, Statistics), and if study integrity is acceptable, the remaining phases of the Plan will be implemented.

[redacted] approved Patient Informed Consents must state that the study sponsor and/or the [redacted] is allowed access to patient files prior to any review of patient files. If the site requires, Lilly personnel who will be conducting activities during Phase II or Phase III of this plan will sign a Letter of Confidentiality prior to reviewing the patient files.

- **Clinical Trial Materials (drug accountability and compliance)**
  - study drug invoices
  - study drug dispensing log
  - documentation of disposition of all study drug at trial completion
  - obtain pharmacy instructions used in preparing the study drug capsules, and documentation of the source of the study drug prior to Lilly's involvement in 1993.
  - randomization codes
  - pill counts
  - documentation of study drug compliance
- **Patient Protection**
  - original and any amended informed consent documents (need blank copy at Lilly and ensure that there is an signed ICD present for all patients at the site)

- obtain a statement signed by the investigator that blinding code remained unbroken until study end, which includes list of identified study participants

- **Regulatory documents**
  - assure that the site has a Clinical Trials Record Binder to house all critical study documents.
  - assure that the site has a copy of the Clinical Investigator Brochure (CIB)
  - CV's for all investigator(s) and all study personnel
  - [redacted] approval of protocol
  - [redacted] approval of ICD
  - [redacted] approval of any protocol or ICD amendments
  - [redacted] approval of advertisements and obtain a copy of advertisement
  - annual reports to [redacted]
  - obtain copies of all pertinent study correspondence between the site and their [redacted]
  - final report to the [redacted] stating that the study is officially closed
  - 1572 (if applicable) and supplements
  - [redacted] membership list at the time of [redacted] approval
  - IND submission cover (if applicable)
  - verify that all Serious Adverse Event reports were reported to [redacted] and Lilly
  - obtain all internal audit reports or evidence of a quality assurance process

- **General information**
  - protocol
  - investigator licensure spanning the duration of the study
  - investigator registration/certification
  - facility licensure spanning the duration of the study
  - laboratory (CLIA and CAP) certifications spanning the duration of the study
  - laboratory units and reference ranges for any blood tests performed on study patients
  - copyright permissions for instruments used in the study
  - any training documentation (i.e. SCID-P)
  - debarment certificate spanning the duration of the trial and currently (separately)
  - affirmation statement signed by the investigator stating that the study was conducted according to GCPs and that all data has been transferred to Lilly
  - any study instructions that may exist

- **Quality Assurance Documents**
  - obtain all documentation that captures any processes used by the site to assure the quality of the data/study (ie, double-data entry, data quality review)
- **Data collection**
  - obtain any audit trail logs used by the site

- Verify that non-discontinued patients were not receiving exclusionary therapy if specified by the protocol.
- Verify that all non-discontinued patients met the eligibility requirements as stated in the protocol's inclusion and exclusion criteria.
- Verify that all informed consent documents were signed and dated by the patient's legal representative prior to the administration of any study procedure or the receipt of study medication. Verify that assent was obtained from the child/adolescent.
- If the ICD was amended, make sure that the ICD signed by the patient's legal representative and child/adolescent reflects the protocol/informed consent document that was currently approved at that time.

Phase II: Data Collection

If any study data has been entered into an electronic database by the investigator, this database will be obtained by Lilly. Electronic case report forms (CRFs) will be used to collect any additional required data for transfer from site source records to Lilly during this phase. Investigative site personnel will perform the data collection. Electronic CRFs will be developed so as to collect data by transcription without interpretation. Site personnel will be required to sign a document stating that they have not altered source. Investigator/designee signature will be required on the Investigator Signature Page verifying the information collected on the CRFs.

Patient Visits

All patient visits were determined based on weeks in the study. Visit 1 (single-blind placebo phase) includes all visits that the patient was taking placebo and occurred prior to the patient being randomized to double-blind treatment. Visits 2-10 (double-blind treatment phase) include all visits in which the patient was currently receiving double-blind treatment; fluoxetine 20 mg/day (if not on alternate day dosing regimen) or placebo. A patient may have come in for an unscheduled visit during both the single-blind placebo phase and the double-blind treatment phase.

- Evaluation Phase: The evaluation period was three weeks in duration in which patients received no study drug. A screening informed consent document was signed during the first evaluation visit. The data from these visits will not be collected.
- Study Period I (Single-blind placebo phase): Visit 1 includes data pertaining to the single-blind, placebo period which was one to two weeks in duration. Informed consent was obtained prior to the administration of any study procedure or the dispensing of the single-blind study drug, placebo. Those patients who met the study inclusion/exclusion criteria as assessed during the first week of Study Period I, including receiving a CDRS-R score ≥ 40 were advanced to Study Period II. Those patients who did not meet the study inclusion/exclusion criteria and/or received a CDRS-R score ≤ 40 were followed for an additional week to rule out placebo response. If at the end of the second week these patients then met study entry criteria, they were advanced to Study Period II. If a patient was seen for

several visits during this study phase, the additional visits will be labeled as Visit 1a, Visit 1b, etc.

- Study Period II (Double-blind treatment phase): Visit 2 through Visit 10 includes data pertaining to the double-blind, randomized, placebo-controlled, 2-arm parallel, 8 week study phase. Randomization occurred at Visit 2. For those patients who met the study inclusion/exclusion criteria as assessed during Study Period I, including a CDRS-R score ≥ 40), active treatment containing blinded study drug was dispensed. Visits will be labeled based on the number of weeks that the patient was active in the study. If the patient skipped a visit (i.e., patient came in for Visit 3, unable to make the next week's visit [Visit 4], and returned the following week [Visit 5],do not consider the visit which occurred two weeks after Visit 3 as Visit 4. This visit should be labeled as Visit 5, which corresponds to the number of weeks that the subject is active in the study. Any unscheduled visits that occurred prior to the next scheduled study visit will be labeled using a differentiating letter corresponding to that visit (ie, 9a, 9b-visits that occurred in between Visit 9 and Visit 10).

Phase III: Source Data Verification and Database Validation

Definition: Source Data Verification (SDV) is the verification of source document data (the location where the data was originally captured) as compared to the data recorded on the CRFs. These CRFs will contain all study data originally entered into the electronic database and the additional required data entered via electronic CRF.

Definition: Case Report Forms will be printouts of the entire database and will be used as a tool for source data verification.

Definition: Electronic Case Report Forms will be used as a vehicle for data collection of the additional required data that is entered into the electronic database.

The following will be source data verified (SDV) during the monitoring visits:

- 100% of **all** data points from **all** visits that occurred during the single-blind placebo phase and the double-blind treatment phase (Visits 1-10).
- 100% of **all** data points from all unscheduled visits that occurred during both the single-blind placebo phase and the double-blind treatment phase.

Adverse Events

- Verify that **all** adverse events found in source documents are entered on the Adverse Event electronic CRF and appropriate comments are entered on the Comments electronic CRF, if needed.
- Verify that **all** serious adverse events found in source documents were reported to the site's ethical review board and to Lilly.

Concomitant Therapy

- Verify that **all** concomitant medications found in source documents are entered on the Concomitant Medication CRF and appropriate comments are entered on the Comments CRF, if needed.
- Verify that reason(s) for allowing use of all exclusionary medications were documented on the Comments CRF.

Inclusion/Exclusion Criteria

- If it was noted that a patient did not meet the entire inclusion/exclusion criteria, make sure that the reason(s) for allowing this patient to enter the study is documented on the Comments CRF.

Drug Compliance

- Verify that the patient's compliance and adherence to the dosing regimen were entered on the Drug Compliance electronic CRF.
- If the patient was non-compliant with the dosing regimen, make sure it is documented on the Comments CRF.

Laboratory Data

- Verify that explanations of **all** clinically significant (CS) laboratory values are entered on the Comments electronic CRF.
- Verify that abnormal laboratory values have not been captured as adverse events.

Data Review

Data Review is an *administrative* review of the data for *computer fit* types of errors. For any data collected via electronic CRFs, data review will not require manual review since the electronic database performs these checks simultaneously as the data are entered into the system.

Data Capture

Once the monitors have source data verified all necessary data, and have appropriately documented any discrepancies on the query log, the monitor should send the following to Lilly for data entry purposes: the white copy of the CRFs, and the investigator signed queries.

Signature Log

The signature log in the CTRB must be signed by the monitor and all others visiting the study site.

Overall Study Documentation

The overall study documentation may be maintained in the Clinical Trial Records Binder (for example, protocols, amendments, informed consent documents, and documentation of approvals by ethical review boards). The Global Clinical Investigation manual and other study binders such as the Clinical Investigator's Brochure must also be available for review. Using the regulatory Compliance Worksheet to check for completeness, monitors should review study documentation at the audit visit, during the source data verification visits, and at the close-out visit. Additional reviews should be considered if there are other revisions to the study that would affect documentation.

Phase IV: Close Out

- Verify that the site has completed all required close-out procedures (i.e., archiving the printouts of the electronic CRFs and associated query logs, source documents, and the CTRB related to this study, ensure that all outstanding queries have been resolved, ensure that drug accountability has been reconciled, verify that all SAEs have been documented and that each contains a resolution, and ensure that the investigator has signed off on all data for each patient).
- Verify that all equipment supplied by Lilly to the site (i.e., laptop computer(s)) is returned.
- The signature log in the CTRB must be signed by the monitor and all others visiting the study site.

Monitor Training

Appropriate documentation of qualifications will be obtained from all study monitors, and study specific training will be provided to all monitors. The Monitoring Plan for LY11040, Protocol B1Y-MC-X065 will be provided to the monitors. Questions regarding the implementation of this document can be directed to the coordinating Lilly CRA(s) or the Lilly Clinical Research Physician (CRP) responsible for the study.

Updates to Plan

The Monitoring Plan will be reviewed periodically and will be updated and altered as necessary. The most recent approved version of the Monitoring Plan will take precedence over any other version.

Plan Approval

This Monitoring Plan has been written/approved by:

[redacted]

6/15/99
Date

6/21/99
Date

Date

d by:

15 June 1999
Date

Jun 15, 1999
Date

6/15/99
Date

[redacted]

6-15-99
Date

06-16-99
Date

16.1.17.
Data Validation Plan

Data Validation Plan and Paperflow Document--Study B1Y-MC-X065 (FLUOXETINE)

Purpose: This document serves as a guide for: 1) mapping out the flow of paper and data throughout the course of the data collection and source data verification segments of this project, and 2) documenting data validation methods, establishing a consistent endpoint at which study data are considered clean.

Abbreviations used in this document are the following: PETS, CRF, CIA, CRA, SDV

Prozac Electronic Transcription System (PETS) is the electronic data transcription system that will serve as the vehicle for data collection of all additional required study data not currently in the Lilly cleaning database. Clinical data will be entered via PETS 'electronic CRFs from the remote site. The data entered electronically in the remote database will be transferred to the Lilly cleaning database. This system will be used by the investigative site through a GRAS connection, and also by in-house personnel, locally. The PETS system is also a data cleaning vehicle, as it contains field edits active at the time of data entry, and will allow cleaning of data from SDV of paper CRFs created electronically by the PETS system.

Source Data Verification (SDV) is the verification of source document data (the location where the data was originally captured) as compared to the data recorded on the CRFs. These CRFs will contain all study data originally entered into the electronic database and the additional required data entered via electronic CRFs.

Case Report Forms (CRF) will be printouts of the Lilly cleaning database and will be used as a tool for source data verification.

Clinical Investigative Assistant (CIA) This is the blinded in-house person with Lilly cleaning database access for the purposes of making data changes (resulting from resolved queries) to the Lilly cleaning database through the PETS system.

Clinical Research Associate (CRA) This is the person responsible for coordination of all cleaning activities and generating queries based on ad-hoc edits.

CRITERIA TO DETERMINE A CLEAN DATABASE

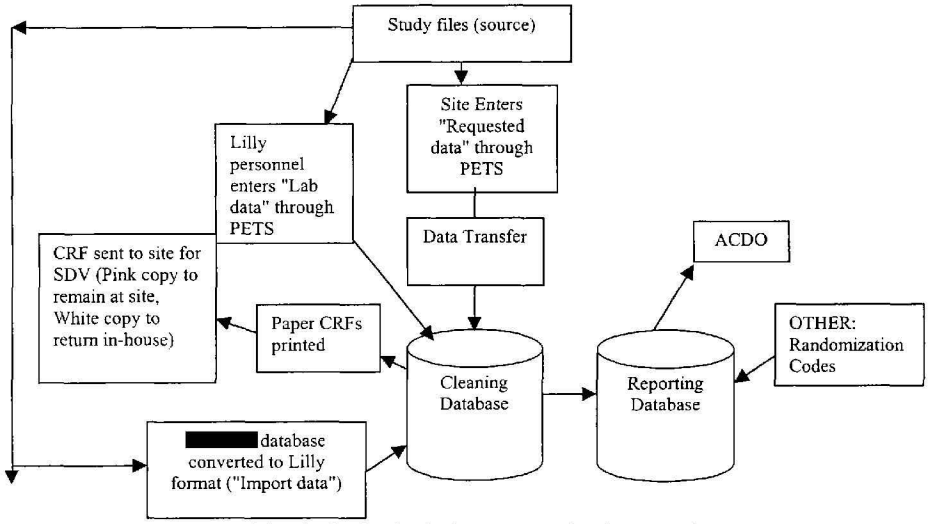
The database will be considered clean when all validation checks listed in this plan have been reviewed and all identified errors corrected.

CLEANING AND VALIDATION STRATEGY:

Dataflow:

The process for data flow and the cleaning strategy for the CRF packets are presented below.

DATAFLOW



Due to the variety of sources of data for the cleaning database, some explanation of terminology is required:

"Import Data" = data collected electronically by the site, and subsequently converted into the Lilly Cleaning database. This data will be SDV'd once printed onto CRFs.

"Requested Data" = data collected during the study but not yet entered electronically. This data will be entered by the site through the PETS system. This data will then be SDV'd once printed onto CRFs.

"Lab Data" = data collected during the study but not yet entered electronically. This data will be entered by Lilly personnel through the PETS system. This data will then be SDV'd once printed onto CRFs.

Due to the fact that data was not originally captured on CRFs, some explanation of CRF generation is required:

There are two sets of "CRFs" in this study. Paper CRFs will be printed for all study data from the cleaning database and will contain the study data present in this database. These will be printed after data entry and prior to data SDV. The electronic CRFs are the mode of data entry for the "Requested data" and the "Lab data", and are transcribed through the PETS system. The paper CRFs correlate to the PETS electronic CRFs as far as their content (i.e. the "Vitals" CRF will contain the same information as displayed on the "Vitals" PETS electronic CRF).

The table below depicts the CRF visit packet layout (numbers in the boxes indicate CRF page numbers). The highlighting corresponds to the classification of that data as "Import Data", "Requested Data" or "Lab Data". The site will have access only to those PETS electronic CRFs containing fields designated to be data

entered by the site (the "Requested data"). The Lilly CIA will have access to all PETS electronic CRFs (the "Import data", "Requested data" and "Lab data"), and the ability to add a patient or a patient visit record into the system via a separate batch process. The Lilly personnel designated to enter the "Labs data" will have access to all PETs electronic CRFs. An audit trail (part of the PETS system) will document and identify changed data, and the personnel who changed it.

Data classification and organization

LILLY VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	SUMMARY
SOURCE VISIT NUMBER	P0,P1, P2,P3	T0	T1	T2	T3	T4	T5	T6	T7	T8, T9	
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											
[redacted]											
DEMOGRAPHICS (INCL ICD)	2										
COMPLIANCE	18	13	14	14	14	14	14	14	14	14	15
COMMENTS	19	15	16	16	16	17	16	16	16	17	18
[redacted]											
[redacted]											
CONCOMITANT MEDICATIONS	20	20	20	20	20	20	20	20	20	20	20
SPONTANEOUS AEs	21	21	21	21	21	21	21	21	21	21	21
ECG	7										
LABS	5					15				15	16
ELECTROLYTES											
ALBUMIN											
ENZYMES											
THYROIDS											
CBC											
URINALYSIS											
UNSCHEDULED LABS	6	14	15	15	15	16	15	15	15	16	17
VITALS	4	2	2	2	2	2	2	2	2	2	3
SUMMARY											1
SUMMARY COMMENTS											19

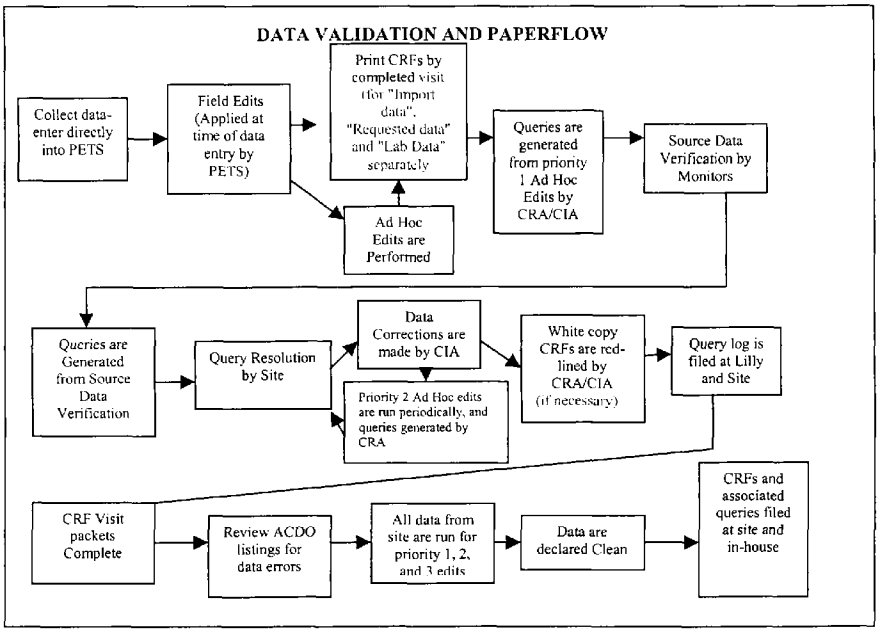
Details of data fields (variables) present on each CRF (electronic or paper) can be found in Attachment 1 of this document.

[redacted]

Requested Data = DATA ENTERED BY SITE, THEN SDV'D AT SITE
Labs Data = DATA ENTERED AT LILLY, THEN SDV'D AT LILLY

Data Validation and Paperflow:

The following flowchart depicts the Data validation process and paperflow.



1. Site data entry personnel enter "Requested data " into the PETS system (electronic CRFs). Once all data for a given patient has been entered, site personnel will acknowledge this via a designated keystroke entry in the PETS system. This data will then become available for printing onto paper CRFs for SDV. Lilly personnel will enter "Lab data" into the PETS system via electronic CRFs. Once data for a given patent has been entered, Lilly personnel will acknowledge this via a paper tracking log. This data will then become available for printing onto paper CRFs for SDV.
2. CRFs are printed by patient visit initially for all pre-existing "Import data".
3. Additional CRFs ("Requested data" and "Lab data") will be printed on a weekly basis from the print queue. "Requested data" CRFs will be sent to the site for SDV on a weekly basis. "Lab data" CRFs will remain in-house, and will be SDV'd in-house, by someone other than who entered the data.
4. Once a CRF has been SDV'd, the Monitor will initial and date each page indicating SDV is complete.
5. Ad hoc edits with a priority of 1 will be printed initially by Systems. These are edits that will identify errors to existing data that would be identified in a field edit as defined in the data formats document if this data were being entered.
6. The ad-hoc edits will be converted into queries by a CRA or CIA.
7. Queries generated from ad-hoc edits will be sent to the site with the accompanying CRFs for SDV.
8. Any data issues arising during SDV that require investigator resolution (see Attachment 4 for those that do not) will generate a query at the time of SDV. These would be issues that could not be detected by an ad-hoc or field edit.
9. Once a query has been resolved by the site, it will be reviewed, initialed, and dated by the Monitor, and sent in-house on a weekly basis.
10. Resolved queries will be directed to the CIA, who will review and make the appropriate changes to the database through the PETS system. The CIA will initial and date each query as the database is changed. A copy will be made and sent to the site.

11. If the CIA identifies an issue with a resolved query, the CIA will generate a new query to be resolved by the site for further explanation.
12. The in-house CRAs will notify the monitors when an entire patient CRF packet is clean, and the CRFs can be separated. The monitor will then verify the patient packet has been signed and dated by the investigator or designee. The CRF will be separated, the white copy sent in house and the pink copy will remain at the site. Pink copies of the "Lab data" will be sent to the site.
13. Priority 2 Ad-hoc edits will be run at least monthly and reviewed only for those datasets/patient visits that have been data entered (i.e. for printed CRFs) and SDV'd, as a check on CIA data correction accuracy.
14. Priority 1 and 2 ad-hoc edits will be re-run once all data collection, SDV, and query resolution is thought complete. ACDO listings will also be reviewed for data errors, and queries generated, if necessary.
15. Priority 3 ad-hoc edits will be run once all priority 1 and 2 ad-hoc edits are resolved. If necessary, queries will be generated to resolve any issues identified from these edits.
16. PETS audit trail will be reviewed to ensure no unauthorized (without a query) changes were made to any data subsequent to the SDV process.

The following table depicts the owners (and their blinding status) of the activities involved in the data validation and paperflow activities. Since the results of this study have been published, certain activities must be performed by blinded personnel (see Blinding Plan).

Functional Groups responsible for Validation and Paperflow Activities

	Clinical	Systems	Site
Collect Data	X (CIA) or O [CRA (Lab data)]		O (Site Coordinators)
Print CRFs		O	
Run Ad Hoc Edits		O	
Source Data Verification	O (Monitors)		
SDV Queries Generated	O (CRAs, Monitors), X(CIA)		
Query Resolution			O (site investigator or designee)
Data Corrections	X (CIA)		
CRFs filed	X(CIA), O(CRA, Monitor)		
PETS audit trail review		O	
Tracking	O (CRA) and X (CIA, AA)		

* X=blinded, O=unblinded

Data Collection and SDV Tracking

Data Entry activities will be tracked by 1) the PETS system (via audit trail, and completion status as keyed by the site personnel) and 2) weekly by tracking logs submitted to a coordinating CRA in-house. Tracking will occur in increments of patient visits for each set of data ("Requested data" and "Lab data").

Data SDV will be tracked weekly by tracking logs submitted to a coordinating CRA in-house. Tracking will be monitored weekly in increments of patient visits for each set of data ("Requested data", "Import data", and "Lab data").

VALIDATION METHODS

There are two types of edits for this study data:

1. Field edits will be applied at the time of data entry (i.e. for the "Requested data" and "Lab data"), and are defined in the data formats document in Attachment 2 of this document).
2. Ad-hoc data integrity checks (edits) will be performed periodically during the data collection process and will be applied to the cleaning database as a whole rather than to a specific patient or patient visit. These ad-hoc edits will include checks equivalent to the field edits for the "Import data", as it already resides in the cleaning database. Queries will be generated from each line-listing item resulting from these edits. Queries will be resolved by the site when necessary. (See Attachment 4 of this document for situations where this is not necessary).

The table of all project specific ad-hoc edits is in Attachment 5 of this document.

DATA VALIDATION PROCESS

The following table identifies and outlines the process flow for the cleaning steps.

Data validation requirements:

Edit or Report type	Query or report name or no. (if an established query)	Responsible Functional area for generation	Responsible Functional Area for Review and F/U	Frequency	Comments
Ad-hoc Priority 1		Systems	Clinical	Initially	To identify all blanks, and invalid data in the "Import data".
Ad- hoc Priority 2		Systems	Clinical	At least monthly	To identify/monitor errors introduced during data collection of "Requested data" or "Lab data" or by data correction.
Ad- hoc Priority 1,2, and 3		Systems	Clinical	During final validation	To identify any remaining blank records, and to determine if system is really clean, and no new issues have arisen during data cleaning, and that no queries have gone unadressed.
ACDO reports	all	Systems	Clinical, Systems, Stats	Periodically, and during final validation	Check for data outliers particularly for key data elements. Provide to stats.
ACDO listings	all	Systems	Clinical, Systems, Stats	Periodically, and during final validation	Check for data outliers particularly for key data elements. Provide to CRAs.
PETS audit trail review		Systems	Clinical	During final validation	To make sure that no unauthorized changes were made to the database after SDV.
Database Quality Review					Comparison of CRF to host listings.

Note: Final validation begins when all known queries have been resolved and data entered.

Database Quality Review

A Database Quality Review is a comparison of output data against the original CRF data.

A Database quality review will be conducted. The statistician will determine the estimated number of patients which will be used for the review and which reports and listings will be needed for the review.

TRANSFERS TO HOST

This study data already resides in the "Host" which is the MVS system. Please refer to the Systems document entitled "Prozac Electronic Transcription System 16 Points of Validation" for procedures involving transfer of data from the cleaning database to the reporting database.

Scheduled data lock transfers

Only one datalock transfer is scheduled. This will take place once the database is declared clean by the terms outlined in this document.

REVISIONS TO THE PLAN

Changes to this plan will be retroactive (if validation methods are added to the plan, they will be applied to previously reviewed CRFs

ATTACHMENTS:

Attachment 1. Unique CRF visit packets and accompanying instructions.
Attachment 2. Data Formats Document
Attachment 3. Monitoring Plan
Attachment 4. Data issues not requiring investigator resolution or signature
Attachment 5. B1Y-MC-X065 Edits

APPROVALS:

Approved by:

DMC or CRA signature Date

Statistician signature Date

Attachment 1. Unique CRF visit packets and accompanying instructions.

Attachment 2. Data Formats Document

Attachment 3. Monitoring Plan

Attachment 4. Data issues not requiring investigator resolution or signature:

1. Verified .X in any num field
2. Blank records in any dataset
3. Spelling errors
4. Reordering AX1DIAG1-5 field data among these fields
5. Deletion of Adverse event or con med data with stop dates prior to ICD dates
6. Info not obtained for missing CDI if have BDI, and vice-versa
7. "Info not obtained" or it's equivalent for a scale/item that should not have been collected for a visit(i.e. CGI-I for Visits 1 and 2

Attachment 5: B1Y-MC-X065 edits (Ad Hoc Edits)

B1Y-MC-X065 Ad-Hoc Edits

Key for "Priority" column: This pertains to run frequency and timing for SDV:
1= Run Initially
2= Run at least monthly
3= Run once all priority 1 and 2 ad-hoc edits are resolved.
Key for "When" column: A-Can be done after Datalock; B-Should be done before Datalock.

CRF Module	Edit	When	Priority
BECKD	Flag if BECKD01-21 value is blank	B	1
	Flag if BECKD01-21 value is invalid (range=0-3, inclusive)	B	1
	Flag if neither data for BECKD01-21 is provided nor "information not obtained" is checked or if both data for BECKD01-21 and "information not obtained" are provided.	B	2
	Verify that no blank records exist in the dataset	B	1
BPRSC	Flag if BPRS01-21 value is blank	B	1
	Flag if BPRS01-21 value is invalid (range=0-6, inclusive)	B	1
	Flag if rater initials are invalid (range = A-Z, -)	B	1
	Flag if neither data for BPRS01-21 is provided nor "information not obtained" is checked or if both data for BPRS01-21 and "information not obtained" are provided.	B	2
	Verify that no blank records exist in the dataset	B	1
CDI	Flag if CDI01-27 value is blank	B	1
	Flag if CDI01-27 value is invalid (range=0-3, inclusive)	B	1
	Verify that no blank records exist in the dataset	B	1
	Flag if neither data for CDI01-27 is provided nor "information not obtained" is checked or if both data for CDI01-27 1 and "information not obtained" are provided.	B	2
CDRSR	Flag if CDRS01-17(EXCLUDING CDRS04, 05,and 16) value is invalid (range=0-7, inclusive)	B	1
	Flag if CDRS01-17 is blank	B	1
	Flag if CDRS04, 05, 0R 16 value is invalid (range=0-5, inclusive)	B	1
	Flag if rater initials are invalid (range = A-Z, -)	B	1
	Verify that no blank records exist in the dataset	B	1
	Flag if neither data for CDRS01-17is provided nor "information not obtained" is checked or if both data for CDRS01-17and "information not obtained" are provided.	B	2
CGIPGI	Flag if CGISEVER value is invalid (range=0-7, inclusive)	B	1
	Flag if CGISEVER or CGIIMPRO are blank	B	1
	Flag if "info not obtained is not checked for V1-2 for CGIIMPRO	B	2
	Verify that no blank records exist in the dataset	B	1
	Flag if rater initials are invalid (range= A-Z, -)	B	1
	Flag if CGIIMPRO value invalid (range=0-7, inclusive)	B	1
	Flag if neither data for CGISEVER OR CGIIMPRO is provided nor "information not obtained" is checked or if both data for CGISEVER OR CGIIMPRO and "information not obtained" are provided.	B	2
COMMENTS			
	Flag if "no comments" is checked and a comment is listed (and vice versa).	B	2
COMPLNCE			
	Flag if SDDOSMIS is greater than 0	A	
	Flag if SD_COMPL = 2 or 97	A	
	Verify that no blank records exist in the dataset	B	3
	Flag if neither data is provided nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2
EVENTS MODULE			
	Flag if any required field is blank	B	2

	Flag if event is serious	B	3
	Flag if COSTART term does not map to a term in the COSTART dictionary. *List both mapped and non-mapped events (including chronic illnesses).*	B	2
	Flag if "no adverse events" is checked and an adverse event is listed (and vice versa).	B	2
	For any EVENT provided on the pre-existing conditions and adverse events page, flag if any of the following are missing: ONSET DATE, STOP DATE, SERIOUS, SOURCE OF INFO.	B	2
	For any EVENT provided on the pre-existing conditions and adverse events page, flag if the onset date is after the stop date.	B	2
	For any EVENT provided on the pre-existing conditions and adverse events page, flag if SERIOUS is YES and at least one outcome code is not provided (CANC_ETC, DISABIL, HOSP).	B	2
GLSLABS			
	Flag if neither data is provided nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2
	Flag if MMDDYYYY (lab draw date) is before 10SEPT1990	B	2
	For laboratory data collection (GLSLABS), flag if neither collection date is provided nor "unknown" is checked or both are provided.	B	2
	For laboratory data collection (GLSLABS), flag if neither date of lab report is provided nor "unknown" is checked or both are provided.	B	2
	Flag if date of lab report or collection date is > 1 year before the visit 1 date or after visit 1 date.	B	3
	For each laboratory test in GLSLABS, flag if RESULTS are provided but any of the following are missing: UNITS (except for URINALYSIS), REFERENCE RANGE (LOW/HIGH).	B	2
	For each laboratory test in GLSLABS, flag if RESULTS are abnormal.	B	3
	For unscheduled labs, flag if collection date is prior to informed consent date or greater than the last visit date.	B	2
	For unscheduled labs, flag if results are greater than 2x the upper limit of normal.	A	
	For unscheduled labs, flag if no unscheduled labs are checked but laboratory data are present (and vice versa).	B	2
	For unscheduled labs, flag if results are provided but no AE code is listed.	B	2
INVECG	Flag if neither data is provided nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2
	If EKG date is provided, flag if it is before SEPT101990.	B	2
	If EKG results are ABNORMAL, flag if no comment is provided.	B	2
	Verify that no blank records exist in the dataset	B	3
OTHERAPY MODULE			
	Flag if STOP DATE is before the ICD DATE	B	2
	Flag is trade drug not found in WHO dict.	B	2
	Flag if ONSET DATE is after STOP DATE	B	2
	Flag if "no medications" is checked and a medication is listed (and vice versa).	B	2
	For each concomitant medication, flag if start date is after stop date.	B	2
	For each concomitant medication, flag if stop date is before the informed consent date.	B	2
PATDEMOG			
	Flag if any required field is blank	B	3
	Flag if consent date is not equal to V1 date.	B	3
	Flag if any ICDDATE is not between 10SEPT1990 and 12DEC1994 inclusive	A	
	Flag if patient age (calculated from PSIBDATE-BIRTHDAT) is not between 8 and 18, inclusive	B	3
	Verify that no blank records exist in the dataset	B	3
	Verify there is exactly one record/patient in the dataset	B	3
PATMISC			

	Flag if any required field is blank	B	2
	Verify that no blank records exist in the dataset	B	3
	Verify there is exactly one record/patient in the dataset	B	3
PSYDIAG			
	Flag if any one of AX1DIAG1-5 =296.4x, 296.5x, 296.6x, 296.7x, 307.1, 307.51, 305.xx	B	3
	Flag if any one of AX1DIAG1 is not = 296.2x OR 296.3x	B	1
	Flag if duration of illness (DURILL) is greater than age in years - 10 or is <=1 year.	B	1
	Flag if PREVTX=8	B	1
	Verify that no blank records exist in the dataset	B	3
	Verify there is exactly one record/patient in the dataset	B	3
SECLFLX			
	Verify that no blank records exist in the dataset	B	1
	Flag if value is invalid (range = 0-4, inclusive)	B	1
	Flag if neither data is provided for FSE01-30 nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2
SECLPT			
	Verify that no blank records exist in the dataset	B	1
	Flag if value is invalid (range = 0-4, inclusive)	B	1
	Flag if neither data is provided for SE01-32 nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2
SUMMARY	Flag If XREFNUM in SUMMARY does not have a "Y" In DRUGDISC field, and vice-versa	B	3
	Verify that no blank records exist in the dataset	B	3
	Flag if DISCDATE is before last visit date	B	2
	Flag if DISCDATE is blank or is before 10SEPT1990	B	2
	Flag if reason for ending participation in the study is PATIENT DECISION-OTHER but no specify is listed	B	2
	Flag if any required field is blank	B	3
	FLAG if patient completed the study (PROTOCOL COMPLETED) but data from visit 10 was not provided on at least one of the efficacy rating scales (CDRS,CGI-I,CGI-S,BPRS)	B	2
	Flag if the reason for ending participation in the study is ADVERSE EVENT but the e-code does not map to a valid E_CODE or the E_CODE is blank	B	2
	Flag if DISCDATE is before consent date or before V1 date	B	2
	Flag if LDOSEDAT is after DISCDATE or before consent date or before Visit 1	B	2
	Verify the dataset has one record and no more than one record for every patient	B	3
VIS_STAT			
	Flag if VISDATE is after DISCDATE or DTH_DATE	B	2
	Flag if VISDATE is before consent date	B	2
	Flag if patient has missing/skipped visit number	B	2
	Flag if the visit dates are not in chronological order	B	2
	Flag if any visit date was not between 10SEPT1990 and 14DEC1994 inclusive	B	2
	Flag if visit interval is >13 days	A	
	Verify that no blank records exist in the dataset	B	3
	Verify the dataset has no more than one record for patient/visit	B	3
VITALS	Flag if neither data is provided nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2
	Flag if any required field is blank.	B	3
	If HEIGHTCM is provided, flag if it is not 36-80, inclusive.	B	2
	If heart rate is provided, flag if it is outside of the range 40-160, inclusive.	B	2
	If systolic blood pressure is provided, flag if it is outside of the range 70-200, inclusive.	B	2
	If diastolic blood pressure is provided, flag if it is outside of the range 40-110,	B	2

	inclusive.		
	If weight (kg) is provided, flag if it is outside of the range 80-350, inclusive.	B	2
	Verify that no blank records exist in the dataset	B	3
	Verify the dataset has no more than one record for patient/visit	B	3
MANUAL EDITS	Flag if the investigator did not sign CRF page XX.	B	3

[redacted] (303) 948-6652 p.2

Confidential

APPROVALS:

Approved by:

[redacted]

6/14/99
Date

6/14/99
Date

Data Validation Plan and Paperflow Document--Study B1Y-MC-X065 (FLUOXETINE)

Purpose: This document serves as a guide for: 1) mapping out the flow of paper and data throughout the course of the data collection and source data verification segments of this project, 2) documenting data validation methods, establishing a consistent endpoint at which study data are considered clean, and 3) documenting the data quality review that will be completed before datalock to assure the data is clean.

Abbreviations used in this document are the following: PETS, CRF, CIA, CRA, SDV

Prozac Electronic Transcription System (PETS) is the electronic data transcription system that will serve as the vehicle for data collection of all additional required study data not currently in the Lilly cleaning database. Clinical data will be entered via PETS 'electronic CRFs from the remote site. The data entered electronically in the remote database will be transferred to the Lilly cleaning database. This system will be used by the investigative site through a GRAS connection, and also by in-house personnel, locally. The PETS system is also a data cleaning vehicle, as it contains field edits active at the time of data entry, and will allow cleaning of data from SDV of paper CRFs created electronically by the PETS system.

Source Data Verification (SDV) is the verification of source document data (the location where the data was originally captured) as compared to the data recorded on the CRFs. These CRFs will contain all study data originally entered into the electronic database and the additional required data entered via electronic CRFs.

Case Report Forms (CRF) will be printouts of the Lilly cleaning database and will be used as a tool for source data verification.

Clinical Investigative Assistant (CIA) This is the blinded in-house person with Lilly cleaning database access for the purposes of making data changes (resulting from resolved queries) to the Lilly cleaning database through the PETS system.

Clinical Research Associate (CRA) This is the person responsible for coordination of all cleaning activities and generating queries based on ad-hoc edits.

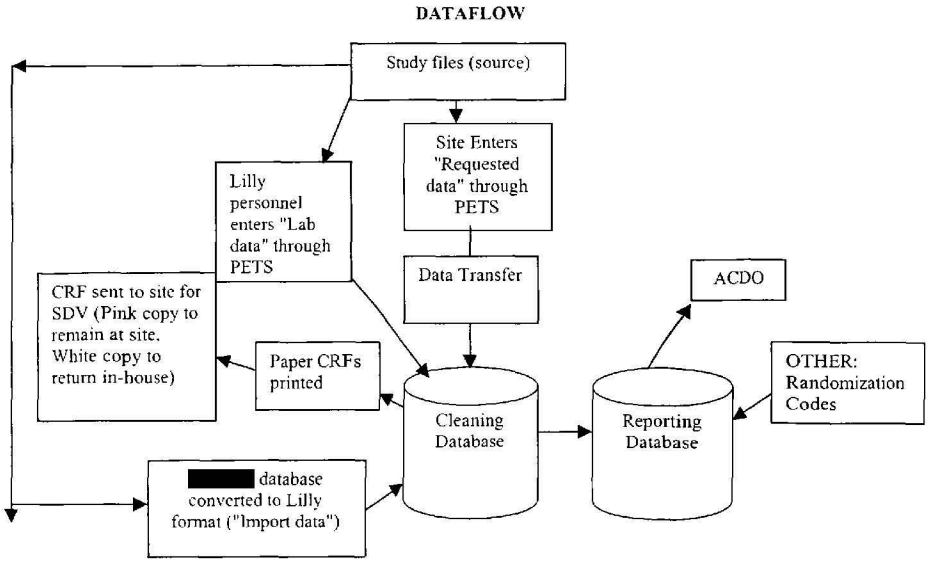
CRITERIA TO DETERMINE A CLEAN DATABASE

The database will be considered clean when all validation checks listed in this plan have been reviewed and all identified errors corrected.

CLEANING AND VALIDATION STRATEGY:

Dataflow:

The process for data flow and the cleaning strategy for the CRF packets are presented below.



Due to the variety of sources of data for the cleaning database, some explanation of terminology is required:

"Import Data" = data collected electronically by the site, and subsequently converted into the Lilly Cleaning database. This data will be SDV'd once printed onto CRFs.

"Requested Data" = data collected during the study but not yet entered electronically. This data will be entered by the site through the PETS system. This data will then be SDV'd once printed onto CRFs.

"Lab Data" = data collected during the study but not yet entered electronically. This data will be entered by Lilly personnel through the PETS system. This data will then be SDV'd once printed onto CRFs.

Due to the fact that data was not originally captured on CRFs, some explanation of CRF generation is required:

There are two sets of "CRFs" in this study. Paper CRFs will be printed for all study data from the cleaning database and will contain the study data present in this database. These will be printed after data entry and prior to data SDV. The electronic CRFs are the mode of data entry for the "Requested data" and the "Lab data", and are transcribed through the PETS system. The paper CRFs correlate to the PETS electronic CRFs as far as their content (i.e. the "Vitals" CRF will contain the same information as displayed on the "Vitals" PETS electronic CRF).

The table below depicts the CRF visit packet layout (numbers in the boxes indicate CRF page numbers). The highlighting corresponds to the classification of that data as "Import Data", "Requested Data" or "Lab Data". The site will have access only to those PETS electronic CRFs containing fields designated to be data

entered by the site (the "Requested data"). The Lilly CIA will have access to all PETS electronic CRFs (the "Import data", "Requested data" and "Lab data"), and the ability to add a patient or a patient visit record into the system via a separate batch process. The Lilly personnel designated to enter the "Labs data" will have access to all PETs electronic CRFs. An audit trail (part of the PETS system) will document and identify changed data, and the personnel who changed it.

Data classification and organization

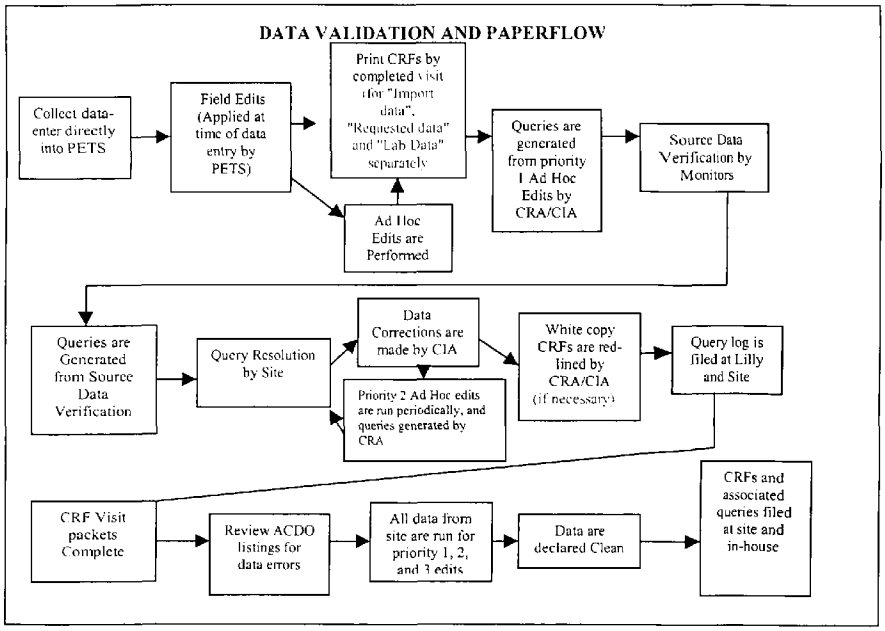
LILLY VISIT NUMBER	1	2	3	4	5	6	7	8	9	10	SUMMARY
SOURCE VISIT NUMBER	P0,P1, P2,P3	T0	T1	T2	T3	T4	T5	T6	T7	T8, T9	
CGI-S	9	4	4	4	4	4	4	4	4	4	5
CGI-I			4	4	4	4	4	4	4	4	5
BPRS	10	11	11	11	11	11	11	11	11	11	12
CDRS	8	3	3	3	3	3	3	3	3	3	4
BDI	10, 11	5,6	5,6	5,6	5,6	5,6	5,6	5,6	5,6	5,6	5,6
CDI	12-15	7-10	7-10	7-10	7-10	7-10	7-10	7-10	7-10	7-10	8-11
PSYCHIATRIC HISTORY	3										
DEMOGRAPHICS (INCL ICD)	2										
COMPLIANCE	18	13	14	14	14	14	14	14	14	14	15
COMMENTS	19	15	16	16	16	17	16	16	16	17	18
FLUOXETINE SE CKLST			13	13	13	13	13	13	13	13	14
SE CHECKLIST	17	12	12	12	12	12	12	12	12	12	13
CONCOMITANT MEDICATIONS	20	20	20	20	20	20	20	20	20	20	20
SPONTANEOUS AEs	21	21	21	21	21	21	21	21	21	21	21
ECG	7										
LABS	5					15				15	16
ELECTROLYTES											
ALBUMIN											
ENZYMES											
THYROIDS											
CBC											
URINALYSIS											
UNSCHEDULED LABS	6	14	15	15	15	16	15	15	15	16	17
VITALS	4	2	2	2	2	2	2	2	2	2	3
SUMMARY											1
SUMMARY COMMENTS											19

Details of data fields (variables) present on each CRF (electronic or paper) can be found in Attachment 1 of this document.

Import Data = DATA SDV'D ONLY
Requested Data = DATA ENTERED BY SITE, THEN SDV'D AT SITE
Labs Data = DATA ENTERED AT LILLY, THEN SDV'D AT LILLY

Data Validation and Paperflow:

The following flowchart depicts the Data validation process and paperflow.



1. Site data entry personnel enter "Requested data " into the PETS system (electronic CRFs). Once all data for a given patient has been entered, site personnel will acknowledge this via a designated keystroke entry in the PETS system. This data will then become available for printing onto paper CRFs for SDV. Lilly personnel will enter "Lab data" into the PETS system via electronic CRFs. Once data for a given patent has been entered, Lilly personnel will acknowledge this via a paper tracking log. This data will then become available for printing onto paper CRFs for SDV.
2. CRFs are printed by patient visit initially for all pre-existing "Import data".
3. Additional CRFs ("Requested data" and "Lab data") will be printed on a weekly basis from the print queue. "Requested data" CRFs will be sent to the site for SDV on a weekly basis. "Lab data" CRFs will remain in-house, and will be SDV'd in-house, by someone other than who entered the data.
4. Once a CRF has been SDV'd, the Monitor will initial and date each page indicating SDV is complete.
5. Ad hoc edits with a priority of 1 will be printed initially by Systems. These are edits that will identify errors to existing data that would be identified in a field edit as defined in the data formats document if this data were being entered.
6. The ad-hoc edits will be converted into queries by a CRA or CIA.
7. Queries generated from ad-hoc edits will be sent to the site with the accompanying CRFs for SDV.
8. Any data issues arising during SDV that require investigator resolution (see Attachment 4 for those that do not) will generate a query at the time of SDV. These would be issues that could not be detected by an ad-hoc or field edit.
9. Once a query has been resolved by the site, it will be reviewed, initialed, and dated by the Monitor, and sent in-house on a weekly basis.
10. Resolved queries will be directed to the CIA, who will review and make the appropriate changes to the database through the PETS system. The CIA will initial and date each query as the database is changed. A copy will be made and sent to the site.

11. If the CIA identifies an issue with a resolved query, the CIA will generate a new query to be resolved by the site for further explanation.
12. The in-house CRAs will notify the monitors when an entire patient CRF packet is clean, and the CRFs can be separated. The monitor will then verify the patient packet has been signed and dated by the investigator or designee. The CRF will be separated, the white copy sent in house and the pink copy will remain at the site. Pink copies of the "Lab data" will be sent to the site.
13. Priority 2 Ad-hoc edits will be run at least monthly and reviewed only for those datasets/patient visits that have been data entered (i.e. for printed CRFs) and SDV'd, as a check on CIA data correction accuracy.
14. Priority 1 and 2 ad-hoc edits will be re-run once all data collection, SDV, and query resolution is thought complete. ACDO listings will also be reviewed for data errors, and queries generated, if necessary.
15. Priority 3 ad-hoc edits will be run once all priority 1 and 2 ad-hoc edits are resolved. If necessary, queries will be generated to resolve any issues identified from these edits.
16. PETS audit trail will be reviewed to ensure no unauthorized (without a query) changes were made to any data subsequent to the SDV process.

The following table depicts the owners (and their blinding status) of the activities involved in the data validation and paperflow activities. Since the results of this study have been published, certain activities must be performed by blinded personnel (see Blinding Plan).

Functional Groups responsible for Validation and Paperflow Activities

	Clinical	Systems	Site
Collect Data	X (CIA) or O [CRA (Lab data)]		O (Site Coordinators)
Print CRFs		O	
Run Ad Hoc Edits		O	
Source Data Verification	O (Monitors)		
SDV Queries Generated	O (CRAs, Monitors), X(CIA)		
Query Resolution			O (site investigator or designee)
Data Corrections	X (CIA)		
CRFs filed	X(CIA), O(CRA, Monitor)		
PETS audit trail review		O	
Tracking	O (CRA) and X (CIA, AA)		

* X=blinded, O=unblinded

Data Collection and SDV Tracking

Data Entry activities will be tracked by 1) the PETS system (via audit trail, and completion status as keyed by the site personnel) and 2) weekly by tracking logs submitted to a coordinating CRA in-house. Tracking will occur in increments of patient visits for each set of data ("Requested data" and "Lab data").

Data SDV will be tracked weekly by tracking logs submitted to a coordinating CRA in-house. Tracking will be monitored weekly in increments of patient visits for each set of data ("Requested data", "Import data", and "Lab data").

VALIDATION METHODS

There are two types of edits for this study data:

1. Field edits will be applied at the time of data entry (i.e. for the "Requested data" and "Lab data"), and are defined in the data formats document in Attachment 2 of this document).
2. Ad-hoc data integrity checks (edits) will be performed periodically during the data collection process and will be applied to the cleaning database as a whole rather than to a specific patient or patient visit. These ad-hoc edits will include checks equivalent to the field edits for the "Import data", as it already resides in the cleaning database. Queries will be generated from each line-listing item resulting from these edits. Queries will be resolved by the site when necessary. (See Attachment 4 of this document for situations where this is not necessary).

The table of all project specific ad-hoc edits is in Attachment 5 of this document.

DATA VALIDATION PROCESS

The following table identifies and outlines the process flow for the cleaning steps.

Data validation requirements:

Edit or Report type	Query or report name or no. (if an established query)	Responsible Functional area for generation	Responsible Functional Area for Review and F/U	Frequency	Comments
Ad-hoc Priority 1		Systems	Clinical	Initially	To identify all blanks, and invalid data in the "Import data".
Ad- hoc Priority 2		Systems	Clinical	At least monthly	To identify/monitor errors introduced during data collection of "Requested data" or "Lab data" or by data correction.
Ad- hoc Priority 1,2, and 3		Systems	Clinical	During final validation	To identify any remaining blank records, and to determine if system is really clean, and no new issues have arisen during data cleaning, and that no queries have gone unadressed.
ACDO reports	all	Systems	Clinical, Systems, Stats	Periodically, and during final validation	Check for data outliers particularly for key data elements. Provide to stats.
ACDO listings	all	Systems	Clinical, Systems, Stats	Periodically, and during final validation	Check for data outliers particularly for key data elements. Provide to CRAs.
PETS audit trail review		Systems	Clinical	During final validation	To make sure that no unauthorized changes were made to the database after SDV.
Database Quality Review		Systems, Clinical	Clinical	During Final validation	Comparison of CRF to host listings and audit trail.

Note: Final validation begins when all known queries have been resolved and data entered.

Database Quality Review

A Database Quality Review is a comparison of output data against the original CRF data.

A Database quality review will be conducted. The statistician will determine the estimated number of patients which will be used for the review and which reports and listings will be needed for the review.

TRANSFERS TO HOST

This study data already resides in the "Host" which is the MVS system. Please refer to the Systems document entitled "Prozac Electronic Transcription System 16 Points of Validation" for procedures involving transfer of data from the cleaning database to the reporting database.

Scheduled data lock transfers

Only one datalock transfer is scheduled. This will take place once the database is declared clean by the terms outlined in this document.

REVISIONS TO THE PLAN

Changes to this plan will be retroactive (if validation methods are added to the plan, they will be applied to previously reviewed CRFs

ATTACHMENTS:

Attachment 1. Unique CRF visit packets and accompanying instructions.
Attachment 2. Data Formats Document
Attachment 3. Monitoring Plan
Attachment 4. Data issues not requiring investigator resolution or signature
Attachment 5. B1Y-MC-X065 Edits
Attachment 6. PETS Issues

APPROVALS:

Approved by:

DMC or CRA signature Date

Statistician signature Date

Attachment 1. Unique CRF visit packets and accompanying instructions.

SITE INSTRUCTIONS FOR DATA COLLECTION STUDY B1Y-MC-X065

SECTION I
GENERAL INSTRUCTIONS

RELEASING DATA TO LILLY

When all data for a given patient has been data entered, proceed to the SUMMARY screen, and respond with a "Y" to the question " **THIS IS THE SUMMARY RECORD. HAVE YOU ENTERED ALL DATA?".** At this point, the system will perform an automatic edit check to ensure the following:

- There is at least one record of comment type "SU" for the patient (which at the summary visit).
- There is at least on record of comment type "PA"(Patient Demographics), "VL"(Vitals), "CP"(Pill Count), or "GN" (General) for each visit for this patient.
- There is one and only one record for PILL COUNTS for each patient visit.
- There is one and only one record for PATIENT DEMOGRAPHICS for this patient
- There is one and only one record for VITAL SIGNS for each patient visit.
- There is at least one record for CONCOMITANT MEDICATIONS for the patient.
- There is at least one record for PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS for the patient

If any of the above edits fails, the system will display an error at the top of the SUMMARY screen, indicating which records are missing. Proceed to the appropriate screen, and make the necessary entries.

Please note that this edit check is at the record, and not the field level. All fields are required at the time of data entry within each screen (exit from the screen will not be allowed otherwise) with the exception of stop dates for concomitant medications and pre-existing conditions and adverse events. Please review all stop date fields for completion before releasing data to Lilly.

CHANGING VISIT NUMBERS

Selecting this item pulls up the screens for Pill Count, Vitals, and Comments for visit numbers to be changed. In order to change a visit number, enter patient number and visit number. Then tab to Pill Count, Vitals, or Comments. After hitting enter, the appropriate screen will appear. At this point, change the visit number to correct number. Hit pf3 to save changes.

SECTION II
DATA COLLECTION INSTRUCTIONS FOR "REQUESTED DATA"

CRF Title: Concomitant Medications

ENTER 'X' IF NO CONCOMITANT MEDICATIONS WERE TAKEN:

If the patient did not take any medications other than study drug **during the entire study**, enter "X". Entry of any other information on this screen will not be allowed, and any existing data on the screen will require deletion prior to exiting the screen. Creating this record will prevent entries of any concomitant medications for this patient, unless this record is deleted first.

START DATE:

For medications that the patient began taking **during** the course of the study, or was already taking upon entering the study (Visit 1), enter the month, day, and year (MM/DD/YY) that the patient began taking the medication. If the start date is unknown, enter a SINGLE dash (-) in those fields. If only the year is known, enter 01/01 as the month and day of that year. If only the month and year are known, enter 01 for the day of that month and year. If the source documents do not reflect a date, the date should be recorded based on the following guidelines:

1. If the patient or clinician recorded a medication on a dated source document with no further follow-up, record the start and stop date as the same date of the source document.

   For example, if a patient's source document dated 03/23/91 reported that the patient had taken tylenol and the start and stop date for this medication was not recorded, use 03/23/91 as both the start and stop date for this medication.

2. If the patient or clinician recorded a medication on a dated source document that said "tylenol for the last week". Record the start date as 7 days prior to the data of the source document it was written on. In other words, if the data can be calculated based on information that was recorded, do so.

Any date prior to 01/01/70 or after 12/31/96 will not be accepted.

STOP DATE:

Enter the month, day, and year (MM/DD/YY) that the patient stopped taking the medication. If the date is unknown, enter a SINGLE dash (-) in that field. If the source documents do not reflect a date, the date should be recorded based on the following guidelines:

3. If the patient or clinician recorded a medication on a dated source document with no further follow-up, record the start and stop date as the same date of the source document.

For example, if a patient's source document dated 03/23/91 reported that the patient had taken tylenol and the start and stop date for this medication was not recorded, use 03/23/91 as both the start and stop date for this medication.

4. If a start date was found for a medication, but no stop date can be found on any of the source documents, assume the medication is ongoing, and record the stop date as a SINGLE dash "-".

5. If the patient or clinician recorded a medication on a dated source document as "tylenol stopped 3 days ago", record the stop date as three days prior to the date of the source document it was written on. In other words, if the data can be calculated based on information that was recorded, do so.

6. If the patient or clinican recorded a medication on a dated source document as "took tylenol 3 times last week", record this as 3 separate records, each with a start date the same as the stop date, for each of the first 3 days of the current visit during which this information was recorded.

   For example, if a patient's source document dated 3/21/91 at Visit 3 reported " took tylenol 3 times last week ", and Visit 2 occurred on 3/14/91, 3 records of "tylenol" would be recorded, one with start and stop dates of 3/15/91, one with start and stop dates of 3/16/91, and the third with start and stop dates of 3/17/91.

If administration of the medication was ongoing at the end of the patient's participation in the study (including death), enter a SINGLE dash (-) in the stop date field.

Any date prior to 9/10/90 or after 12/31/96 will not be accepted. In addition, any stop date that is prior to the entered start date will not be accepted.

INDICATION FOR USE (IFU):

This field will be automatically defaulted for your convenience to "97"= "unknown". If the indication for use was written in the source documents then choose ONE of the appropriate codes:

XREFNUM

If the medication was being used to treat a pre-existing condition or adverse event, record the XREFNUM event code (1, 2, etc.) from the patient's PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS screen to indicate which condition was being treated. Only XREFNUMs that currently exist will be permitted for entry.

"X01"

If the medication was being used to treat the primary study condition, record "X1".

"X02"

If the medication is being used for prophylaxis (eg, Benadryl prior to blood transfusion) or non-therapeutic use (eg, vitamins), record "X2".

If the drug was taken for more than one condition, record the code for the ***primary*** indication for use.

Valid entries for this field are : X01, X02, or 1-99. Note that uppercase letters MUST be used.

DRUG NAME

Enter all medication (other than study drug), using brand or trade names as the drug is recorded in the source documents, that the patient was taking **at study entry** and **during the study**. Include all prescription medications and over-the-counter medications. Non-drug therapies that have healing or curative qualities can also be entered on this page; ***do not*** record non-therapeutic agents (eg, mouthwash, cold packs) or therapeutic classes of drugs. Refer to the dictionary that is provided by Lilly; this dictionary contains a listing of drugs (based on the World Health Organization (WHO) dictionary). It is important to record the drug name **EXACTLY** as noted in the WHO dictionary, including all spacing, punctuation, and spelling, since the computer sees the drug name as a code.

Intermittent or cyclical drug therapies should be collected each time that the patient took the medication. For example, if the patient took aspirin PRN for 3 days from May 1, 1991-May 3, 1991, then enter each day that the patient took the aspirin as a separate day recording that day's date as both the start and stop date.

This is a 40 character field.

PREFERRED TERM

This field can be ignored at the time of data entry. Do not make any entries into this field. This field is automatically populated with the WHO term for the drug entered in the DRUG NAME field, if possible, once the data is released to Lilly.

GENERAL INFORMATION:

When creating a record, mandatory fields include DRUG NAME, START DATE, and IFU. The STOP DATE must be entered prior to releasing data to Lilly for any given patient.

CRF Title: Vital Signs

INFORMATION NOT OBTAINED:

If no information on vital signs can be found in the source, enter an "X" in this field, and no other information should appear on this CRF. Any existing data on the screen will require deletion prior to exiting the screen.

HEIGHT/UNITS:

Valid range for height is 24-84 inches, or 61-213 centimeters. Enter as appears in source. Valid options for units include: C = centimeters and I = inches. The system will default to "C" for units for your convenience. A conversion table is provided in Attachment 2 of this document for conversion to height in inches.

WEIGHT/UNITS:

Valid range for weight is 40-300 pounds, or 18.0-136.1 kilograms. Enter as appears in source. Valid options for units include: K = kilograms and P = pounds. The system will default to "K" for units for your convenience.

HEART RATE:

Valid range for heart rate = 40-160 bpm.

BLOOD PRESSURE:

Valid range for systolic blood pressure = 70-200 mmHg.
Valid range for diastolic blood pressure = 40-110 mmHg.

NOTE:

The patient was assumed to have been in the sitting position when the blood pressure and heart rate was measured. If it is noted in the progress note that these items were measured using an alternative positioning of the patient, it should be noted on the COMMENTS CRF.

CRF Title: Pre-Existing Conditions and Study Adverse Events Data

NO CONDITIONS OR EVENTS BOX

If the patient had no pre-existing conditions or events during the entire study, an "X" should appear in the "NO CONDITIONS OR EVENTS" box, and no other information should appear on the screen. Entry of any other information on this screen will not be allowed, and any existing data on the screen will require deletion prior to exiting the screen. Creating a record with no events, will prevent entries of any Pre-existing conditions or adverse events for this patient, unless this record is deleted first.

DESCRIPTION

A ***pre-existing condition*** is any chronic or acute sign, symptom, illness, or condition that the patient has at the time of entering the trial (i.e.Visit 1). Include those conditions that are seasonal, cyclical, or intermittent (e.g., premenstrual syndrome, seasonal allergies, etc.). The actual primary study condition (depression) need not be recorded, nor do those signs and symptoms associated with the primary study condition.

An ***event*** is any physiological or psychological change (including surgical procedures) that occurred to the patient *at any time* during the study. Do not to record procedures that were required by the protocol. ALL events must be reported, whether or not they were believed to be possibly related to the study drug or protocol. Injuries and accidents should be reviewed for possible causes (i.e., dizziness or somnolence).

Because scales were used when doing a clinical interview, signs and symptoms associated with the primary study condition were captured on the scales, any signs and symptoms recorded on research notes are considered solicited, and should not be captured on the Pre-existing Conditions and Study Adverse Events CRF, with the exception of events of injury/accident or an illness.

Psychiatric Axis I pre-existing conditions diagnoses are found under the visit titled "CN", on a worksheet titled "Consensus Diagnosis", under a heading of "DSMIII-R Dx", and are codes as DSM-III codes. If the patient elicited features of a disorder, (this will be indicated by _OD (Only when depressed), or _R (residual) following an uncoded abbreviation of the disorder), this information must be captured on the CRF, and distinguished as a feature rather than a diagnosis in the event description.

When reviewing the patient's charts for adverse events, make sure to review the physician's progress notes, and any handwritten notation by item #32 on the Side Effect Checklist. On the Side Effect Checklist, if the patient answered affirmatively to Item #32, "Other" record what was entered by the patient as an adverse event on the Pre-existing Conditions and Study Adverse Events CRF screen.

Begin recording all pre-existing conditions that were present at the time of study entry (Visit 1). As new events occurred, record them at the appropriate visit. Monitor all pre-existing conditions and events until each event was resolved.

If an event stopped and later restarted, the stop date of the original event must be entered and the new event must be recorded on another line with a new event code.

If the patient had a syndrome, such as deep vein thrombosis, a separate entry for each sign or symptom (e.g., redness, swelling, and pain) must be entered as well as the diagnosis (deep vein thrombosis).

For treatment under this protocol, an overdose was any intentional or unintentional consumption of the study drug (by any route) that exceeded the maximum daily number of dosage units permitted in the fluoxetine package insert. Record this as an "accidental overdose" or "intentional overdose," whichever applies, as an event.

If the patient had an event that was considered an unexpected or ***unanticipated benefit*** to the patient (e.g., sleeping longer), the condition or event's description must include the word "benefit" (e.g., "benefit of sleeping longer").

Record all clinically relevant abnormalities found on the physical exam.

Record each event name exactly as it appears in source, even if the wording of the event is not clear. This is an 80 character field.

START DATE

For a ***pre-existing condition***, if the start date is unknown, enter a SINGLE dash in that field. A date prior to 1/1/70 or later than 12/31/96 will not be accepted.

A complete date of month, day, and year MUST be given for the onset date of each event. The date must be recorded in the format MM/DD/YY. If only the year is known, enter 01/01 as the month and day of that year. If only the month and year are known, enter 01 for the day of that month and year. If the source documents do not reflect a date, the date should be recorded based on the following guidelines:

7. If the patient or clinician recorded an event on a dated source document with no further follow-up, record the start and stop date as the same date of the source document.

   For example, if a patient's source document dated 03/23/91 reported that the patient had an ear infection and the start and stop date for this event was not recorded, use 03/23/91 as both the start and stop date for this event.

8. If the patient or clinician recorded an event on a dated source document that said "headache for the last week". Record the start date as 7 days prior to the data of the source document it was written on. In other words, if the data can be calculated based on information that was recorded, do so.

STOP DATE

If the pre-existing condition or event was ongoing at the end of the patient's participation in the study or at Visit 10 (including death), enter a SINGLE dash (-) in the stop date field.

A complete date of month, day, and year MUST be given for the stop date of each event. The date must be recorded in the format MM/DD/YY. A date prior to 1/1/90 or later than 12/31/96 will not be accepted. If the source documents do not reflect a date, the date should be recorded based on the following guidelines:

9. If the patient or clinician recorded an event on a dated source document with no further follow-up, record the start and stop date as the same date of the source document.

   For example, if a patient's source document dated 03/23/91 reported that the patient had an ear infection and the start and stop date for this event was not recorded, use 03/23/91 as both the start and stop date for this event.

10. If a start date was found for an event, but no stop date can be found on any of the source documents, assume the event is ongoing, and record the stop date as a SINGLE dash "-".

11. If the patient or clinician recorded an event on a dated source document as "headache stopped 3 days ago", record the stop date as three days prior to the date of the source document it was written on. In other words, if the data can be calculated based on information that was recorded, do so.

12. If the patient or clinican recorded an event on a dated source document as "had 3 headaches last week", record this as 3 separate events, each with a start date the same as the stop date, for each of the first 3 days of the current visit during which this information was recorded.

    For example, if a patient's source document dated 3/21/91 at Visit 3 reported "3 headaches last week", and Visit 2 occurred on 3/14/91, 3 events of "headache" would be recorded, one with start and stop dates of 3/15/91, one with start and stop dates of 3/16/91, and the third with start and stop dates of 3/17/91.

SERIOUS CRITERIA (DEATH, RESULT IN SEVERE OR PERMANENT DISABILITY, REQUIRE OR PROLONG HOSPITALIZATION, CANCER, OD, LIFE THREATENING, CONGENITAL ANOMOLY, DURING TRIAL?)

Ascertain whether the event was serious or not. Valid responses were 1= Yes, or 2=No for each of the above four questions.

A serious adverse event was defined as any event that meets the following criteria (consistent with the Food and Drug Administration criteria at the time the study was conducted):

Cancer - Is the condition or event a cancer of any kind?

A congenital anomaly - Is the condition or event a birth defect in the offspring of the patient exposed to the study drug?

Did an overdose occur?: An overdose occurred if the patient took more study drug than is specified in the CIB or meets what the protocol defines as an overdose.

Excessive doses of concomitant medications must also be reported as an overdose.

Life-threatening - Was the patient in *immediate* risk of dying? It does not include a reaction that, had it occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Permanently disabling - Did the condition or event cause the patient to be permanently disabled, physically or mentally?

Hospitalization - Did the condition or event require or prolong *inpatient* hospitalization? This does not include a visit to the hospital emergency room. The patient must have been admitted to the hospital (usually includes an overnight stay).

Fatal - Did the patient die?

The seriousness of a ***pre-existing condition*** should be evaluated only DURING the study; if a pre-existing condition was considered serious *prior* to the patient entering the study, do not record this condition as "serious" on the clinical report form, unless it became serious during the study.

If after Visit 1, a pre-existing condition met any of the serious criteria (e.g., caused the patient to be hospitalized), the sign or symptom causing the condition to become serious should be recorded as a new event; the pre-existing condition should remain the same and is left ongoing.

Example: At Visit 1 the patient had a pre-existing condition of severe diabetes. At Visit 7 the patient was hospitalized for hyperglycemia. The new event, "hyperglycemia," is recorded at Visit 7, while the pre-existing diabetes entry remains open and unchanged.

If a pre-existing condition or event never became serious *at any time during the study*, enter 2 for "NO" for each of the questions (e.g., did the event cause death, did the event require inpatient hospitalization, etc.) If a pre-existing condition or event became serious at any time *during the study*, enter 1 for "YES" to indicate the outcome of the event (e.g., event caused patient to discontinue from the study, event resulted in congenital anomaly, etc.). Enter 1 for "YES" for all answers that are applicable.

If the serious condition or event reverted back to a "non-serious" state (e.g., the patient's dehydration was corrected and the patient was discharged from the hospital) DO NOT DELETE THE SERIOUS CODE on the clinical report form (i.e., do not delete the 1 for "YES", for the hospitalization question or enter 2 for "NO". Once an event is designated as serious (i.e., a serious code is recorded) on the clinical report form, it should always remain that way (unless an error was made).

All events that result in a serious outcome should be designated "serious."

If a pre-existing condition or event was serious and was permanently disabling, caused hospitalization, congenital anomaly, cancer, overdose, or other reason, Lilly must be notified *within 24 hours* by telephone or fax. If the pre-existing condition or event was fatal or life-threatening, Lilly must be notified IMMEDIATELY by telephone.

Contact [redacted] if you have any questions. Their offices are open from 8:30 a.m. to 5:15 p.m. (Eastern Standard Time) Monday through Friday. All other times call [redacted] and your call will be directed to the appropriate person on duty.

XREFNUM CODE:

This field is automatically assigned by the PETs system, and provides that each pre-existing condition and event does indeed have its own *unique* XREFNUM (event reference number) code (e.g., 1, 2, 3). XREFNUMs are assigned sequentially.

IS THIS EVENT RELATED TO STUDY DRUG?:

Valid options include 1 = Yes, 2 = No, and "-" = Unknown.

The relationship of an event to a study drug (defined as Lilly investigational drug, active comparator [or placebo for *blinded* studies], or combination of Lilly drug used with another drug product) must have been assessed and documented by the investigator, in order for this information to be entered into the electronic database). For those events that were ongoing at the patient's final visit, the relationship must have been assessed and recorded at the time the event stopped or at the patient's final visit (early termination visit or Visit 10 if patient completed the trial).

Enter 1 if "YES" the condition, illness, sign, symptom, or event was thought, in the opinion of the investigator, to be possibly related to the study drug. Enter 2 if "NO", the condition, illness, sign, symptom, or event was NOT thought to be possibly related to study drug. Enter "-" for "UNKNOWN".

DID THIS EVENT CAUSE DISCONTINUATION?

Valid responses are 1 = Yes, 2 = No.

CRF Title: Summary

DATE OF DISCONTINUATION

This field may already be populated with data from the initial electronic database. If modifications are necessary, valid range is ≥ 9/10/90, and correct format is MM/DD/YY.

PRIMARY REASON FOR DISCONTINUATION

This field may already be populated with data from the initial electronic database. If modifications are necessary, valid reasons for discontinuation include:

011 = Protocol complete (if a patient completed Visit 10 or beyond)
081 = Adverse event (if a patient discontinued to an or multiple adverse events)
044 = Noncompliance (if a patient was discontinued due to noncompliance)
063 = Interim criteria not met (if a patient did not meet interim criteria at Visit 2)
062 = entry criteria not met (if a patient did not meet entry criteria at Visit 1 or 2)
041 = patient decision (if the patient/parent decided to discontinue the study)
021 = Lack of efficacy (if the patient/parent or physician felt the study drug was not effective)
031 = Lost to follow-up
091 = Death
051 = Physician decision (if the physician decided to discontinue the patient)
999 = Other

If a reason for discontinuation is not discernible for any patient, 031(Lost to follow-up) should be recorded.

DATE OF PATIENT DEATH

If the reason for discontinuation was DEATH (091), enter the date of death in MM/DD/YY format. A death date will not be accepted unless the reason for discontinuation was death. Conversely, a death date will be required if the reason for discontinuation was death.

IF OTHER, PLEASE SPECIFY

If the reason for discontinuation was OTHER (999) you will be required to provide further explanation as to why the patient discontinued from the study in this field. This field allows responses up to 30 characters in length. If more space is needed, enter the additional information onto the COMMENTS screen.

IF DUE TO AN ADVERSE EVENT, SPECIFY PRIMARY EVENT:

If the reason for discontinuation was ADVERSE EVENT (081) you will be required to enter the event reference number (XREF_NUM) that corresponds with the associated primary adverse event that led to the patient's discontinuation from the study. If the

patient discontinued due to multiple events, enter 999, and make sure that all events causing discontinuation are identified as such in the PRE-EXISTING CONDITIONS AND STUDY ADVERSE EVENTS DATA screen by entering a "1" in the "Did this event cause discontinuation?" field. Valid entries include only existing XREFNUM's.

DATE OF LAST STUDY DRUG DOSE

This date will automatically default to the date of study discontinuation. Valid range < 9/10/90. Valid format = MM/YY/DD. This is assumed to be the last visit date, or the discontinuation date, whichever is later. Please verify that this is the last known date that the patient was taking study drug. Dates later than that entered in DATE OF STUDY DISCONTINUATION will not be accepted. Acceptable ranges otherwise for this field are >/=9/10/90, and </=12/31/96.

THIS IS THE SUMMARY RECORD. HAVE YOU ENTERED ALL DATA?

Once ALL data has been entered for a given patient, reply "Y" to this question, otherwise answer "N". An edit check will be performed by the PETS system to ensure that all data entry fields have been completed. If not, the PETS system will prompt you of the fields that need to be addressed. Please refer to Section 1, General Instructions for more details surrounding this function.

CRF Title: Summary Comments

NOTE: Comments are labeled as Summary Comments (type SU) when accessed from the SUMMARY screen. The visit entered on the menu (which must correspond to the patient's last study visit) when accessing the SUMMARY screen will be the visit that the comment is associated with. At least one comment of type SU is required by the PETS system prior to releasing data to Lilly.

NO COMMENTS

If there are no comments, an "X" should appear in the box, and no other information should appear on this screen. Any existing information that is displayed on the screen will be required to be removed.

COMMENTS

Do not repeat information recorded previously as any other comment type. If an adverse event is discussed as a comment, it must also be recorded on the Pre-existing Conditions and Study Adverse Events Data screen.

Enter comments for any pertinent information that needs further explanation, i.e., concurrent medications; attempts made by site to contact a patient before declaring the patient "lost to follow-up"; significant clinical information; concomitant medications; non-compliance; etc.

To ensure confidentiality, avoid the use of a patient's full or partial name (including initials) on the "COMMENTS" CRF screen. If reference is made to the patient, use the phrase "this patient . . ."

Do not use abbreviations.

CRF Title: Comments

NOTE: Comments are labeled as General Comments (type GN) when accessed from the COMMENTS screen. Comments are labeled with other unique identifiers when accessed through other screens ("Do you have any comments Y/N?" at the bottom of the Vital Signs [type VL], Pill Counts [type CP, Patient Demographics [type PA]), At least one comment of any of the above type is required by the PETS system for each patient visit prior to releasing data to Lilly.

NO COMMENTS

If there are no comments, an "X" should appear in the box, and no other information should appear on this screen. Any existing information that is displayed on the screen will be required to be removed.

COMMENTS

If an adverse event (whether spontaneously reported or solicited from the checklists) is discussed on this CRF, verify that it is also recorded on the Pre-existing Conditions and Study Adverse Events CRF.

To ensure confidentiality, verify that the COMMENTS do not contain the patient's full or partial name (including initials). If reference is made to the patient, use the phrase "this patient . . .". The same is true for proper names of Lilly personnel. Use terms like Clinical Research Monitor (CRM), Lilly Clinical Research Associate (CRA), Lilly Physician or Clinical Investigation Assistant (CIA).

Provide comments for all clinically significant laboratory values that are outside a clinically accepted reference range or clinically significant values that differ importantly from previous values, if documented in source.

If it is noted in the progress note that the patient's vitals were measured using an alternative positioning of the patient (the patient was assumed to have been in the sitting position when the blood pressure and heart rate was measured), note this on the COMMENTS CRF.

If appropriate, indicate the CRF screen or scale to which the comment refers.

Enter all significant comments regarding the following:

- study drug compliance: if, when, and why the patient may have missed doses
- missed efficacy/safety scales/study procedures: why a scale was not administered, or why labs were not drawn

- concomitant medications: why a patient may have been on an exclusionary medication
- missed visits or visit intervals: record any skipped visits and why they were skipped
- unscheduled visits: why a patient may have had an unscheduled visit
- inclusion/exclusion criteria: why a patient who may not have met inclusion/exclusion criteria was admitted into the study
- GCP issues: record any issues regarding Informed Consent Documents (not signed, dated, wrond version used, etc.)

Do not use abbreviations.

CRF Title: Pill Counts

INFORMATION NOT OBTAINED

If no information was available, an "X" should appear in this box, and no other information should appear on this screen. Any existing information that is displayed on the screen will require removal prior to exiting the screen.

DOSING REGIMEN

Valid responses are 1=every day, 2= every other day, or 96 = not applicable. This field will automatically default to indicate that the patient was receiving 1 capsule a day (dosing regimen will equal "1"). Enter "2" if patient was to take one capsule every other day. It is assumed, unless otherwise noted in source documents, that the regimen was 1=every day.

The response should be "96" for the patient's last study visit.

If further explanation regarding the patient's compliance to his/her dosing regimen, is warranted, enter these comments onto the COMMENTS CRF screen. If the patient missed a full dose of study drug, then record the reason which the dose was missed. If a patient came in for an unscheduled visit and his/her study drug dose was adjusted then provide further explanation on the COMMENTS CRF screen.

CAPSULES DISPENSED

Valid options include: 0-99 or ".X" if missing or not applicable.
Do not include data pertinent to the follow-up phase (i.e. enter a ".X" in this field for the patient's last study visit.

CAPSULES RETURNED

Valid options include: 0-99 or ".X" if missing or not applicable.

CRF Title: Patient Demographics

Some of the data for the Patient Demographics Screen was previously entered as part of the initial electronic database. This data includes the following fields: DATE OF BIRTH, ORIGIN, SEX, HOLLINGSHEAD SOCIAL POSITION SCALE, STUDY DRUG KIT # . This data is view only. The cursor will not allow entry into these fields.

FAMILY STRUCTURE

Valid response range 0-10, or a dash "-" if missing or unknown.

PATIENT INITIALS

Enter the patient's initials (First, Middle, Last). If the patient did not have a middle name, then enter a "-" for this character. Enter a "-" if patient initials is unknown.

INFORMED CONSENT SIGNED DATE

The informed consent date must be entered in the MM/DD/YY format. If date is unknown or missing, a SINGLE dash "-" should be entered for this item. If the date is missing, this should be noted on the COMMENTS screen. The Informed Consent Document signed at study entry (Visit 1) is the one whose date should be entered. Verify appropriate signatures and dating on the document, and ensure that all comments are recorded on the COMMENTS CRF for any ICD issues.

DATE OF FIRST STUDY DRUG DOSE

This field will default to the day after Visit 1. Verify that the date the patient took his/her first dose of study drug was on the day after Visit 1. If the date was unknown or missing, enter a SINGLE dash (-) for this item. Valid range is >9/10/90. Date of first study drug dose was assumed to be the day after Visit 1, unless otherwise specified in source.

NOTES:

ATTACHMENT 1: CONVERSION TABLE FOR HEIGHT

ft	inches=	inches	ft	Inches=	inches
2	0	24	4	0	48
2	1	25	4	1	49
2	2	26	4	2	50
2	3	27	4	3	51
2	4	28	4	4	52
2	5	29	4	5	53
2	6	30	4	6	54
2	7	31	4	7	55
2	8	32	4	8	56
2	9	33	4	9	57
2	10	34	4	10	58
2	11	35	4	11	59
3	0	36	5	0	60
3	1	37	5	1	61
3	2	38	5	2	62
3	3	39	5	3	63
3	4	40	5	4	64
3	5	41	5	5	65
3	6	42	5	6	66
3	7	43	5	7	67
3	8	44	5	8	68
3	9	45	5	9	69
3	10	46	5	10	70
3	11	47	5	11	71
			6	0	72
			6	1	73
			6	2	74
			6	3	75
			6	4	76
			6	5	77
			6	6	78
			6	7	79
			6	8	80
			6	9	81
			6	10	82
			6	11	83
			7	0	84

Attachment 2. Data Formats Document

MAP OF DATA SETS TO CASE REPORT FORM PAGES

DATA SET NAME	DESCRIPTION	CRF PAGES	SORT BY
BECKD	Beck Depression Inventory		Patient, visit
BPRSC	Brief Psychiatric Rating Scale for Children		Patient, visit
CDI	Children's Depression Inventory		Patient, visit
CDRSR	Childhood Depression Rating Scale - Revised		Patient, visit
CGIPGI	Clinical Global Impressions		Patient, visit
COMMENTS	Comments		Patient, visit, com_type, line_num
COMPLNCE	Compliance		Patient, visit
EVENTS	Unsolicited Spontaneous Adverse Events		Patient, visit, xref_num
GLSLABS	Laboratory Results		Patient, visit, testcode
INVECG	ECG (EKG) Results		Patient, visit
OTHERAPY	Concomitant Medications		Patient, visit
PATDEMOG	Patient Demographics, randomized patients		Patient
PATDEMNR	Patient Demographics, nonrandomized patients		Patient
PATMISC	Miscellaneous Patient Demographics		Patient
PSYDIAG	Psychiatric Diagnosis Information		Patient
SECLFLX	Side Effects Check List for Fluoxetine		Patient, visit
SECLPT	Side Effects Check List completed by patient		Patient, visit
SUMMARY	Discontinuation Information		Patient
VIS_STAT	Visit Status		Patient, visit
VITALS	Vital Signs, Weight and Height		Patient, visit

BECKD DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_BDI DATA SET	*BECKD DATA SET*					*BECK DEPRESSION INDEX (SELF-RATING)*
CRFS	BDI_A	BECKD01	NUM	8	BECK FEELING SAD ITEM A	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_B	BECKD02	NUM	8	BECK DISCOURAGED FUTURE ITEM B	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_C	BECKD03	NUM	8	BECK FAILURE ITEM C	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_D	BECKD04	NUM	8	BECK SATISFIED ITEM D	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_E	BECKD05	NUM	8	BECK GUILTY ITEM E	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_F	BECKD06	NUM	8	BECK PUNISHED ITEM F	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_G	BECKD07	NUM	8	BECK SELF DISAPPOINTMENT ITEM G	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_H	BECKD08	NUM	8	BECK CRITICAL OF SELF ITEM H	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_I	BECKD09	NUM	8	BECK KILLING SELF ITEM I	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_J	BECKD10	NUM	8	BECK CRYING ITEM J	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_K	BECKD11	NUM	8	BECK IRRITATED ITEM K	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_L	BECKD12	NUM	8	BECK INTEREST IN OTHERS ITEM L	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_M	BECKD13	NUM	8	BECK DECISIONS ITEM M	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_N	BECKD14	NUM	8	BECK APPEARANCE ITEM N	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_O	BECKD15	NUM	8	BECK EFFORT ITEM O	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_P	BECKD16	NUM	8	BECK SLEEP ITEM P	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_Q	BECKD17	NUM	8	BECK TIRED ITEM Q	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_R	BECKD18	NUM	8	BECK APPETITE ITEM R	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS	BDI_S	BECKD19	NUM	8	BECK LOST WEIGHT ITEM S	Possible values: . , 0, 1, 2, 3	KEEP [redacted] VARIABLE LABEL
CRFS		BECKD19A	CHAR	1	BECK YES/NO TRYING TO LOSE WEIGHT ITEM S EXTRA QUESTION	1=Yes, 2=No, . = Not Available (DEFAULT)	
CRFS	BDI_T	BECKD20	NUM	8	BECK PHYSICAL PROBLEMS ITEM T	Possible values: . , 0, 1, 2, 3	KEEP [redacted] E VARIABLE LABEL
CRFS	BDI_U	BECKD21	NUM	8	BECK SEXUAL INTEREST ITEM U	Possible values: . , 0, 1, 2, 3	KEEP [redacted] E VARIABLE LABEL
CALC		BECKDTL	NUM	8	TOTAL SCORE BECKD01-BECKD21	POSSIBLE RANGE = ., 0 - 63 (cleaning edit only)	WARNING: DO NOT USE SUM FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING. DO NOT INCLUDE ITEM 19A.
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFS		INDBDI	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE = 'X065'	

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_BDI DATA SET	*BECKD DATA SET*					*BECK DEPRESSION INDEX (SELF-RATING)*
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	

BPRSC DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_FEV & R_TX DATA SET	*BPRSC DATA SET*					*BRIEF PSYCHIATRIC RATING SCALE FOR CHILDREN*
CRFS	BPR1	BPRS01	NUM	8	BPRS 1 UNCOOPERATIVENESS	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR2	BPRS02	NUM	8	BPRS 2 HOSTILITY	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR3	BPRS03	NUM	8	BPRS 3 MANIPULATIVENESS	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR4	BPRS04	NUM	8	BPRS 4 DEPRESSIVE MOOD	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR5	BPRS05	NUM	8	BPRS 5 FEELINGS OF INFERIORITY	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR6	BPRS06	NUM	8	BPRS 6 SUICIDAL IDEATION	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR7	BPRS07	NUM	8	BPRS 7 PECULIAR FANTASIES	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR8	BPRS08	NUM	8	BPRS 8 DELUSIONS	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR9	BPRS09	NUM	8	BPRS 9 HALLUCINATIONS	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR10	BPRS10	NUM	8	BPRS 10 HYPERACTIVITY	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR11	BPRS11	NUM	8	BPRS 11 DISTRACTIBILITY	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR12	BPRS12	NUM	8	BPRS 12 SPEECH OR VOICE PRESSURE	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR13	BPRS13	NUM	8	BPRS 13 UNDERPRODUCTIVE SPEECH	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR14	BPRS14	NUM	8	BPRS 14 EMOTIONAL WITHDRAWAL	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR15	BPRS15	NUM	8	BPRS 15 BLUNTED AFFECT	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR15	BPRS16	NUM	8	BPRS 16 TENSION	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR17	BPRS17	NUM	8	BPRS 17 ANXIETY	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR18	BPRS18	NUM	8	BPRS 18 SLEEP DIFFICULTIES	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR19	BPRS19	NUM	8	BPRS 19 DISORIENTATION	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_FEV & R_TX DATA SET	***BPRSC DATA SET***					***BRIEF PSYCHIATRIC RATING SCALE FOR CHILDREN***
CRFS	BPR20	BPRS20	NUM	8	BPRS 20 SPEECH DEVIANCE	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CRFS	BPR21	BPRS21	NUM	8	BPRS 21 STEREOTYPY	.=missing, 0=Not Present, 1=Very Mild, 2 =Mild, 3=Moderate, 4=Mod. Severe, 5 = Severe, 6=Extremely Severe	
CALC		BPRSTL	NUM	8	TOTAL SCORE BPRS01-BPRS21	POSSIBLE RANGE = ., 0-126 (cleaning edit only)	WARNING: DO NOT USE SUM FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING.
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC"	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFS		INDBPRS	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE = 'X065'	
CRFS	RATER	RATER	CHAR	3	INITIALS OF THE EVALUATOR	Valid Initials: A-Z, - = Initial Not Available	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	***(rater – for a pt at a visit select the Emslie visit with the X.1 extension. If X.1 not avail, then select X.2)***

CDI DATA SET

VARAIBLE SOURCE	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_CDI DATA SET	*CDI DATASET*					*CHILDREN'S DEPRESSION INVENTORY*
CRFS	CDI_1	CDI01	NUM	8	CDI ITEM 1 SAD FEELING	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_2	CDI02	NUM	8	CDI ITEM 2 WORK OUT	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_3	CDI03	NUM	8	CDI ITEM 3 DO THING OK	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_4	CDI04	NUM	8	CDI ITEM 4 FUN	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_5	CDI05	NUM	8	CDI ITEM 5 BAD	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_6	CDI06	NUM	8	CDI ITEM 6 WORRY	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_7	CDI07	NUM	8	CDI ITEM 7 HATE SELF	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_8	CDI08	NUM	8	CDI ITEM 8 FAULT	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_9	CDI09	NUM	8	CDI ITEM 9 KILLING SELF	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_10	CDI10	NUM	8	CDI ITEM 10 CRYING	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_11	CDI11	NUM	8	CDI ITEM 11 IRRITATION	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_12	CDI12	NUM	8	CDI ITEM 12 LIKE PEOPLE	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_13	CDI13	NUM	8	CDI ITEM 13 DECISIONS	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_14	CDI14	NUM	8	CDI ITEM 14 APPEARANCE	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_15	CDI15	NUM	8	CDI ITEM 15 EFFORT	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_16	CDI16	NUM	8	CDI ITEM 16 SLEEPING	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_17	CDI17	NUM	8	CDI ITEM 17 TIRED	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_18	CDI18	NUM	8	CDI ITEM 18 APPETITE	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_19	CDI19	NUM	8	CDI ITEM 19 PHYSICAL COMPLAINTS	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_20	CDI20	NUM	8	CDI ITEM 20 FEELS ALONE	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_21	CDI21	NUM	8	CDI ITEM 21 FUN SCHOOL	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_22	CDI22	NUM	8	CDI ITEM 22 FRIENDS	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_23	CDI23	NUM	8	CDI ITEM 23 SCHOOL WORK	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_24	CDI24	NUM	8	CDI ITEM 24 GOOD AS OTHERS	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_25	CDI25	NUM	8	CDI ITEM 25 LOVES ME	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_26	CDI26	NUM	8	CDI ITEM 26 DO AS TOLD	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CRFS	CDI_27	CDI27	NUM	8	CDI ITEM 27 FIGHTING WITH OTHERS	Possible values: ., 0, 1, 2	KEEP [redacted] VARIABLE LABEL
CALC		CDITL27	NUM	8	TOTAL SCORE CDI01-CDI27	POSSIBLE RANGE = ., 0 - 54 (cleaning edit only)	WARNING: DO NOT USE SUM FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING.
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFS		INDCDI	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	

VARAIBLE SOURCE	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_CDI DATA SET	*CDI DATASET*					*CHILDREN'S DEPRESSION INVENTORY*
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE = 'X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	

CDRSR DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_CK1 AND R_TX DATA SETs	*CDRSR DATA SET*					*CHILDHOOD DEPRESSION RATING SCALE – REVISED*
CRFS	CDR1	CDRS01	NUM	8	CDRSR ITEM 1 SCHOOLWORK	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR2	CDRS02	NUM	8	CDRSR ITEM 2 FUN	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR3	CDRS03	NUM	8	CDRSR ITEM 3 SOCIAL WITHDRAWAL	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR4	CDRS04	NUM	8	CDRSR ITEM 4 SLEEP	Possible Values: . , 1-5	KEEP [redacted] VARIABLE LABEL
CRFS	CDR5	CDRS05	NUM	8	CDRSR ITEM 5 APPETITE	Possible Values: . , 1-5	KEEP [redacted] VARIABLE LABEL
CRFS	CDR6	CDRS06	NUM	8	CDRSR ITEM 6 FATIQUE	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR7	CDRS07	NUM	8	CDRSR ITEM 7 PHYSICAL COMPLAINTS	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR8	CDRS08	NUM	8	CDRSR ITEM 8 IRRITABILITY	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR9	CDRS09	NUM	8	CDRSR ITEM 9 GUILT	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR10	CDRS10	NUM	8	CDRSR ITEM 10 SELF-ESTEEM	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR11	CDRS11	NUM	8	CDRSR ITEM 11 DEPRESSED	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR12	CDRS12	NUM	8	CDRSR ITEM 12 MORBID IDEATION	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR13	CDRS13	NUM	8	CDRSR ITEM 13 SUICIDAL	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR14	CDRS14	NUM	8	CDRSR ITEM 14 WEEPING	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR15	CDRS15	NUM	8	CDRSR ITEM 15 DEPRESSED AFFECT	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR16	CDRS16	NUM	8	CDRSR ITEM 16 SPEECH	Possible Values: . , 1-5	KEEP [redacted] VARIABLE LABEL
CRFS	CDR17	CDRS17	NUM	8	CDRSR ITEM 17 HYPOACTIVITY	Possible Values: . , 1-7	KEEP [redacted] VARIABLE LABEL
CRFS	CDR18	CDRS18	CHAR	2	CDRSR ITEM 18 MOOD	Possible Values: ' ', A-E	KEEP AS CHARACTER VARIABLE
CALC		CDRSBEHA	NUM	8	BEHAVIOR SUBTOTAL (SUM OF CDRS ITEMS 1, 2, 3)	POSSIBLE RANGE: ., 3-21 (cleaning edit only)	BEHAVIOR SUBTOTAL (SUM OF CDRS ITEMS 1, 2, 3) WARNING: DO NOT USE SUM FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING.
CALC		CDRSMOOD	NUM	8	MOOD SUBTOTAL (SUM OF CDRS ITEMS 8, 11, 14, 15)	POSSIBLE RANGE: ., 4-28 (cleaning edit only)	MOOD SUBTOTAL (SUM OF CDRS ITEMS 8, 11, 14, 15) WARNING: DO NOT USE SUM FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING.
CALC		CDRSSOMA	NUM	8	SOMATIC SUBTOTAL (SUM OF CDRS ITEMS 4, 5, 6, 7, 16, 17)	POSSIBLE RANGE: ., 6-36 (cleaning edit only)	SOMATIC SUBTOTAL (SUM OF CDRS ITEMS 4, 5, 6, 7, 16, 17) WARNING: DO NOT USE SUM FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING.
CALC		CDRSSUBJ	NUM	8	SUBJECTIVE SUBTOTAL (SUM OF CDRS ITEMS 9, 10, 12, 13)	POSSIBLE RANGE: ., 4-28 (cleaning edit only)	SUBJECTIV SUBTOTAL (SUM OF CDRS ITEMS 9, 10, 12, 13) WARNING: DO NOT USE SUM

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_CK1 AND R_TX DATA SETs	***CDRSR DATA SET***					***CHILDHOOD DEPRESSION RATING SCALE – REVISED***
							FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING.
CALC		CDRSTL17	NUM	8	TOTAL SCORE CDRS01-CDRS17	POSSIBLE RANGE: .. 17-113 (cleaning edit only)	WARNING: DO NOT USE SUM FUNCT. TOTAL = MISSING IF ANY INDIV ITEM MISSING.
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC"	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFS	RATER	RATER	CHAR	3	INITIALS OF THE EVALUATOR	Valid Initials: A-Z, - = Initial Not Available	
CRFS		INDCDR	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE = 'X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y"	
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	***(rater – for a pt at a visit select the Emslie visit with the X.1 extension. If X.1 not avail, then select X.2)***

CGIPGI DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_FEV AND R_TX DATA SETS	*CGIPGI DATA SET*					*CLINICAL GLOBAL IMPRESSIONS*
CRFS	CGI_IMP	CGIIMPRO	NUM	8	CGI - IMPROVEMENT	Possible Values: . , 0-7 for Visits 3-10	at Visit 1 (P0) and Visit 2 (T0) default = . (MISSING). Cleaning edit should allow for missing at baseline if indicator variable is 'INFO NOT OBTAINED'
CRFS	CGI	CGISEVER	NUM	8	CGI - SEVERITY	Possible Values: . , 0-7	
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC''	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFS		INDCGII	CHAR	1	INDICATES INFO NOT OBTAINED-CGI-I	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
CRFS		INDCGIS	CHAR	1	INDICATES INFO NOT OBTAINED-CGI-S	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE = 'X065'	
CRFS	RATER	RATER	CHAR	3	INITIALS OF THE EVALUATOR	Valid Initials: A-Z, - = Initial Not Available	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	***(rater – for a pt at a visit select the Emslie visit with the X.1 extension. If X.1 not avail, then select X.2)***

COMMENTS DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	DATA SET (NONE)	*COMMENTS*					
CRFD		COM_TEXT	CHAR	80	COMMENT TEXT		
CALC		COM_TYPE	CHAR	2	COMMENT RECORD TYPE	GN = General SU = Summary EC=ECG	ASSIGNED A VALUE AT COMMENT DATA ENTRY DEPENDING ON THE PARENT DATA ENTRY SCREEN.
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC"	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFD		INDCOM	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
DEFA		LINE_NUM	CHAR	5	LINE NUMBER	ASSIGN SEQUENTIALLY WITHIN RECORD TYPE	
CRFS		PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE = 'X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFD		SIGNATUR	CHAR	30	COMMENTS SIGNATURE FLAG	BLANK	
CRFD		SIGNDATE	CHAR	6	COMMENTS SIGNATURE DATE	BLANK	
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS		VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	

COMPLNCE DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	DATSET (R_PRS)	*COMPLNCE*					*PILL COUNT INFORMATION*
CRFD		DRGREG	CHAR	2	PROSPECTIVE DRUG REGIMEN (EVERY DAY OR EVERY OTHER DAY)	1=EVERY DAY (DEFAULT TO 1 AT VISITS 3 THRU NEXT TO LAST PT VISIT) 2=EVERY OTHER DAY 96=NOT APPLICABLE (DEFAULT AT LAST VISIT)	
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFS		INDCOMP	CHAR	1	INDICATES DISP, RETN, DRGREG INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE = 'X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CALC		SD_COMPL	CHAR	2	PATIENT COMPLIANT?	1=Yes, 2=No, 97=Unknown (if not able to calculate) IF DRGREG=1 THEN DO; IF SDDOSMIS <=2 THEN SD_COMPL=1; ELSE SD_COMPL=2; END; IF DRGREG=2 THEN DO; IF SDDOSMIS <=1 THEN SD_COMPL=1; ELSE SD_COMPL=2; END;	DERIVED VARIABLE, NOT COLLECTED
CRFS	MED_G	SDCAPDIS	NUM	8	STUDY DRUG - CAPSULES DISPENSED (PROSPECTIVE)	Range for edits 0-99, - if not available	DRUG INVENTORY - QUANTITY DISPENSED
CRFS	MED_R	SDCAPRET	NUM	8	STUDY DRUG - CAPSULES RETURNED (CURRENT)	Range for edits 0-99, - if not available	DRUG INVENTORY - QUANTITY RETURNED
CALC		SDDOSMIS	NUM	8	NUMBER OF MISSED DOSES (RETROSPECTIVE)	NUMDAYS=VISIT DATE-LAST VISIT DATE; CAPS TAKEN=LAST SDCAPDIS-SDCAPRET; IF DRGREG='2' THEN NUMDAYS=ROUND(NUMDAYS/2.1); IF CAPS TAKEN > . AND NUMDAYS > . THEN DO; IF CAPS TAKEN >= NUMDAYS THEN SDDOSMIS=0; ELSE SDDOSMIS=NUMDAYS-CAPS TAKEN;	
DEFA		T_RSNMIS	CHAR	1	REASON FOR MISSED DOSE	BLANK	

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	

EVENTS DATA SET (UNSOLICITED ADVERSE EVENTS)

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	DATA SET (NONE)	*EVENTS DATA SET*					*UNSOLICITED ADVERSE EVENTS*
DEFA		ABATED	CHAR	1	ABATED AFTER STOPPING DRUG	BLANK, NOT ON CRF	
CRFD		ACT_TERM	CHAR	80	ACTUAL TERMINOLOGY		Make Uppercase
DEFA		BODYSYS	CHAR	5	BODY SYSTEM		(Lookup by COSTART)
CRFD		CANC_ETC	CHAR	1	CANCER, OD, LIFETHREAT, CONGENANOM	1=Yes, 2=No	Default to 2
CALC		CLASTERM	CHAR	64	EVENT CLASSIFICATION TERM – ELECT (COSTART)	Must exist in COSTART dictionary	Mapped from standard actual term. If actual term not standard - must be manually assigned during cleaning process.
CRFD		DEATH	CHAR	1	PATIENT DIED?	1=Yes, 2= No	Default to 2
CRFD		DISABIL	CHAR	1	RESULT IN SEVERE OR PERM DISABILITY	1=Yes, 2= No	Default to 2
CRFD		DRUGDISC	CHAR	1	WAS STUDY DRUG DISCONTINUED?	1- Yes, 2=No	Flag to identify this event as a reason for discontinuation. Default to NO(2)
CALC		DURDAYS	NUM	8	EVENT DURATION IN DAYS	= STOPDATN - ONSETDTN	DERIVED VARIABLE
DEFA		EV_TYPE	CHAR	1	EVENT RECORD TYPE	HARDCODE='E' (for Events after visit T0) and 'B'(for Baseline before or at visit T0) and 'S' (for Secondary Conditions before or at visit P0)	
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFD		HOSP	CHAR	1	REQUIRE OR PROLONG HOSPITALIZATION?	1=Yes, 2= No	Default to 2
CRFD		INDAE	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)		
CRFD		ONSETDAT	CHAR	6	ONSET DATE (YYMMDD)	Valid date or '- ' if missing. If EV_TYPE = 'E' or 'B' (after visit one), must have at least a valid month and year. (MM- - YY).	If day not available, default to day='01'.
DEFA		ONSETDTN	NUM	8	ONSET DATE (SAS DATE)	Derived	
DEFA		ONSETIME	CHAR	5	ONSET TIME (HH:MM)	BLANK	
DEFA		OUTCOME	CHAR	1	OUTCOME OF EVENT	BLANK	
CRFS		PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
		REAPPEAR	CHAR	1	REAPPEAR AFTER REINTRODUCING	BLANK	

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
					DRUG?		
CRFD		RELSDRUG	CHAR	1	RELATIONSHIP TO STUDY DRUG	1=No, 2=Yes, - = unknown	Default to "-"
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
		SEVERITY	NUM	8	SEVERITY OF EVENT	BLANK	
CRFD		STOPDATE	CHAR	6	STOP DATE (YYMMDD)	Valid date or "- " if missing, "- " if event ongoing through discontinuation. If EV_TYPE = 'E' or 'B' (after first visit), must have at least a valid month and year. (MM- -YY). STOPDATE MUST BE >= ONSETDAT.	
DEFA		STOPDATN	NUM	8	STOP DATE (SAS DATE)	Derived	
		STOPTIME	CHAR	5	STOP TIME (HH:MM)	BLANK	
CALC		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CALC		VISIT	NUM	8	VISIT NUMBER	Calculate VISIT: If ONSETDAT =< VIS_DATE of VISIT AND STOPDATE >= VIS_DATE of VISIT-1 or STOPDATE = "- ".	
DEFA		XREF_NUM	CHAR	3	CROSS REFERENCE NUMBER	Calculated: Numeric and left filled with zeroes.	

GLSLABS DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	DATA SET (NONE)	*GLSLABS DATA SET*					
CRFD		COLLDATE	CHAR	6	DATE SAMPLE WAS COLLECTED (YYMMDD)	Range for edits 1/1/90- 12/31/96	CRF entry in mmddyy
CRFD		COLLTIME	CHAR	5	TIME SAMPLE WAS COLLECTED (HHMM)	Range for edits = 0000- 2400, - if missing	Recorded in military time
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFD		HIGH_LIM	NUM	8	UPPER LIMIT OF NORMAL RANGE		
CRFD		INDLAB	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFD		LOW_LIM	NUM	8	LOWER LIMIT OF NORMAL RANGE		
CALC		NORM	CHAR	1	FLAG COMPARING RESULT W/ LAB'S RANGE	H=High; L=Low; A=Abnormal; otherwise N=Normal. Blank if unavailable.	
CRFD		PATIENT	CHAR	4	PATIENT NUMBER		
CALC		PROCCODE	CHAR	8	PROCEDURE CODE (LAB TEST GROUP)		From reference table. Derived from Testcode
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFD		RESULT	CHAR	9	LABORATORY RESULT		
DEFA		RSLTTYPE	CHAR	1	RESULT TYPE	O=ORDINAL, N=NUMERIC,S=SUBJECTIVE	
CALC		SIFACTOR	NUM	8	SI CONVERSION FACTOR		From reference table. Derived from Testcode
CALC		SIHI_LIM	NUM	8	UPPER LIMIT OF SI LILLY STD RANGE		Calculated from LOW_LIM based on SIFACTOR if result type = numeric.
CALC		SILO_LIM	NUM	8	LOWER LIMIT OF SI LILLY STD RANGE		Calculated from HIGH_LIM based on SIFACTOR if result type = numeric.
CALC		SINORM	CHAR	1	FLAG COMP SI RESULT W/ LILLY STD. RANGE	H=High; L=Low; A=Abnormal; otherwise N=Normal. Blank if unavailable.	Same as NORM
CALC		SIRESULT	NUM	8	RESULT VALUE IN SI UNITS		Calculated from RESULT based on SIFACTOR. (If SIFACTOR =1 then will be same as RESULT).
CALC		SIUNITCD	CHAR	5	UNIT CODE FOR SI VALUE		From reference table. Derived from Testcode
CRFD		TESTCODE	CHAR	3	TESTCODE	Must be a valid Lilly Testcode (from reference table)	From reference table (based on Lab

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
							Name?) or manually entered.
CRFD		UNITCODE	CHAR	5	UNIT CODE OF LAB RESULT		If have unique unitcode per testcode. Derived from Testcode in reference table. Otherwise must be manually entered
CRFD		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFD		VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	
CALC		SIFACTOR	NUM	8	SI FACTOR		From reference table. Derived from Testcode
CRFD		INDLAB	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'

INVECG DATA SET

VARIABLE SOURSE	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	DATA SET (NONE)	*INVECG DATA SET*					*ECG*
CRFD		ECGDATE	CHAR	6	DATE OF ECG (YYMMDD)	Valid Date. '- ' if missing. Range for edits= 1/1/90- 12/31/96	
CRFD		ECGEVAL	CHAR	1	OVERALL EVALUATION	1 = Normal, 2 = Abnormal, - if missing	
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFD		INDECG	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFD		PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFD		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie. P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFD		VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	

OTHERAPY DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	DATA SET (NONE)	*OTHERAPY*				*CONCOMITANT MEDICATIONS*	*CONCOMITANT MEDICATIONS*
CRFD		C_DOSE	CHAR	7	DOSE	BLANK	
CALC		C_DRUG	CHAR	40	DRUG PREFFERED TERM		Lookup in WHO dictionary using C_TRDRUG. Manually enter IF C_TRDRUG is a non-standard name not in WHO dictionary.
CRFD		C_FREQY	CHAR	4	FREQUENCY	BLANK	
CRFD		C_ROUTE	CHAR	10	ROUTE	BLANK	
CRFD		C_STPDAT	CHAR	6	STOP DATE (YYMMDD)		MMDDYY ON CRF
CRFD		C_STRDAT	CHAR	6	START DATE (YYMMDD)		MMDDYY ON CRF
CRFD		C_TRDRUG	CHAR	40	DRUG TRADE NAME	Must not be blank	
DEFA/ CALC		C_TYPE	CHAR	2	OTHER THERAPY RECORD TYPE	CO if Concomitant Med after visit 2 (T0). CU if at visit 1 or 2. PR if prior to visit 1.	
CRFD		C_UNITS	CHAR	12	UNITS	BLANK	
		CCIFU	CHAR	4	EVENT OCCURED	'NNN' For the Event (eg. 001) 'X01' Primary Condition 'X02' Prophylaxis or Non -Therapeutic use ' 97' Unknown	Default to Unknown
CALC		CLASTERM	CHAR	64	CLASSIFICATION TERM FOR USE OF THERAPY		
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFD		INDMED	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	ON CLEANING DATABASE ONLY
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
DEFA		LINE_NUM	NUM	8	LINE NUMBER	ASSIGN SEQUENTIALLY WITHIN VISIT	ON CLEANING DATABASE ONLY
CRFD		PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFD		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFD		VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	
DEFA		XREF_NUM	CHAR	3	CROSS REFERENCE NUMBER		

PATDEMOG DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_EPISOD DATA SET	*PATDEMOG DATA SET*					*PATIENT DEMOGRAPHICS*
CALC		AGEYEARS	NUM	8	AGE OF PATIENT IN YEARS AT ADMISSION	CALCULATED IN SAS: PSIGDATE - BIRTHDAT	UNIT IS YEARS
CRFS	DOB	BIRTHDAT	CHAR	6	DATE OF BIRTH (YYMMDD)	Valid Date. Can not be blank. Range for edits: < 9/10/90	Enter/Print as mmddyy
CALC		BIRTHDTE	CHAR	8	DATE OF BIRTH (CCYYMMDD)		
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
DEFA		GEOCODE	CHAR	3	GEOCODE	HARDCODE = 'US'	
CRFD		INITIALS	CHAR	3	PATIENT INITIALS	A-Z or - if missing initial (cannot be blank)	
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
CRFS	DRUG_NO	KIT_NUM	CHAR	4	STUDY DRUG KIT NUMBER	Range for edits= 1000-2999	
DEFA		LCHGDATE	CHAR	6	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFS	RACE	ORIGIN	CHAR	2	ORIGIN	Emslie to Lilly Code: 1=White=1=Caucasion, 2=Black=2=African Descent, 3=3=Hispanic, 4=99=other	CONVERT TO STANDARD LILLY FORMAT
DEFA		PATCLEAN	CHAR	1	PATIENT DECLARED CLEAN?	BLANK	
DEFA		PATEVAL	CHAR	1	PATIENT DECLARED EVALUABLE?	BLANK	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PCLNDATE	CHAR	6	DATE PATIENT DECLARED CLEAN (YYMMDD)	BLANK	
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
CRFS		PSIGDATE	CHAR	6	DATE PT SIGN ON INFORMED CONSENT (YYMMDD)	Valid Date. - if missing OR can not be blank? Range for edits: > 9/10/90	Enter/Print as mmddyy
		PUNEVAL1	CHAR	2	UNEVALUABLE REASON #1	BLANK	
		PUNEVAL2	CHAR	2	UNEVALUABLE REASON #2	BLANK	
		PUNEVAL3	CHAR	2	UNEVALUABLE REASON #3	BLANK	
		PUNEVAL4	CHAR	2	UNEVALUABLE REASON #4	BLANK	
		PUNEVAL5	CHAR	2	UNEVALUABLE REASON #5	BLANK	
		PUNEVAL6	CHAR	2	UNEVALUABLE REASON #6	BLANK	
		PUNEVAL7	CHAR	2	UNEVALUABLE REASON #7	BLANK	
		PUNEVAL8	CHAR	2	UNEVALUABLE REASON #8	BLANK	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS	GENDER	SEX	CHAR	1	PATIENT SEX	1=FEMALE, 2=MALE	
	DRUG_TYP	THERAPY	CHAR	4	TREATMENT GROUP CODE	TX GROUP, FX20=20MG FLUOXETINE, STAB=PLACEBO	Keep blinded therapy code until after data lock
CALC		PLACEBO	CHAR	1	PLACEBO TYPE	IF THERDATE < '930929' THEN 'E'; ELSE 'L'	Blank if THERDATE missing
CALC		THERDAT8	CHAR	8	DATE OF 1ST DOSE OF CT MATERIAL		CCYYMMDD
CRFD		THERDATE	CHAR	6	DATE OF 1ST DOSE OF CT MATERIAL	Valid Date. - if missing. Range for edits: > 9/10/90	YYMMDD(Enter/Print as mmddyy)

PATDEMNR DATA SET (NON-RANDOMIZED PATIENTS FROM P0, ADD MISC DEMOG??)

VARAIBLE SOURCE	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_EPISOD DATA SET	*PATDEMOG DATA SET*					*NON-RANDOMIZED PATIENT DEMOGRAPHICS*
CALC		AGEYEARS	NUM	8	AGE OF PATIENT IN YEARS AT ADMISSION	CALCULATED IN SAS. PSIGDATE - BIRTHDAT	UNIT IS YEARS
CRFS	DOB	BIRTHDAT	CHAR	6	DATE OF BIRTH (YYMMDD)	Valid Date. Can not be blank. Range for edits: < 9/10/90	
CALC		BIRTHDTE	CHAR	8	DATE OF BIRTH (CCYYMMDD)		
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
DEFA		GEOCODE	CHAR	3	GEOCODE	HARDCODE = 'US'	What is this?? Found on another Lilly example.
CRFD		INITIALS	CHAR	3	PATIENT INITIALS	A-Z or - if missing initial (cannot be blank)	
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
CRFS	DRUG_NO	KIT_NUM	CHAR	4	STUDY DRUG KIT NUMBER		
DEFA		LCHGDATE	CHAR	6	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFS	RACE	ORIGIN	CHAR	2	ORIGIN	Emslie to Lilly Code: 1=White=1=Caucasion, 2=Black=2=African Descent, 3=3=Hispanic, 4=99=other	CONVERT TO STANDARD LILLY FORMAT
DEFA		PATCLEAN	CHAR	1	PATIENT DECLARED CLEAN?	BLANK	
DEFA		PATEVAL	CHAR	1	PATIENT DECLARED EVALUABLE?	BLANK	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PCLNDATE	CHAR	6	DATE PATIENT DECLARED CLEAN (YYMMDD)	BLANK	
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
CRFS		PSIGDATE	CHAR	6	DATE PT SIGN ON INFORMED CONSENT (YYMMDD)	Valid Date. - if missing OR can not be blank? Range for edits: > 9/10/90	
		PUNEVAL1	CHAR	2	UNEVALUABLE REASON #1	BLANK	
		PUNEVAL2	CHAR	2	UNEVALUABLE REASON #2	BLANK	
		PUNEVAL3	CHAR	2	UNEVALUABLE REASON #3	BLANK	
		PUNEVAL4	CHAR	2	UNEVALUABLE REASON #4	BLANK	
		PUNEVAL5	CHAR	2	UNEVALUABLE REASON #5	BLANK	
		PUNEVAL6	CHAR	2	UNEVALUABLE REASON #6	BLANK	
		PUNEVAL7	CHAR	2	UNEVALUABLE REASON #7	BLANK	
		PUNEVAL8	CHAR	2	UNEVALUABLE REASON #8	BLANK	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS	GENDER	SEX	CHAR	1	PATIENT SEX	1=FEMALE, 2=MALE	
	DRUG_TYP	THERAPY	CHAR	4	TREATMENT GROUP CODE	BLANK	
CALC		PLACEBO	CHAR	1	PLACEBO TYPE	IF THERDATE < '930929' THEN 'E'; ELSE 'L'	Blank if THERDATE missing
CALC		THERDAT8	CHAR	8	DATE OF 1ST DOSE OF CT MATERIAL		CCYYMMDD
CRFS		THERDATE	CHAR	6	DATE OF 1ST DOSE OF CT MATERIAL	Valid Date. - if missing . Range for edits: > 9/10/90	Enter/Print as mmddyy

PATMISC DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_EPISOD DATA SET	*PATMISC DATA SET*					*PATIENT MISCELLANEOU DEMOGRAPHICS*
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
CRFD		FAMSTR	CHAR	2	FAMILY STRUCTURE	0=both parents, 1=natural mother, 2=natural mother and stepfather, 3=natural father, 4=natural father and stepmother, 5=grandparents, 6=other relatives, 7= adoptive parents, 8=college, 9=has own apartment, 10=other	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	CHAR	6	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFD	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFD	SES	SES	CHAR	1	HOLLINGSHEAD SOCIAL POSITION SCALE	- = missing 1 =Major business and professional 2 =Medium business, minor professional, technical 3 =Skilled craftsman, clerical, sales workers 4 =Machine operators, semiskilled workers 5 = Unskilled laborers, menial service workers	

PSYDIAG DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_EPISOD DATA SET	*PSYDIAG DATA SET*					
CRFS	DSM3R_01	AX1DIAG1	CHAR	8	DSM AXIS I DIAGNOSIS 1	NEED MAPPING OF DSM DIAGNOSIS NUMBERING TO CHARACTER DESCRIPTION. USE EMSLIE CODES - STANDARD THROUGHOUT INDUSTRY. - = missing	SHOULD BE MAJOR DESPRESSIVE DISORDER FOR ALL PATIENTS
CRFS	DSM3R_02	AX1DIAG2	CHAR	8	DSM AXIS I DIAGNOSIS 2	NEED MAPPING OF DSM DIAGNOSIS NUMBERING TO CHARACTER DESCRIPTION. - = missing	
CRFS	DSM3R_03	AX1DIAG3	CHAR	8	DSM AXIS I DIAGNOSIS 3	NEED MAPPING OF DSM DIAGNOSIS NUMBERING TO CHARACTER DESCRIPTION. - = missing	
CRFS	DSM3R_04	AX1DIAG4	CHAR	8	DSM AXIS I DIAGNOSIS 4	NEED MAPPING OF DSM DIAGNOSIS NUMBERING TO CHARACTER DESCRIPTION. - = missing	
CRFS	DSM3R_05	AX1DIAG5	CHAR	8	DSM AXIS I DIAGNOSIS 5	NEED MAPPING OF DSM DIAGNOSIS NUMBERING TO CHARACTER DESCRIPTION. - = missing	
CRFS	DURATION	DURCEPI	NUM	8	DURATION CURRENT EPISODE (WEEKS)	Range for edits= 0-250	
CRFS	LILLNESS	DURILL	NUM	8	LENGTH OF ILLNESS (MONTHS)	Range for edits= 0-216	
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
CRFS	FHEDPTX	FPHISTAT	CHAR	2	FAMILY PSYCH. HIST - AXIS I	1=Yes, 2=No, - = missing	
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
CRFS	AONSET	ONSETAGE	NUM	8	ONSET AGE OF FIRST EPISODE (YEARS)	Range for edits= </= 18	
CRFS	EPNO	NOEPISOD	NUM	8	NUMBER OF EPISODES	Range for edits= 0-999, and "."	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
CRFS	PREVTX	PREVTX	NUM	8	PREVIOUS TREATMENT THIS EPISODE	0= No Rx 1= 'Anxiolytics' 2= 'Tricyclics' 3= 'Antipsychotics' 4= 'Lithium' 5= 'MAOI' 6= 'Psychotherapy' 7= 'Other' 8= Fluoxetine 9= Other SSRIs 10='Tricyclics and Other SSRIs'	
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	

SECLFLX DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_FLXSE DATA SET	*SECLFLX DATA SET*					*FLUOXETINE SIDE EFFECTS CHECKLIST COMPLETED BY INVESTIGATOR*
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
CRFS	FSE_01	FSE01	NUM	8	FSE 1 TROUBLE SLEEPING	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_02	FSE02	NUM	8	FSE 2 HEART RACING	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_03	FSE03	NUM	8	FSE 3 HEART POUNDING	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_04	FSE04	NUM	8	FSE 4 FEELING DIZZY	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_05	FSE05	NUM	8	FSE 5 FEELING THE ROOM SPIN	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_06	FSE06	NUM	8	FSE 6 FEELING TENSE INSIDE	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_07	FSE07	NUM	8	FSE 7 RESTLESSNESS	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_08	FSE08	NUM	8	FSE 8 NUMBNESS OF HANDS OR FEET	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_09	FSE09	NUM	8	FSE 9 TINGLING OF HANDS OR FEET	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_10	FSE10	NUM	8	FSE 10 TROUBLE KEEPING BALANCE	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_11	FSE11	NUM	8	FSE 11 DRY MOUTH	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_12	FSE12	NUM	8	FSE 12 BLURRY VISION	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_13	FSE13	NUM	8	FSE 13 SEEING DOUBLE	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_14	FSE14	NUM	8	FSE 14 CONSTIPATION	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_15	FSE15	NUM	8	FSE 15 DIARRHEA	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_16	FSE16	NUM	8	FSE 16 DELAYS IN URINATING	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_17	FSE17	NUM	8	FSE 17 ITCHINESS	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_18	FSE18	NUM	8	FSE 18 LIGHT HURTING EYES	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_19	FSE19	NUM	8	FSE 19 NAUSEA	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_20	FSE20	NUM	8	FSE 20 VOMITING	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_21	FSE21	NUM	8	FSE 21 NO APPETITE	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_22	FSE22	NUM	8	FSE 22 STOMACH PAINS	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_23	FSE23	NUM	8	FSE 23 DROWSY	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_24	FSE24	NUM	8	FSE 24 LEG SPASMS AT NIGHT	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_25	FSE25	NUM	8	FSE 25 SWEATING	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_26	FSE26	NUM	8	FSE 26 TREMOR	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_27	FSE27	NUM	8	FSE 27 TINNITUS	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_28	FSE28	NUM	8	FSE 28 HEADACHE	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_29	FSE29	NUM	8	FSE 29 NIGHTMARES	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS	FSE_30	FSE30	NUM	8	FSE 30 WEIGHT CHANGE	0=Never, 1, 2=Somewhat, 3, 4=Constantly.	
CRFS		INDSEFLX	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		

DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	

SECLPT DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_SEI DATA SET	*SECLPT DATA SET*					*SIDE EFFECTS CHECKLIST COMPLETED BY PATIENT*
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
CRFS		INDSE	CHAR	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
CRFS	SE_01	SE01	NUM	8	SE01 EATING 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_02	SE02	NUM	8	SE02 DRINKING 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_03	SE03	NUM	8	SE03 DRY 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_04	SE04	NUM	8	SE04 WETNESS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_05	SE05	NUM	8	SE05 CONSTIPATION 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_06	SE06	NUM	8	SE06 DIARRHEA 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_07	SE07	NUM	8	SE07 STOMACHACHES 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_08	SE08	NUM	8	SE08 MUSCLE CRAMPS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_09	SE09	NUM	8	SE09 SICK STOMACH 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_10	SE10	NUM	8	SE10 WETTING BED 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_11	SE11	NUM	8	SE11 URINATING 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_12	SE12	NUM	8	SE12 ITCHY SKIN 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_13	SE13	NUM	8	SE13 RASHES 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_14	SE14	NUM	8	SE14 COLD 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_15	SE15	NUM	8	SE15 HEADACHE 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW

CRFS	SE_16	SE16	NUM	8	SE16 DIZZINESS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_17	SE17	NUM	8	SE17 PLAYING SPORTS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_18	SE18	NUM	8	SE18 SHAKINESS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_19	SE19	NUM	8	SE19 PRONOUNCING WORDS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_20	SE20	NUM	8	SE20 HAND DEXTARITY 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_21	SE21	NUM	8	SE21 SITTING STILL 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_22	SE22	NUM	8	SE22 TIREDNESS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_23	SE23	NUM	8	SE23 SLEEPY 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_24	SE24	NUM	8	SE24 TROUBLE 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_25	SE25	NUM	8	SE25 BAD DREAMS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_26	SE26	NUM	8	SE26 ALONG PARENTS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_27	SE27	NUM	8	SE27 ALONG KIDS 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_28	SE28	NUM	8	SE28 CRYING 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_29	SE29	NUM	8	SE29 MAD 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_30	SE30	NUM	8	SE30 NOT HAPPY 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_31	SE31	NUM	8	SE31 BEING SAD 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS	SE_32	SE32	NUM	8	SE32 ATTENTION 0-3 SCALE (4=DON'T KNOW)	0=not at all, 1=just a little, 2=pretty much, 3=very much, 4=don't know.	WILL NOT ANALYZE 4=DON'T KNOW
CRFS		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFS		VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	

SUMMARY DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	R_EP DATA SET	*SUMMARY DATA SET*					*DISCONTINUATION SUMMARY*
DEFA		BODYSYS	CHAR	5	BODY SYSTEM		
DEFA		CLASTERM	CHAR	64	CLASSIFICATION TERM FOR DISCONTINUATION		NEEDS TO BE HARDCODED.
CRFS		DESCOTH	CHAR	30	DESCRIPTION OF OTHER REASON FOR DISC.		
CRFS	DATE_EX	DISCDATE	CHAR	6	DATE OF STUDY DISCONTINUATION (YYMMDD)	Range for edits= >9/10/90	
DEFA		DISCDATN	NUM	8	DATE OF STUDY DISCONTINUATION (SAS DATE)		
CRFS		DTH_DATE	CHAR	6	DATE OF PATIENT DEATH (YYMMDD)	Range for edits= >9/10/90	
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST		
CALC		GENRSND	CHAR	3	GENERAL REASON FOR DISCONTINUATION	DERIVED FROM PRIMRSND	
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)		
CRFS	DATE_EX	LDOSEDAT	CHAR	6	DATE OF LAST STUDY DRUG DOSE (YYMMDD)	Range for edits= >9/10/90	Default to DISC DATE. Print/Enter as mm/dd/yy
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
CRFS	EX_CODE	PRIMRSND	CHAR	3	PRIMARY REASON FOR DISCONTINUATION	[redacted] TO LILLY MAPPING: SE=side effect=081=ADVERSE EVENT PSE=placebo side effect=081=ADVERSE EVENT H=hospitalized=081=ADVERSE EVENT R=responder =011=PROTOCOL COMPLETE (if PHASE_EX=T8) IDE=improved during evaluation=062=ENTRY CRITERIA NOT MET NR=nonresponder (lack of efficacy)=011=PROTOCOL COMPLETE (if PHASE_EX=T8) NR=nonresponder (lack of efficacy)=021=LACK OF EFFICACY (if PHASE_EX<T8) NC=non-compliant=051=PHYSICIAN DECISION LB=language barrier=062=ENTRY CRITERIA NOT MET RS=refused study=041=PATIENT DECISION NMC=not met MDD criteria=062=ENTRY CRITERIA NOT MET P=placebo responder=063=INTERIM CRITERIA NOT MET	

						PR=placebo responder=063=INTERIM CRITERIA NOT MET EC=exclusion criteria=062=ENTRY CRITERIA NOT MET IM1=needed immediate tx=062=ENTRY CRITERIA NOT MET ' '=BLANK=031=LOST TO FOLLOW-UP (if no other reason found) 004=066=NONCOMPLIANCE 999=121=OTHER	
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	HARDCODE = 'X065'
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE		HARDCODE = 'B1Y'
DEFA		SUM_TYPE	CHAR	2	TYPE OF SUMMARY (DB, OL, XO, FN, IN)		
CALC		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CALC		VISEVT	NUM	8	VISIT NUMBER OF EVENT CAUSING DISC	DERIVED FROM XREF_NUM	
CALC		VISEVTUN	CHAR	1	UNSCH VISIT LETTER CORR WITH VISEVT	DERIVED	
CRFS	PHASE_EX	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	
CRFS		XREF_NUM	CHAR	3	CROSS REFERENCE NUMBER	Must be present if PRIMRSND=081	Unique within patient

VIS_STAT DATA SET

VARIABLE SOURCE*	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/SPECIFIC TRANSFER INSTRUCTIONS
	R_PRS	*VIS_STAT*					
DEFA		DATERCV1	CHAR	6	DATE RECEIVED AT 1ST LILLY SITE (YYMMDD)		
DEFA		ENTRDATE	NUM	8	DATE OF FIRST ENTRY INTO LILLY COMPUTER		
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
CRFS	IDNO	PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE = 'B1Y'	
DEFA		SITE1	CHAR	2	1ST LILLY SITE WHERE RECEIVED		
CALC		STHERAPY	CHAR	4	STHERAPY	'PRE'= pre-therapy (for visits 1 and 2), 'DURD'=double-blind therapy (for visits 3-10)	
DEFA		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
DEFA		VCLNDATE	CHAR	6	DATE VISIT DECLARED CLEAN (YYMMDD)		
DEFA		VIS_MISS	CHAR	1	WAS VISIT MISSED?	HARDCODE = 2	
DEFA		VISCLEAN	CHAR	1	VISIT DECLARED CLEAN?	HARDCODE ALL ='Y'	
CRFS	DATE_E	VISDATE	CHAR	6	VISIT DATE (YYMMDD)	VALID DATE>=Study Start Date AND <= Study end date. MUST NOT BE BLANK.	Make field editable for data collection
CALC		VISDTE8	CHAR	8	VISIT DATE (CCYYMMDD)		
		VISEVAL	CHAR	1	VISIT DECLARED EVALUABLE?	BLANK	
CRFS	PHASE	VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED). 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	Only select records with valid phases.
		VUNEVAL1	CHAR	2	VISIT UNEVALUABLE REASON #1	BLANK	
		VUNEVAL2	CHAR	2	VISIT UNEVALUABLE REASON #2	BLANK	
		VUNEVAL3	CHAR	2	VISIT UNEVALUABLE REASON #3	BLANK	
		VUNEVAL4	CHAR	2	VISIT UNEVALUABLE REASON #4	BLANK	
		VUNEVAL5	CHAR	2	VISIT UNEVALUABLE REASON #5	BLANK	
		VUNEVAL6	CHAR	2	VISIT UNEVALUABLE REASON #6	BLANK	

VITALS DATA SET

VARIBLE SOURCE	[redacted] VAR	LILLY VAR	TYPE	LEN	LABEL	FIELD EDIT VALUES FOR DATA ENTRY SCREEN	COMMENTS/INSTRUCTIONS
	DATA SET (NONE)	*VITALS DATA SET*					*PATIENT VITAL SIGNS*
DEFA		FACILITY	CHAR	2	SITE CODE (FACILITY CODE)	HARDCODE = 'MC'	
DEFA		FTRNDATE	NUM	8	SAS DATE OF 1ST CLEAN TRANS TO HOST	BLANK	
CRFD/ CALC		HEIGHT	NUM	8	HEIGHT IN CM	Convert to CM	HEIGHTCM ON CLEANING DB
CRFD		HTTYPE	CHAR	2	HEIGHT UNITS OF MEASURE	C= CM, I= IN Range for edits= 24-84in	ON CLEANING DATABASE ONLY
CRFD		INDVIT	Char	1	INDICATES INFO NOT OBTAINED	'X'='Information Not Obtained' BLANK=' '='Information Available' (DEFAULT)	Cleaning edit - Print if record blank and indicator blank or print if record not blank and indicator='X'
DEFA		INV	CHAR	3	INVESTIGATOR NUMBER	HARDCODE = '001'	
DEFA		LCHGDATE	NUM	8	DATE OF LAST CHANGE (SAS DATE)	BLANK	
CRFD		PATIENT	CHAR	4	PATIENT NUMBER		
DEFA		PROJECT	CHAR	4	PROJECT CODE (STUDY NUMBER)	HARDCODE='X065'	
DEFA		RESPROJ	CHAR	3	RESEARCH PROJECT CODE	HARDCODE='B1Y'	
CRFD		SI_DIABP	NUM	8	SITTING DIASTOLIC BLOOD PRESSURE	Range for overrideable edits = 40-110	Blank if not Collected
CRFD		SI_HR	NUM	8	SITTING HEART RATE (PULSE)	Range for overrideable edits = 40-160	Blank if not Collected
CRFD		SI_SYSBP	NUM	8	SITTING SYSTOLIC BLOOD PRESSURE	Range for overrideable edits = 70-200	Blank if not Collected
CRFD		UNVISIT	CHAR	1	UNSCHEDULED VISIT LETTER	UNSCHED VISIT = A, B, C, ETC. FOR EACH UNSCHED VISIT WITHIN A VISIT INTERVAL (ie, P1=A, P2=B, P3=C, T9=A). SCHEDULED VISIT = BLANK.	
CRFD		VISIT	NUM	8	VISIT NUMBER	1=P0, (P1, P2, P3 ARE UNSCHEDULED), 2=T0, 3=T1, 4=T2, 5=T3, 6=T4, 7=T5, 8=T6, 9=T7, 10=T8, (T9 IS UNSCHEDULED)	
CRFD		WEIGHT	NUM	8	WEIGHT IN KG OR LBS		ON CLEANING DATABASE ONLY
CALC		WEIGHTKG	NUM	8	WEIGHT IN KG	Convert to KG	
CRFD		WTTYPE	CHAR	2	WEIGHT UNITS OF MEASURE	K= KG, P=LBS Range for edits= 40-300 lbs	ON CLEANING DATABASE ONLY

Attachment 3. Monitoring Plan

Monitoring Plan for LY110140
Protocol B1Y-MC-X065

Introduction

Outlined below is the process Lilly has established to address verification of non-Lilly clinical trial data. This process addresses the evaluation of all major areas of concern, including medical quality assurance, medical /regulatory issues, and study outcomes. This Plan will therefore be used while monitoring at a previously completed non-Lilly clinical trial site. The following outlines the minimum process for doing so.

Study

"Fluoxetine in Depression with Biological Correlates"

Phase I: Initial Audit Process

A Medical Audit of the study site will be conducted by Lilly MQA and Medical personnel to assess basic study data and documentation integrity, patient safety, and site and investigator qualifications. The following study documentation will be requested from the study site by Lilly, and sent to Lilly for review either prior to this visit, or as a result of this visit. In addition, patient files will be reviewed, and data collected to enable assessment of site decisions based on patient safety and study inclusion/exclusion criteria. Based on information collected during the audit, a risk analysis profile will be completed by Lilly area representatives (Regulatory, MQA, Medical, Statistics), and if study integrity is acceptable, the remaining phases of the Plan will be implemented.

[redacted] approved Patient Informed Consents must state that the study sponsor and/or the [redacted] is allowed access to patient files prior to any review of patient files. If the site requires, Lilly personnel who will be conducting activities during Phase II or Phase III of this plan will sign a Letter of Confidentiality prior to reviewing the patient files.

- **Clinical Trial Materials (drug accountability and compliance)**
  - study drug invoices
  - study drug dispensing log
  - documentation of disposition of all study drug at trial completion
  - obtain pharmacy instructions used in preparing the study drug capsules, and documentation of the source of the study drug prior to Lilly's involvement in 1993.
  - randomization codes
  - pill counts
  - documentation of study drug compliance
- **Patient Protection**
  - original and any amended informed consent documents (need blank copy at Lilly and ensure that there is an signed ICD present for all patients at the site)
  - obtain a statement signed by the investigator that blinding code remained unbroken until study end, which includes list of identified study participants
- **Regulatory documents**
  - assure that the site has a Clinical Trials Record Binder to house all critical study documents.
  - assure that the site has a copy of the Clinical Investigator Brochure (CIB)
  - CV's for all investigator(s) and all study personnel

- [redacted] approval of protocol
- [redacted] approval of ICD
- [redacted] approval of any protocol or ICD amendments
- [redacted] approval of advertisements and obtain a copy of advertisement
- annual reports to [redacted]
- obtain copies of all pertinent study correspondence between the site and their [redacted]
- final report to the [redacted] stating that the study is officially closed
- 1572 (if applicable) and supplements
- [redacted] membership list at the time of [redacted] approval
- IND submission cover (if applicable)
- verify that all Serious Adverse Event reports were reported to [redacted] and Lilly
- obtain all internal audit reports or evidence of a quality assurance process

- **General information**
  - protocol
  - investigator licensure spanning the duration of the study
  - investigator registration/certification
  - facility licensure spanning the duration of the study
  - laboratory (CLIA and CAP) certifications spanning the duration of the study
  - laboratory units and reference ranges for any blood tests performed on study patients
  - copyright permissions for instruments used in the study
  - any training documentation (i.e. SCID-P)
  - debarment certificate spanning the duration of the trial and currently (separately)
  - affirmation statement signed by the investigator stating that the study was conducted according to GCPs and that all data has been transferred to Lilly
  - any study instructions that may exist
- **Quality Assurance Documents**
  - obtain all documentation that captures any processes used by the site to assure the quality of the data/study (ie, double-data entry, data quality review)
- **Data collection**
  - obtain any audit trail logs used by the site

- Verify that non-discontinued patients were not receiving exclusionary therapy if specified by the protocol.
- Verify that all non-discontinued patients met the eligibility requirements as stated in the protocol's inclusion and exclusion criteria.
- Verify that all informed consent documents were signed and dated by the patient's legal representative prior to the administration of any study procedure or the receipt of study medication. Verify that assent was obtained from the child/adolescent.
- If the ICD was amended, make sure that the ICD signed by the patient's legal representative and child/adolescent reflects the protocol/informed consent document that was currently approved at that time.

Phase II: Data Collection

If any study data has been entered into an electronic database by the investigator, this database will be obtained by Lilly. Electronic case report forms (CRFs) will be used to collect any additional required data for transfer from site source records to Lilly during this phase. Investigative site personnel will perform the data collection. Electronic CRFs will be developed so as to collect data by transcription without interpretation. Site personnel will be required to sign a document stating that they have not altered source. Investigator/designee signature will be required on the Investigator Signature Page verifying the information collected on the CRFs.

Patient Visits

All patient visits were determined based on weeks in the study. Visit 1 (single-blind placebo phase) includes all visits that the patient was taking placebo and occurred prior to the patient being randomized to double-blind treatment. Visits 2-10 (double-blind treatment phase) include all visits in which the patient was currently receiving double-blind treatment; fluoxetine 20 mg/day (if not on alternate day dosing regimen) or placebo. A patient may have come in for an unscheduled visit during both the single-blind placebo phase and the double-blind treatment phase.

- Evaluation Phase: The evaluation period was three weeks in duration in which patients received no study drug. A screening informed consent document was signed during the first evaluation visit. The data from these visits will not be collected.

- Study Period I (Single-blind placebo phase): Visit 1 includes data pertaining to the single-blind, placebo period which was one to two weeks in duration. Informed consent was obtained prior to the administration of any study procedure or the dispensing of the single-blind study drug, placebo. Those patients who met the study inclusion/exclusion criteria as assessed during the first week of Study Period I, including receiving a CDRS-R score ≥ 40 were advanced to Study Period II. Those patients who did not meet the study inclusion/exclusion criteria and/or received a CDRS-R score ≤ 40 were followed for an additional week to rule out placebo response. If at the end of the second week these patients then met study entry criteria, they were advanced to Study Period II. If a patient was seen for several visits during this study phase, the additional visits will be labeled as Visit 1a, Visit 1b, etc.

- Study Period II (Double-blind treatment phase): Visit 2 through Visit 10 includes data pertaining to the double-blind, randomized, placebo-controlled, 2-arm parallel, 8 week study phase. Randomization occurred at Visit 2. For those patients who met the study inclusion/exclusion criteria as assessed during Study Period I, including a CDRS-R score $\geq$ 40), active treatment containing blinded study drug was dispensed. Visits will be labeled based on the number of weeks that the patient was active in the study. If the patient skipped a visit (i.e., patient came in for Visit 3, unable to make the next week's visit [Visit 4], and returned the following week [Visit 5],do not consider the visit which occurred two weeks after Visit 3 as Visit 4. This visit should be labeled as Visit 5, which corresponds to the number of weeks that the subject is active in the study. Any unscheduled visits that occurred prior to the next scheduled study visit will be labeled using a differentiating letter corresponding to that visit (ie. 9a, 9b-visits that occurred in between Visit 9 and Visit 10).

Phase III: Source Data Verification and Database Validation

Definition: Source Data Verification (SDV) is the verification of source document data (the location where the data was originally captured) as compared to the data recorded on the CRFs. These CRFs will contain all study data originally entered into the electronic database and the additional required data entered via electronic CRF.

Definition: Case Report Forms will be printouts of the entire database and will be used as a tool for source data verification.

Definition: Electronic Case Report Forms will be used as a vehicle for data collection of the additional required data that is entered into the electronic database.

The following will be source data verified (SDV) during the monitoring visits:

- 100% of **all** data points from **all** visits that occurred during the single-blind placebo phase and the double-blind treatment phase (Visits 1-10).
- 100% of **all** data points from all unscheduled visits that occurred during both the single-blind placebo phase and the double-blind treatment phase.

Adverse Events

- Verify that **all** adverse events found in source documents are entered on the Adverse Event electronic CRF and appropriate comments are entered on the Comments electronic CRF, if needed.
- Verify that **all** serious adverse events found in source documents were reported to the site's ethical review board and to Lilly.

Concomitant Therapy

- Verify that **all** concomitant medications found in source documents are entered on the Concomitant Medication CRF and appropriate comments are entered on the Comments CRF, if needed.
- Verify that reason(s) for allowing use of all exclusionary medications were documented on the Comments CRF.

Inclusion/Exclusion Criteria

- If it was noted that a patient did not meet the entire inclusion/exclusion criteria, make sure that the reason(s) for allowing this patient to enter the study is documented on the Comments CRF.

Drug Compliance

- Verify that the patient's compliance and adherence to the dosing regimen were entered on the Drug Compliance electronic CRF.
- If the patient was non-compliant with the dosing regimen, make sure it is documented on the Comments CRF.

Laboratory Data

- Verify that explanations of **all** clinically significant (CS) laboratory values are entered on the Comments electronic CRF.
- Verify that abnormal laboratory values have not been captured as adverse events.

Data Review

Data Review is an *administrative* review of the data for *computer fit* types of errors. For any data collected via electronic CRFs, data review will not require manual review since the electronic database performs these checks simultaneously as the data are entered into the system.

Data Capture

Once the monitors have source data verified all necessary data, and have appropriately documented any discrepancies on the query log, the monitor should send the following to Lilly for data entry purposes: the white copy of the CRFs, and the investigator signed queries.

Signature Log
The signature log in the CTRB must be signed by the monitor and all others visiting the study site.

Overall Study Documentation
The overall study documentation may be maintained in the Clinical Trial Records Binder (for example, protocols, amendments, informed consent documents, and documentation of approvals by ethical review boards). The Global Clinical Investigation manual and other study binders such as the Clinical Investigator's Brochure must also be available for review. Using the regulatory Compliance Worksheet to check for completeness, monitors should review study documentation at the audit visit, during the source data verification visits, and at the close-out visit. Additional reviews should be considered if there are other revisions to the study that would affect documentation.

Phase IV: Close Out

- Verify that the site has completed all required close-out procedures (i.e., archiving the printouts of the electronic CRFs and associated query logs, source documents, and the CTRB related to this study, ensure that all outstanding queries have been resolved, ensure that drug accountability has been reconciled, verify that all SAEs have been documented and that each contains a resolution, and ensure that the investigator has signed off on all data for each patient).

- Verify that all equipment supplied by Lilly to the site (i.e., laptop computer(s)) is returned.

- The signature log in the CTRB must be signed by the monitor and all others visiting the study site.

Monitor Training
Appropriate documentation of qualifications will be obtained from all study monitors, and study specific training will be provided to all monitors. The Monitoring Plan for LY11040, Protocol B1Y-MC-X065 will be provided to the monitors. Questions regarding the implementation of this document can be directed to the coordinating Lilly CRA(s) or the Lilly Clinical Research Physician (CRP) responsible for the study.

Updates to Plan
The Monitoring Plan will be reviewed periodically and will be updated and altered as necessary. The most recent approved version of the Monitoring Plan will take precedence over any other version.

Plan Approval

This Monitoring Plan has been written/approved by:

Signature- Date

Title: Clinical Research Associate

Signature- Date

Title: Clinical Research Associate

Signature- Date

Title: Clinical Research Associate

This Monitoring Plan has been read and approved by:

Signature Date

Title: Clinical Research Associate

Signature Date

Title: Clinical Research Associate

Signature- Date

Title: Clinical Research Associate

Signature- Date

Title: Clinical Research Associate

Signature-

Date

Title: Clinical Research Associate

Attachment 4. Data issues not requiring investigator resolution or signature:

1. Verified .X in any num field
2. Blank records in any dataset
3. Spelling errors
4. Reordering AX1DIAG1-5 field data among these fields
5. Deletion of Adverse event or con med data with stop dates prior to ICD dates
6. Info not obtained for missing CDI if have BDI, and vice-versa
7. "Info not obtained" or it's equivalent for a scale/item that should not have been collected for a visit(i.e. CGI-I for Visits 1 and 2
8. For rater initials, the addition of a dash for middle initial.

Attachment 5: B1Y-MC-X065 edits (Ad Hoc Edits)
Emslie edits:

Key for "When" column: A-Can be done after Datalock; B-Should be done before Datalock.
Key for "Priority" column: See data Cleaning document. This pertains to run frequency and timing for SDV.

CRF Module	Edit	When	Priority	Programmed?
BECKD				
EMSMISS	Flag if BECKD01-21 value is blank	B	1	Y
	Flag if BECKD01-21 value is invalid (range=0-3, inclusive)	B	1	Y
EMSDUPS/ EMSEVIS3	Verify that one and only one record exists in the dataset/patient visit	B	3	Y
BPRSC				
EMSMISS	Flag if BPRS01-21 value is blank	B	1	Y
	Flag if BPRS01-21 value is invalid (range=0-6, inclusive)	B	1	Y
E2BPRSC	Flag if rater initials are invalid (range = A-Z, -)	B	2	Y
EMSDUPS/ EMSEVIS3	Verify that one and only one record exists in the dataset/patient visit	B	3	Y
CDI				
EMSMISS	Flag if CDI01-27 value is blank	B	1	Y
	Flag if CDI01-27 value is invalid (range=0-3, inclusive)	B	1	Y
EMSDUPS/ EMSEVIS3	Verify that one and only one record exists in the dataset/patient visit	B	3	Y
CDRSR				
EMSMISS	Flag if CDRS01-17(EXCLUDING CDRS04, 05,and 16) value is invalid (range=0-7, inclusive)	B	1	Y
	Flag if CDRS01-17 is blank	B	1	Y
	Flag if CDRS04, 05, 0R 16 value is invalid (range=0-5, inclusive)	B	1	Y
E2CDRSR	Flag if rater initials are invalid (range = A-Z, -)	B	2	Y
EMSDUPS/ EMSEVIS3	Verify that one and only one record exists in the dataset/patient visit	B	3	Y
CGIPGI				
EMSMISS	Flag if CGISEVER value is invalid (range=0-7, inclusive)	B	1	Y
	Flag if CGISEVER or CGIIMPRO are blank	B	1	Y
	Flag if CGIIMPRO value invalid (range=0-7, inclusive)	B	1	Y
E2CGIPGI	Flag if "0" is not checked for V1-2 for CGIIMPRO	B	2	Y
	Flag if rater initials are invalid (range= A-Z, -)	B	2	Y
EMSDUPS/ EMSEVIS3	Verify that one and only one record exists in the dataset/patient visit	B	3	Y
COMMENTS				
E2COMMNTS	Flag if "no comments" is checked and a comment is listed (and vice versa).	B	2	Y
COMPLNCE				
After Data Lock	Flag if SDDOSMIS is greater than 0	A	3	
After Data Lock	Flag if SD_COMPL = 2 or 97	A	3	

EVENTS MODULE				
E2EVENT	Flag if "stop date" field is blank	B	2	Y
	Flag if event is serious (CANC_ETC, DEATH, DIABIL, HOSP)	B	3	Y
E2EVNTS3	Flag if event onset date after last visit date OR stop date before first visit data	B	2	Y
E2EVNTS9	Flag if event stop date after last visit date	B	2	Y
EMSEVOT EMSEVT1	Flag if COSTART term does not map to a term in the COSTART dictionary. *List both mapped and non-mapped events (including chronic illnesses).*	B	2	Y
GLSLABS				
E2LABS	Flag if neither data is provided nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2	Y
E2LABS1	Flag if MMDDYYYY (lab draw date) is before 10SEPT1990	B	2	Y
E2LABS2	Flag if date of lab report or collection date is > 1 year before the visit 1 date or after visit 1 date.	B	3	Y
	For each laboratory test in GLSLABS, flag if RESULTS are provided but any is missing REFERENCE RANGE (LOW/HIGH). Flag if result type = 'N' and UNIT CODE missing .	B	2	Y
E2LABS4	For each laboratory test in GLSLABS, flag if RESULTS are abnormal, low, high	B	3	Y
E2LABS3	For All labs, flag if collection date is prior to informed consent date or greater than the last visit date.	B	2	Y
After data lock	For All labs, flag if results are greater than 2x the upper limit of normal.	A	3	
Not done	For unscheduled labs, flag if no unscheduled labs is checked but laboratory data are present (and vice versa).	B		
INVECG				
E2INVECG	Flag if neither data is provided nor "information not obtained" is checked or if both data and "information not obtained" are provided.	B	2	Y
	If EKG date is provided, flag if it is before SEPT101990.	B	2	Y
	If EKG results are ABNORMAL, flag if no specify is provided.		3	Y
EMSMISS	Verify that no blank records exist in the dataset	B	3	Y
OTHERAPY MODULE				
E2OTHER	Flag if STOP DATE is before the ICD DATE	B	2	Y
	For each concomitant medication, flag if stop date is blank	B	2	Y
E2OTHER1	Flag if Conmed start date after last visit date OR stop date before first visit data	B	2	Y
EMSOTHE	Flag if trade drug not found in WHO dict.	B	2	Y
PATDEMOG				
E2PATDM1	Flag if any required field is blank (ICD date, patient initials, study drug kit #)	B	2	Y
E2PATDEM	Flag if consent date is not equal to V1 date.	B	3	Y
	Flag if any ICDDATE is not between 10SEPT1990 and 12DEC1994 inclusive	A	3	
	Flag if patient age (calculated from PSIBDATE-BIRTHDAT) is not between 8 and 18, inclusive	B	3	Y
PATMISC				
E2PATMSC	Flag if any required field is blank (family structure)	B	2	Y
PSYDIAG		B	2	Y
E2PSYDIG	Flag if AX1DIAG1=296.2x and episode # does not = 1	B	2	Y
	Flag if AX1DIAG1=296.3x and episode # is not >/= 2	B	2	Y
	Flag if any one of AX1DIAG1-5 =296.4x, 296.5x, 296.6x, 296.7x, 307.1, 307.51, 305.xx	B	3	Y
	Flag if any one of AX1DIAG1 is not = 296.2x OR 296.3x	B	3	Y
E2PSYDG1	Flag if duration of illness (DURILL) is greater than age in years (or <=2 months)	B	3	Y
E2PSYDG2	Flag If duration of Episode less than 2 weeks	B	3	Y
EMSMISS	Flag if PREVTX=8	B	1	?
EMSDUPS/	Verify there is exactly one record/patient in the dataset	B	3	Y

EMSEVIS4				
SECLFLX				
EMSMISS	Flag is value is invalid (range = 0-4, inclusive)	B	1	Y
EMSDUPS/ EMSEVIS3	Verify that one and only one record exists in the dataset/patient visit(all visits but 1 and 2) There should not be any records for these visits.	B	3	Y
SECLPT				
EMSMISS	Flag if value is invalid (range = 0-4, inclusive)	B	1	Y
EMSDUPS/ EMSEVIS3	Verify that one and only one record exists in the dataset/patient visit	B	3	Y
SUMMARY				
E2SUMMRY	Flag If XREFNUM in SUMMARY does not have a "Y" In DRUGDISC field, and vice-versa	B	2	Y
E2SUMRY2	Flag if XREFNUM in summary =999, and only one (or none) records in events are marked "Y" for causing discontinuation	B	2	Y
E2SUMRY3	Flag if DISCDATE is before last visit date or before ICD date	B	3	Y
E2SUMRY	FLAG if patient completed the study (PROTOCOL COMPLETED ,PRIMSND='011') but data from visit 10 was not provided on at least one of the efficacy rating scales (CDRS.CGI-I,CGI-S.BPRS)	B	2	Y
	Flag if the reason for ending participation in the study is ADVERSE EVENT(PRIMSND ='081') but the e-code(XREF_NUM) does not map to a valid E_CODE in EVENTS(not one that says "info not obtained")	B	2	Y
E2SUMRY1	Flag if LDOSEDAT is after DISCDATE or before consent date or before Visit 1	B	2	Y
E2SUMRY5	Flag if visit number in Summary does not match last visit number in Vis_stat	B	2	Y
VIS_STAT				
E2VISIT	Flag if any VISDATE is after DISCDATE or DTH_DATE	B	2	Y
	Flag if any VISDATE is before consent date	B	3	Y
E3VISIT	Flag if any visit date was not between 10SEPT1990 and 31DEC1996 inclusive	B	3	Y
After Data Lock	Flag if visit interval is >13 days	A	3	
EMSMISS	Verify that no blank records exist in the dataset	B	3	Y
EMSEVIS	Flag if patient has missing/skipped visit number	B	3	Y
EMSEVIS	Flag if the visit dates are not in chronological order	B	2	Y
VITALS				
E3VITALS	If heart rate is provided, flag if it is outside of the range 40-160, inclusive.	B	3	Y
	If systolic blood pressure is provided, flag if it is outside of the range 70-200, inclusive.	B	3	Y
	If diastolic blood pressure is provided, flag if it is outside of the range 40-110, inclusive.	B	3	Y
E2MISVAR	Flag non-blank character fields in Beckd, CPRSR, Complnce when IND = 'X'	B	2	Y
MANUAL EDITS	Flag if the investigator did not sign CRF page XX.	B	3	

Attachment 6: PETS ISSUES

This table documents the constraints of the PETS for entering data. For a more detailed look at the constraints of the programming and how it was handled by the CIA, please refer to the CIA PETS ISSUE document, as well as Notes-to-File.

Module	Item	Constraint
CDRS	#18	"--" appear on item even though X for information not obtained is marked, systems correct issue
Vitals	Height/Weight	If a weight is given, but no height is available, a .x appears in the num field; however, the units field cannot be left blank, therefore a cm or in appears in field and on CRF. (The vise versa is true with height given but not weight.)
Comment	Any Comment field	On any given screen, "the question do you have a comment appears?", one must enter a Y or Yes or an N for No in order to exit the screen. This act of entering a Y or N appears on the audit trail, although no information has been altered.
PatDemog	Origin	If the CIA enters this screen to view the information, the CIA must re-enter the information given for origin in order to exit the screen. This act of re-entering the origin appears on the audit trail.
PatDemog	Origin	If the CIA enters this screen to view the information and the kit number is blank, the CIA must enter a "-" for the kit number in order to exit the screen. This action of entering of a "-" would be done with a query. This act of entering a "-" for a blank kit number appears on the audit trail.

APPROVALS:

Approved by:

[redacted]

12/1/99
Date

3/13/00
Date

16.2
Patient Data Listings

16.2.1. Adverse Event Listings by Patient
16.2.2. Patient Disposition Listing
16.2.3. Protocol Violations
16.2.4. Patients Excluded from the Efficacy Analysis
16.2.5. Demographic Data
16.2.6. Compliance Data
16.2.7. Individual Efficacy Response Data
16.2.8. Listing of Individual Laboratory Measurements by Patient

16.2.1.
Adverse Event Listings by Patient

Please see SAS Transport file located in Item 11 of this submission.

16.2.2.
Patient Disposition Listing

Please see SAS Transport file located in Item 11 of this submission.

16.2.3.
Protocol Violations

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Violation of Inclusion/Exclusion Criteria				
	Flx 20mg	2185	1	Patient was 7 years old at trial entry
	Placebo	2087		Patient diagnosed with Alcohol Abuse
	Placebo	2233	1	Patient was 7 years old at trial entry
Missing Informed Consent Documents				
	Flx 20mg	2014		
	Placebo	2061		
Missing Parent/Guardian Signature on Informed Consent Documents				
	Placebo	2052		
	Placebo	2057		
Excluded Concomitant Medication				
	Flx 20mg	2124	7, 9	Patient smoked marijuana
	Flx 20mg	2178	8	Patient smoked marijuana
	Placebo	2220	3	Patient smoked marijuana
Patient Not Compliant with Study Medication				
	Flx 20mg	2029	7	
	Flx 20mg	2033	5	
	Flx 20mg	2040	5	
	Flx 20mg	2073	5, 6	
	Placebo	2002	1	
	Placebo	2025	9, Sum	
	Placebo	2038	6	
	Placebo	2050	4	
	Placebo	2057	4	
Missed Visits				
	Flx 20mg	2067	6	
	Flx 20mg	2073	7	
	Flx 20mg	2075	6	
	Flx 20mg	2244	6	
	Placebo	2007	6	
	Placebo	2066	6	
Visit Outside Designated Study Interval				
	Flx 20mg	2169	10	14 days between Visits 9 and 10
	Placebo	2002	2	37 days between Visits 1 and 2
	Placebo	2002	10	14 days between Visits 9 and 10
	Placebo	2057	2	14 days between Visits 1 and 2
	Placebo	2096	2	14 days between Visits 1 and 2
	Placebo	2207	2	14 days between Visits 1 and 2
	NR	2132	2	14 days between Visits 1 and 2
Received Incorrect Study Assessment				
	Flx 20mg	2012	4, 5	Received the BDI instead of the CDI
	Flx 20mg	2040	9, 10	Received the BDI instead of the CDI
	Placebo	2002	2	Received the CDI instead of the BDI
	Placebo	2007	10	Received the BDI instead of the CDI

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Abnormal Laboratory Results				
	Flx 20mg	2012	6	Atypical lymphocytes = 2
	Flx 20mg	2029	1	Atypical lymphocytes = 1
	Flx 20mg	2030	1	Atypical lymphocytes = 1
	Flx 20mg	2067	1	Atypical lymphocytes = 3
	Flx 20mg	2067	7	Atypical lymphocytes = 1
	Flx 20mg	2153	1	Atypical lymphocytes = 1
	Flx 20mg	2162	6	Atypical lymphocytes = 1
	Flx 20mg	2230	1	Eosinophils = 11; upper limit = 5
	Flx 20mg	2235	10	Atypical lymphocytes = 1
	Flx 20mg	2237	1	SGOT = 113; upper limit = 46
	Placebo	2052	1	Atypical lymphocytes = 1
	Placebo	2057	1	Atypical lymphocytes = 2
	Placebo	2087	1	Atypical lymphocytes = 1
	Placebo	2096	1	Atypical lymphocytes = 1
	Placebo	2167	1	SGPT = 143; upper limit = 45
	Placebo	2167	10	Atypical lymphocytes = 1
	Placebo	2207	1	Atypical lymphocytes = 2
	Placebo	2220	6	Atypical lymphocytes = 1
	Placebo	2246	10	Atypical lymphocytes = 1
Missing Study Assessments - Laboratories				
	Flx 20mg	2010	1, 6, 10	
	Flx 20mg	2012	1, Sum	
	Flx 20mg	2014	6, 10	
	Flx 20mg	2019	1, 6	
	Flx 20mg	2029	10	
	Flx 20mg	2030	5	
	Flx 20mg	2033	6	
	Flx 20mg	2040	Sum	
	Flx 20mg	2042	Sum	
	Flx 20mg	2047	1, 6, 10	
	Flx 20mg	2051	1, 5	
	Flx 20mg	2067	6, Sum	
	Flx 20mg	2073	6, Sum	
	Flx 20mg	2075	6, 10	
	Flx 20mg	2083	1, Sum	
	Flx 20mg	2085	Sum	
	Flx 20mg	2090	10	
	Flx 20mg	2119	Sum	
	Flx 20mg	2120	Sum	
	Flx 20mg	2123	Sum	
	Flx 20mg	2124	Sum	
	Flx 20mg	2125	Sum	
	Flx 20mg	2126	6, Sum	
	Flx 20mg	2142	Sum	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - Laboratories				
	Flx 20mg	2149	Sum	
	Flx 20mg	2153	10	
	Flx 20mg	2162	10	
	Flx 20mg	2163	6, 10	
	Flx 20mg	2169	Sum	
	Flx 20mg	2173	Sum	
	Flx 20mg	2174	Sum	
	Flx 20mg	2178	Sum	
	Flx 20mg	2184	Sum	
	Flx 20mg	2185	1, 6, Sum	
	Flx 20mg	2186	Sum	
	Flx 20mg	2195	Sum	
	Flx 20mg	2197	Sum	
	Flx 20mg	2210	Sum	
	Flx 20mg	2212	Sum	
	Flx 20mg	2214	Sum	
	Flx 20mg	2230	6, Sum	
	Flx 20mg	2231	Sum	
	Flx 20mg	2235	Sum	
	Flx 20mg	2237	Sum	
	Flx 20mg	2242	Sum	
	Flx 20mg	2244	6, Sum	
	Flx 20mg	2249	Sum	
	Flx 20mg	2250	Sum	
	Placebo	2001	1 ,7	
	Placebo	2002	1, 6, 10	
	Placebo	2007	6, 10	
	Placebo	2013	6, 10	
	Placebo	2017	6, Sum	
	Placebo	2025	Sum	
	Placebo	2026	5	
	Placebo	2032	10	
	Placebo	2038	10	
	Placebo	2050	7	
	Placebo	2052	Sum	
	Placebo	2057	1, 4, Sum	
	Placebo	2061	Sum	
	Placebo	2064	Sum	
	Placebo	2066	6, Sum	
	Placebo	2068	Sum	
	Placebo	2069	10	
	Placebo	2087	Sum	
	Placebo	2093	Sum	
	Placebo	2095	Sum	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - Laboratories				
	Placebo	2096	Sum	
	Placebo	2098	Sum	
	Placebo	2100	1, Sum	
	Placebo	2102	10	
	Placebo	2107	Sum	
	Placebo	2114	Sum	
	Placebo	2115	Sum	
	Placebo	2133	Sum	
	Placebo	2147	Sum	
	Placebo	2166	Sum	
	Placebo	2167	Sum	
	Placebo	2172	6, Sum	
	Placebo	2177	1, Sum	
	Placebo	2179	Sum	
	Placebo	2180	1, 6, Sum	
	Placebo	2187	Sum	
	Placebo	2204	Sum	
	Placebo	2207	Sum	
	Placebo	2211	Sum	
	Placebo	2213	Sum	
	Placebo	2215	Sum	
	Placebo	2220	Sum	
	Placebo	2229	Sum	
	Placebo	2233	5	
	Placebo	2238	Sum	
	Placebo	2246	Sum	
	Placebo	2251	Sum	
	Placebo	2252	Sum	
	NR	2060	Sum	
	NR	2104	Sum	
	NR	2112	Sum	
	NR	2132	Sum	
	NR	2138	Sum	
	NR	2146	Sum	
	NR	2188	Sum	
Missing Study Assessments - Side-Effects Checklist				
	Flx 20mg	2010	9	
	Flx 20mg	2012	3, 4, 8	
	Flx 20mg	2033	4	
	Flx 20mg	2051	5	
	Flx 20mg	2067	6	
	Flx 20mg	2073	7	
	Flx 20mg	2075	6	
	Flx 20mg	2124	7	
	Flx 20mg	2126	6	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - Side-Effects Checklist				
	Flx 20mg	2169	3	
	Flx 20mg	2173	5	
	Flx 20mg	2244	6	
	Placebo	2001	1, 4, 5	
	Placebo	2002	1A, 10	
	Placebo	2007	6-9	
	Placebo	2013	1	
	Placebo	2017	3	
	Placebo	2032	2	
	Placebo	2061	4	
	Placebo	2066	6	
	Placebo	2093	9	
	Placebo	2098	8	
	Placebo	2180	4	
	Placebo	2204	3	
	Placebo	2207	3	
Missing Study Assessments - Fluoxetine Side-Effects Checklist				
	Flx 20mg	2010	1-10	
	Flx 20mg	2012	1-9	
	Flx 20mg	2014	1-10	
	Flx 20mg	2019	1-6	
	Flx 20mg	2029	1-10	
	Flx 20mg	2030	1-6	
	Flx 20mg	2033	1-7	
	Flx 20mg	2040	1-10	
	Flx 20mg	2042	1-10	
	Flx 20mg	2047	1-10	
	Flx 20mg	2051	1-5	
	Flx 20mg	2067	1-10	
	Flx 20mg	2073	1, 7	
	Flx 20mg	2075	1-10	
	Flx 20mg	2083	1-10	
	Flx 20mg	2085	1-10	
	Flx 20mg	2090	1-10	
	Flx 20mg	2119	1-3	
	Flx 20mg	2120	1, 2, 8,10	
	Flx 20mg	2123	1, 6	
	Flx 20mg	2124	1, 6, 7, 10	
	Flx 20mg	2125	1, 2, 5	
	Flx 20mg	2126	1, 2, 6	
	Flx 20mg	2142	1-1A	
	Flx 20mg	2149	1	
	Flx 20mg	2153	1	
	Flx 20mg	2162	1	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - Fluoxetine Side-Effects Checklist				
	Flx 20mg	2163	1	
	Flx 20mg	2169	1	
	Flx 20mg	2173	1, 5, 6	
	Flx 20mg	2174	1, 2, 8, 9	
	Flx 20mg	2178	1	
	Flx 20mg	2184	1	
	Flx 20mg	2185	1, 2, 10	
	Flx 20mg	2195	1, 2	
	Flx 20mg	2197	1, 4, 5	
	Flx 20mg	2210	1	
	Flx 20mg	2212	1	
	Flx 20mg	2214	1	
	Flx 20mg	2230	1	
	Flx 20mg	2231	1	
	Flx 20mg	2235	1	
	Flx 20mg	2237	1	
	Flx 20mg	2242	1	
	Flx 20mg	2244	1, 5, 6	
	Flx 20mg	2249	1	
	Flx 20mg	2250	1	
	Placebo	2001	1-7	
	Placebo	2002	1-10	
	Placebo	2007	1-10	
	Placebo	2013	1-10	
	Placebo	2017	1-10	
	Placebo	2025	1-10	
	Placebo	2026	1-6	
	Placebo	2032	1-10	
	Placebo	2038	1-10	
	Placebo	2050	1-7	
	Placebo	2052	1-8	
	Placebo	2057	1-4	
	Placebo	2061	1-7	
	Placebo	2064	1-10	
	Placebo	2066	1-8	
	Placebo	2068	1-8	
	Placebo	2069	1-10	
	Placebo	2087	1-3	
	Placebo	2093	1-10	
	Placebo	2095	1-10	
	Placebo	2096	1-5	
	Placebo	2098	1-10	
	Placebo	2100	1-10	
	Placebo	2102	1-8	
	Placebo	2107	1-7	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - Fluoxetine Side-Effects Checklist				
	Placebo	2114	1, 2	
	Placebo	2115	1, 10	
	Placebo	2133	1	
	Placebo	2147	1	
	Placebo	2166	1	
	Placebo	2167	1, 10	
	Placebo	2172	1	
	Placebo	2177	1	
	Placebo	2179	1, 2, 10	
	Placebo	2180	1	
	Placebo	2187	1	
	Placebo	2204	1, 3	
	Placebo	2207	1, 3	
	Placebo	2211	1	
	Placebo	2213	1	
	Placebo	2220	1	
	Placebo	2229	1	
	Placebo	2233	1, 2	
	Placebo	2238	1	
	Placebo	2246	1	
	Placebo	2251	1, 5	
	Placebo	2252	1	
	NR	2016	1	
	NR	2060	1-7	
	NR	2104	1, 1A	
	NR	2112	1, 1A	
	NR	2132	1	
	NR	2136	1	
	NR	2138	1, 1A	
	NR	2146	1, 1A	
	NR	2155	1	
	NR	2188	1	
	NR	2190	1	
	NR	2221	1	
Missing Study Assessments - CDRS-R				
	Flx 20mg	2010	9	
	Flx 20mg	2033	4	
	Flx 20mg	2051	5	
	Flx 20mg	2067	6	
	Flx 20mg	2073	7	
	Flx 20mg	2075	6	
	Flx 20mg	2124	7	
	Flx 20mg	2126	6	
	Flx 20mg	2173	5	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - CDRS-R				
	Flx 20mg	2244	6	
	Placebo	2007	6, 9	
	Placebo	2061	4	
	Placebo	2066	6	
	Placebo	2102	1	
	Placebo	2204	3	
	Placebo	2207	3	
	NR	2112	1	
Missing Study Assessments - CGI				
	Flx 20mg	2010	9	
	Flx 20mg	2033	4	
	Flx 20mg	2051	5	
	Flx 20mg	2067	6	
	Flx 20mg	2073	7	
	Flx 20mg	2075	6	
	Flx 20mg	2124	7	
	Flx 20mg	2173	5	
	Flx 20mg	2244	6	
	Placebo	2061	4	
	Placebo	2066	6	
	Placebo	2204	3	
	Placebo	2207	3	
Missing Study Assessments - BPRS-C				
	Flx 20mg	2010	9	
	Flx 20mg	2012	5, 8	
	Flx 20mg	2014	2, 6	
	Flx 20mg	2019	6	
	Flx 20mg	2029	8	
	Flx 20mg	2030	2	
	Flx 20mg	2033	4	
	Flx 20mg	2040	1	
	Flx 20mg	2051	5	
	Flx 20mg	2067	6	
	Flx 20mg	2073	7	
	Flx 20mg	2075	6	
	Flx 20mg	2124	7	
	Flx 20mg	2126	6	
	Flx 20mg	2173	5	
	Flx 20mg	2244	6	
	Placebo	2007	6, 7, 8, 9	
	Placebo	2013	6	
	Placebo	2026	5	
	Placebo	2032	4	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - BPRS-C				
	Placebo	2061	4	
	Placebo	2066	6	
	Placebo	2095	6	
	Placebo	2204	3	
	Placebo	2207	3	
Missing Study Assessments - BDI				
	Flx 20mg	2014	1, 3, 5, 8	
	Flx 20mg	2029	1, 3, 5, 6, 8	
	Flx 20mg	2042	1, 3, 5, 8	
	Flx 20mg	2051	3, 5	
	Flx 20mg	2067	1, 3, 5, 6, 8	
	Flx 20mg	2073	1, 3, 5, 7, 8	
	Flx 20mg	2075	1, 3, 5, 6, 8	
	Flx 20mg	2085	1, 3, 5, 8	
	Flx 20mg	2090	1, 3, 5, 8	
	Flx 20mg	2123	1, 3, 5	
	Flx 20mg	2124	1, 3, 5, 7, 8	
	Flx 20mg	2149	1, 3, 5, 8	
	Flx 20mg	2153	1, 3, 5, 8	
	Flx 20mg	2163	1, 3, 5, 8	
	Flx 20mg	2169	1, 3, 5, 8	
	Flx 20mg	2174	3, 5	
	Flx 20mg	2178	1, 3, 5, 8	
	Flx 20mg	2184	1, 3, 4, 5, 8	
	Flx 20mg	2195	1, 3, 5	
	Flx 20mg	2235	1, 3, 5, 8	
	Flx 20mg	2237	1, 3, 5, 8	
	Flx 20mg	2244	3, 5, 6, 8	
	Flx 20mg	2249	3, 5, 8	
	Flx 20mg	2250	1, 3, 5	
	Placebo	2002	1, 2, 5, 6, 8, 9	
	Placebo	2013	1, 3, 5, 6, 8, 9	
	Placebo	2017	1, 3, 5, 8	
	Placebo	2038	1, 3, 5, 8, 10	
	Placebo	2050	1, 3, 5	
	Placebo	2052	3, 5	
	Placebo	2057	1, 3	
	Placebo	2064	1, 3, 5, 8	
	Placebo	2087	1, 3	
	Placebo	2096	1, 3, 5	
	Placebo	2100	1, 3, 5, 8	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - BDI				
	Placebo	2102	1, 3, 5, 8	
	Placebo	2107	1, 3, 5	
	Placebo	2114	1, 3, 5, 8	
	Placebo	2133	1, 3, 5, 6, 8	
	Placebo	2167	1, 3, 5, 8	
	Placebo	2179	1, 3, 5, 8	
	Placebo	2187	1, 3, 5	
	Placebo	2204	1, 3, 5, 8	
	Placebo	2215	1, 3, 5	
	Placebo	2220	1, 3, 5	
	Placebo	2238	3, 5	
	Placebo	2246	3, 5, 8	
	Placebo	2251	3, 5	
	NR	2104	1	
	NR	2132	1	
	NR	2138	1	
	NR	2146	1	
	NR	2155	1	
	NR	2188	1	
	NR	2190	1	
	NR	2221	1	
Missing Study Assessments - CDI				
	Flx 20mg	2010	1, 3, 5, 6, 8, 9	
	Flx 20mg	2012	1, 3, 5, 6, 8, 9	
	Flx 20mg	2019	1, 3, 5, 6	
	Flx 20mg	2030	1, 3, 5	
	Flx 20mg	2033	1, 3, 4	
	Flx 20mg	2040	1, 3, 5, 8, 9, 10	
	Flx 20mg	2047	1, 3, 5, 8	
	Flx 20mg	2083	1, 3, 5, 8	
	Flx 20mg	2119	1, 3, 5	
	Flx 20mg	2120	1, 3, 5, 8	
	Flx 20mg	2125	1, 3, 5	
	Flx 20mg	2126	1, 3, 5, 6, 8	
	Flx 20mg	2142	1, 3, 5, 8	
	Flx 20mg	2162	1, 3, 5, 8	
	Flx 20mg	2173	1, 3, 5	
	Flx 20mg	2185	1, 3, 5, 6, 8	
	Flx 20mg	2186	1, 3, 5	
	Flx 20mg	2197	1, 3, 5, 8	

(continued)

Type of Violation	Therapy	Patient Number	Visit Number	Comments
Missing Study Assessments - CDI				
	Flx 20mg	2210	1, 3, 5, 8	
	Flx 20mg	2212	1, 3, 5, 8	
	Flx 20mg	2214	1, 3, 5, 8	
	Flx 20mg	2230	3, 5, 8	
	Flx 20mg	2231	3, 5, 8	
	Flx 20mg	2242	3, 5, 8	
	Placebo	2001	3, 5	
	Placebo	2007	1, 4, 5, 6, 7, 8, 9, 10	
	Placebo	2025	1, 3, 5, 8, 10	
	Placebo	2026	1, 3, 5, 6	
	Placebo	2032	1, 2, 3, 5, 8	
	Placebo	2061	1, 3, 4, 5	
	Placebo	2066	1, 3, 5, 6	
	Placebo	2068	1, 3, 5, 6	
	Placebo	2069	1, 3, 5, 8	
	Placebo	2093	1, 3, 5, 8	
	Placebo	2095	1, 3, 5, 8	
	Placebo	2098	1, 3, 5, 8	
	Placebo	2115	1, 3, 5, 8	
	Placebo	2147	1, 3, 5, 8	
	Placebo	2166	1, 3, 5, 8	
	Placebo	2172	1, 3, 5, 8	
	Placebo	2177	1, 3, 5, 8	
	Placebo	2180	1, 3, 4, 5, 8	
	Placebo	2207	1, 3	
	Placebo	2211	3, 5, 8	
	Placebo	2213	1, 3, 5	
	Placebo	2229	1, 3	
	Placebo	2233	1, 2, 3, 5	
	Placebo	2252	3	
	NR	2016	1	
	NR	2060	1, 1A	
	NR	2136	1	

Data for this table were taken from Note-to-File data.

Abbreviations: ADHD = attention-deficit hyperactivity disorder; NR = not randomized; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; Sum = summary visit (last visit for the patient).

16.2.4.
Patients Excluded from the Efficacy Analysis

All randomized patients with a baseline and at least one postbaseline measurement were included in the efficacy analyses. Of the 96 randomized patients, 95 patients were analyzed. Patient 2207 was not included in the primary analysis because she did not have a postbaseline CDRS-R assessment.

16.2.5.
Demographic Data

Please see SAS Transport file located in Item 11 of this submission.

16.2.6.
Compliance Data Listing

Please see SAS Transport file located in Item 11 of this submission.

16.2.7.
Individual Efficacy Response Data

Please see SAS Transport file located in Item 11 of this submission.

16.2.8.
Listing of Individual Laboratory Measurements by Patient

Please see SAS Transport file located in Item 11 of this submission.

16.3
Clinical Report Forms (CRFs)

Please refer to Item 12 of this submission.

16.4
Individual Patient Data Listings

16.4.1. Concomitant Medications Listing by Patient
16.4.2. Vital Signs, Height, and Weight Listing by Patient
16.4.3. Electrocardiograms Listing by Patient
16.4.4. Comments Listing by Patient
16.4.5. Patient Summary Listing

Please see SAS Transport file located in Item 11 of this submission.