

The pervasive financial and scientific corruption of psychiatric drug trials

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Abstract

BACKGROUND: Placebo-controlled trials of psychiatric drugs are often biased by design. We assessed the pivotal trials for serious bias in FDA approved drugs between 2013 and 2017 and subsequent review articles and the money flow from the companies to the key psychiatrists.

METHODS: Critical assessment and searching information in databases on the money flow and on sales to Medicaid and Medicare in USA.

RESULTS: One depression pill, four psychosis pills and two treatments for tardive dyskinesia were approved. All reviewed trials included company employees as authors. The inclusion criteria favoured the drug cohorts; and, except for the tardive dyskinesia studies, all trials had "placebo" groups that were exposed to withdrawal effects. Despite this iatrogenic harm, the effects were mostly below the minimal clinically relevant effect. Subsequent review articles frequently touted the new drugs as having advantages over existing drugs. Key psychiatrist authors and key speakers have received substantial amounts of money from the manufacturers.

CONCLUSIONS: The testing and marketing of psychiatric drugs is a commercial enterprise that is scientifically corrupt. This corruption turns drugs that fail to provide a clinically meaningful benefit into "safe and effective" medications that generate revenues exceeding \$1 billion in their first years on the market.

Introduction

The 2013 Open Payments legislation in the United States requires pharmaceutical companies to disclose their direct payments to physicians. It was expected to help counter the corrupting influence of such payments, but an extensive 2021 investigation indicated that the corruption of psychiatric practices is more entrenched than ever and affects the testing of new drugs, the reporting of results in medical journals, and the marketing.¹ We report here a summary of these findings and provide additional information.

Material and methods

One of us (RW) identified new psychiatric drugs approved by the FDA between 2013 and 2017 and identified the pivotal phase II/phase III studies cited in review articles of the drugs up to and including 2020. RW used the Open Payments database to identify those psychiatrists who received the most money from the drug industry, and the Centers for Medicare and Medicaid Services to find their payments to the companies for individual drugs. Review articles about

the new drugs were retrieved from searches on PubMed for articles that listed the chemical names of the drugs, without any time constraints, and provided information about clinical trial results.

Results

Seven new psychotropic drugs were approved by the FDA from 2013 to 2017: a depression pill, four psychosis pills and two treatments for tardive dyskinesia (Table 1).

The million dollar club

Following the passage of the disclosure law, direct payments to US psychiatrists increased slightly, from \$48 million in 2014 to \$55 million in 2019, but fell in 2020 due to the COVID-19 pandemic.¹ From 2014 to 2020, pharmaceutical companies paid \$340 million to US psychiatrists to serve as their consultants, advisers, and speakers, or to provide free food, beverages and lodging to those attending promotional events. Research support and payments for continuing medical education (CME) lectures are not included in this amount. Approximately 75% of all US psychiatrists were listed in the Open Payments database (this database includes listings of psychiatrists who received free meals or other such smaller gifts.) Each year, before the pandemic year of 2020, more than 200 US psychiatrists earned at least \$50,000 for serving as speakers or consultants to pharmaceutical companies. Sixty-two psychiatrists received \$1 million or more from 2014 through 2020.¹

The top earner was Stephen Stahl (Table 2). He earned \$8.6 million, with \$6.6 million coming from Takeda that sells vortioxetine, one of the drugs in Table 1. In 1991, the Office of Scientific Integrity at the US Department of Health and Human Services determined that Stahl had been the lead author on two papers that were "seriously misleading" and that he was guilty of plagiarism in a book chapter.² Stahl, then a professor of psychiatry at Stanford University, moved to a position at the University of San Diego, and the scandal was quickly forgotten.

For the past 25 years, Stahl has been one of the most influential psychiatrists in the world regarding the use of psychotropic medications. His textbook, *Stahl's Essential Psychopharmacology*, and his clinical manual, *Essential Psychopharmacology Prescriber's Guide*, can be found on the bookshelves of many of those who prescribe psychiatric drugs. In 2000, he founded the Neuroscience Education Institute, a medical education company that produces webinars and CME courses on psychopharmacology.³ It openly promises pharmaceutical companies that it can help them sell their drugs. It also publishes *CNS Spectrums*, a peer-reviewed journal with Stahl as Editor-in-Chief. As new drugs are tested and earn FDA approval, he frequently writes articles about them, often in his own journal.

Stahl's lectures and scientific presentations have been distributed as more than a million CD-ROMs, internet educational programs, videotapes, audiotapes, and programmed home study texts for continuing CME to hundreds of thousands of professionals in many different languages.¹

The other top earners are also highly influential. Number three on the list is Leslie Citrome, currently

Table 1. New FDA approved psychotropic drugs from 2013 to 2017.

Sponsor	Trade Name	Chemical	FDA Approval	Indication
Takeda/Lundbeck	Brintellix/Trintellix	vortioxetine	2013, 30 Sept	depression
Otsuka/Lundbeck	Abilify Maintena	aripiprazole injection	2013, 28 Feb	schizophrenia/bipolar
Alkermes	Aristada	aripiprazole lauroxil	2015, 5 Oct	schizophrenia
Otsuka/Lundbeck	Rexulti	brexpiprazole	2015, 10 July	schizophrenia/depression
Allergan/Forest/Gedeon Richter	Vraylar	cariprazine	2015, 17 Sept	schizophrenia/bipolar
Teva	Austedo	deutetrabenazine	2017, 3 April	tardive dyskinesia
Neurocrine Biosciences	Ingrezza	valbenazine	2017, 11 April	tardive dyskinesia

Table 2. Top ten in the million dollar club.

	Name	Total	Medical school affiliation	Title
1	Stephen Stahl	\$8,609,877	UC San Diego	Adjunct Professor
2	Rakesh Jain	\$4,866,501	Texas Tech University	Clinical Professor
3	Leslie Citrome	\$4,275,025	New York Medical College	Clinical Professor
4	Gustavo Alva	\$4,133,270	UC Riverside	Assistant Clinical Professor
5	Andrew Cutler	\$3,262,411	SUNY Upstate Medical University	Clinical Associate Professor
6	Gregory Mattingly	\$3,257,025	Washington University	Associate Clinical Professor
7	Jason Kellogg	\$3,140,550	None	
8	Henry Nasrallah	\$2,714,676	University of Cincinnati	Professor Emeritus
9	Vladimir Maletic	\$2,668,650	University of South Carolina	Clinical Professor
10	Michael Measom	\$2,553,124	None	

president of the American Society of Clinical Psychopharmacology, which publishes the *Journal of Clinical Psychiatry*, a favourite venue for pharmaceutical companies.

Jelena Kunovac is one of several on the list with experience of running a for-profit company that conducts industry-funded clinical trials. In 2012, she founded Altea Research in Las Vegas, and most of her income of \$1.3 million for her regular presence on the speaker's circuit came from three companies: Sunovion, which sells Latuda (lurasidone), a psychosis pill; Alkermes, which sells Aristada (aripiprazole); and Otsuka, which sells Rexulti (brexpiprazole) and Abilify Maintena (aripiprazole). The three latter drugs are among the seven in Table 1.

Prakash Masand has founded two companies providing CME services. Drug firms provide support to CME companies, which is used to pay the speakers, but since the CME companies "independently" select the speakers, these payments don't show up in the Open Payments database. Much of Masand's recent income from the drug industry came from Allergan for promoting Vraylar (cariprazine), yet another drug in Table 1. These CME speakers are often the same psychiatrists that are being paid by the drug companies to serve as their consultants and speakers. Critics of this non-disclosure practice have likened it to money laundering.⁴ From 2014 through 2020, industry payments to CME companies totalled \$5.1 billion.⁵ A rough estimate, based on available data, is that this would have provided an additional \$100 million in speaking fees to US psychiatrists during this period.

Lack of independent clinical trials

We sampled 22 published reports of the pivotal clinical trials, which were sufficiently detailed to allow a critical analysis of the methods, results and conclusions (Table 3).

In total, there were 187 named authors on the 22 reports. As several authors appeared repeatedly, the number of authors was much less than 187. Company employees were listed 119 times, and every article listed at least two company employees as authors. Other people were listed 68 times, and there were only five instances (3%) where an author didn't have a financial tie to the sponsor.

Pretense of science

The 22 published trial reports we assembled tell a story of "statistically significant" results and of drugs being "safe and effective," which is a standard conclusion useful for marketing but detached from what the trials actually showed. The scientific dressing up obscures the obvious, that the testing of psychiatric drugs and the reporting or non-reporting of the results occurs within a commercial context where the companies are in total control with respect to how the trials are designed and analysed, and what is published.

The clinical trial results are often published in journals with substantial financial conflicts of interest in relation to the drug companies. One such journal is the *Journal of Clinical Psychiatry*, the official journal of

Table 3. Authorship of trial reports of pivotal clinical trials.

Chemical name	No. of studies sampled	No. of employee authors	No. of non-employee authors	No. of authors with no financial tie to sponsor
Vortioxetine	4	10	6	1
Aripiprazole monthly	3	29	4	0
Aripiprazole lauroxil	2	12	5	0
Brexpiprazole	3	23	4	0
Cariprazine	6	35	15	0
Deutetrabenazine	2	4	24	4
Valbenazine	2	6	10	0
Totals	22	119	68	5

Table 4. Articles on the seven new drugs in *Journal of Clinical Psychiatry*

	No. of studies in J Clin Psychiatry	ASCP officer or board member as author	ASCP officer or board member as lead author
Vortioxetine	12	6	1
Aripiprazole monthly	6	5	4
Arpiprazole lauroxil	6	1	0
Brexpiprazole	6	1	1
Cariprazine	7	3	3
Deutetrabazine	7	3	3
Valbenazine	9	5	4
Totals	53	24	16

Table 5. Articles in *CNS Spectrums* authored by Stahl or Citrome

	No. of studies in CNS Spectrums	With Stahl as author	With Citrome as author
Vortioxetine	21	5	0
Aripiprazole monthly	3	0	1
Arpiprazole lauroxil	10	0	3
Brexpiprazole	5	1	1
Cariprazine	10	2	2
Deutetrabenazine	13	1	1
Valbenazine	9	1	2
Totals	71	10	10

the American Society of Clinical Psychopharmacology (ASCP), which states on its website that it is the "World's most cited independent, indexed, clinical psychiatry journal."⁶

Seven of the 22 reports were published in this journal. Moreover, Stephen Stahl and Leslie Citrome often support the marketing effort by publishing review articles, which suggest that the new drugs, perhaps due to a novel mechanism of action, will prove to be more effective or have fewer side effects than their competitors. The *Journal of Clinical Psychiatry* serves as home for such articles, too (Table 4).

We found 53 articles about the seven new drugs in this journal published from 2012 onward, of which 24 had an ASCP officer or board member listed as an author. An ASCP board member was the lead author on 16 of the articles. Sixteen of the 17 officers and board members of the ASCP had financial ties to the drug industry.⁷ The president, Leslie Citrome, was paid \$4.3 million by pharmaceutical companies from 2014-2020; in total, the officers and board members were paid \$8 million during this period.

We found 71 articles about these drugs in *CNS Spectrums* that were published since 2012. Stahl and Citrome each authored 10 of them (Table 5).

Together, they were paid \$12.9 million by pharmaceutical companies from 2014 to 2020, most of which (\$9.3 million) was for giving talks.

In the following, we describe the pivotal studies of the seven new drugs and reviews about the drugs.

Trintellix or Brintellix (vortioxetine)

Three trials assessed various doses of the drug versus placebo in patients with depression.⁸⁻¹⁰ Five comparisons with placebo were positive and one was not. A fourth study found that the drug reduced the risk of relapse.¹¹

As the placebo groups were composed of drug-withdrawn patients, these trials cannot assess if vortioxetine is better than placebo. This withdrawal design causes abstinence depression in some people, as illustrated in a 1998 trial of 242 patients with remitted depression.¹² The patients had received open maintenance therapy with fluoxetine, sertraline, or paroxetine for 4 to 24 months after they had become well. They then had their therapy changed to a double-blind placebo for 5-8 days at a time unknown to the patients and clinicians. The study was funded by Eli Lilly, the maker of fluoxetine, which had an obvious interest in showing that fluoxetine causes fewer withdrawal

symptoms than the two other drugs because of the very long half-life of its active metabolite, about one to two weeks.

The three most common withdrawal symptoms were worsened mood, irritability, and agitation. Out of 122 patients on sertraline or paroxetine, 25 fulfilled the authors' criteria for depression. Without the abrupt withdrawal, likely none or at most one patient among 122 whose depression had been in remission for 4-24 months would be expected to become depressed during 5-8 days.

In spite of such research, the trials of vortioxetine used a drug-withdrawn group as the placebo group. Based on the published results from six flawed trials, five well-known US psychiatrists, led by Alan Schatzberg, along with a Canadian psychiatrist, praised the drug in "Academic highlights: an overview of vortioxetine" in the *Journal of Clinical Psychiatry*.¹³ They wrote that the drug had "shown superiority over placebo;" that it enhanced levels of serotonin, norepinephrine, dopamine, acetylcholine and histamine in "specific" areas of the brain, which, at least in theory, could provide "potentially unique, beneficial outcomes in patients treated with the agent;" that its "multimodal pharmacologic activity may convey benefit in cognitive function;" and that its "favorable tolerability profile may have meaningful advantages with regard to weight gain and low sexual dysfunction that may benefit patients."

In several of the trials, the investigators had avoided asking patients questions about specific harms known to be caused by depression pills (such as sexual dysfunction, which patients are not likely to report about unless asked). The protocols told investigators to simply ask patients, "How do you feel?" This approach led to a conclusion that vortioxetine was less likely to cause sexual dysfunction than other depression pills.

In a review of the data submitted to the FDA, the Institute for Safe Medication Practices reported that there had been ten trials of vortioxetine, rather than the six cited by Schatzberg and colleagues.¹⁴ In four of them, which had not been published, the drug was no better than placebo. The Institute also found that once vortioxetine was on the market, adverse events reported to the FDA told of a problematic drug. In a 12-month period, there were 45 deaths associated with vortioxetine use, adverse behavioural changes (suicide, self-injury, hostility, and aggression), numerous reports of sexual dysfunction, and the emergence of eating disorders.

Patient Drug News reported a long list of harms associated with vortioxetine and advised avoiding use of the drug because the most recent evidence from the FDA showed that the drug has "little benefit" and "significant risks."¹⁵ Meanwhile, the FDA informed Lundbeck and Takeda that they couldn't state that their drug produced cognitive benefits, as the data didn't support this.¹⁶

Medicaid and Medicare paid \$1.3 billion to the makers of Trintellix/Brintellix from 2014 to 2019, with sales rising each year (\$406 million in 2019).

Abilify Maintena (injectable aripiprazole)

Abilify Maintena is a long-acting formulation of aripiprazole.

In a maintenance trial in schizophrenia, the researchers enrolled 843 patients who had their psychosis pill replaced by oral aripiprazole.¹⁷ Those who stabilized on this drug were transitioned to injectable aripiprazole once monthly, and those who stabilized on the injectable for three months were randomized into a double-blind trial. This design

produced a select group of good responders for the randomized trial (403 of the initial 843 subjects), with one cohort following randomization maintained on the injectable and the other given a placebo injection. Only 10% in the drug-maintained group relapsed versus 40% in the placebo group. Another maintenance trial, in patients with bipolar 1, had a similar design.¹⁸

In the study in schizophrenia, 62% in the placebo group suffered "treatment emergent" adverse events, including 6% with akathisia. Placebo cannot cause akathisia, which is a withdrawal symptom. As akathisia increases the risk of suicide, violence and homicide,^{19,20} these studies put patients at great risk of harm, and they cannot assess if Abilify Maintena is better than placebo.

Patients switched to placebo began to worsen within two weeks, but even given this flawed design, the difference in scores on the Positive and Negative Syndrome Scale (PANSS) was only 12, which is less than the minimal clinically relevant difference of 15.²¹ Moreover, the researchers stopped the trial early, such that there were only 23 patients in the study who remained stable on Abilify Maintena for 52 weeks, a long-term stabilization rate of 3%. As for adverse events, two patients in the Abilify Maintena arm died, including one from a coronary event, but the investigators concluded that these deaths were unrelated to the treatment.

Even though Abilify Maintena did not provide a meaningful clinical benefit, the authors told of a treatment that was "effective for preventing relapse in schizophrenia."

A third study was said to provide evidence of the injectable's efficacy in curbing an acute psychotic episode.²² However, first-episode patients were excluded from the study. Instead, chronic patients with a long history of psychosis pill use were withdrawn from their medication and then randomized either to placebo or to the injectable (and an oral dose of aripiprazole for two weeks). As the placebo group was composed of chronic drug-withdrawn patients, the trial cannot assess the effect of Abilify Maintena as a treatment for acute episodes of schizophrenia.

Sales to Medicare and Medicaid totalled \$3 billion from 2014 to 2019.

Aristada (aripiprazole lauroxil)

This injectable form of aripiprazole was touted as being an improvement over the once-monthly Abilify Maintena because of its more long-lasting effect.

The pivotal study, in patients with an acute exacerbation of schizophrenia, was flawed for several reasons,²³ e.g. patients who had had an "inadequate response to oral aripiprazole" were excluded, and patients randomized to placebo were exposed to withdrawal symptoms. The 12-point difference in the PANSS scores between drug and placebo also did not rise to the level of a "minimally clinical important" difference of 15 points. Yet, the investigators concluded that, "This study demonstrated robust efficacy of multiple doses of aripiprazole lauroxil" and that, "The clinical profile of aripiprazole combined with the flexibility afforded by novel technology and ability to administer in the deltoid and gluteal muscles may represent a new treatment option for both clinicians and their patients with schizophrenia."

The percentage of patients who suffered a "treatment-emergent adverse event" was *highest* for the placebo group (62% vs 58%), which included 4% with akathisia.

Aristada sales to Medicaid and Medicare amounted to \$726 million for 2015-2019.

Rexulti (brexpiprazole)

In all three pivotal trials in schizophrenia, the usual drug-withdrawal group masqueraded as a placebo group.²⁴⁻²⁶ First-episode patients were not eligible for the trials, which assured that there would be no drug-naïve patients in the so-called placebo group.

None of the doses of brexpiprazole came close to providing a minimal clinically relevant benefit. In a pooled analysis of the studies,²⁶ the 2 mg dose provided only a 5.5-point difference on PANSS and the 4 mg dose only a 6.7-point difference.

After the results were published, Citrome authored several articles on brexpiprazole and concluded that it "may be particularly beneficial for patients who have struggled with restlessness or akathisia during past medication trials or those who are looking for an alternative medication that is not highly sedating."

Otsuka and Lundbeck had previously jointly brought Abilify Maintena to market, and they once again regularly employed the same top-earning quartet of speakers, all on the million dollar list: Rebecca Roma, Matthew Brams, Rifaat El-Mallakh and Charles Nguyen.

Sales to Medicaid and Medicare grew steadily from 2015 to 2019, with \$1.4 billion in total sales.

Vraylar (cariprazine)

The only investigator listed as author on one or more of the six pivotal trials in schizophrenia and bipolar²⁷⁻³² who had no financial ties to the companies, Henry Nasrallah, was subsequently paid \$75,823 by Allergan, mostly for speaking services.

All the trials were flawed by their abrupt withdrawal design. Even though first-episode patients were excluded from the three trials in schizophrenia and thus all in the placebo group were suffering from drug-withdrawal hazards,²⁷⁻²⁹ a pooled analysis found a differences in PANSS scores of only 6.5 to 9.5 points according to dose.²⁸ Once again, these scores did not rise to the level of a clinically important difference. Yet, the researchers concluded that, "cariprazine was effective versus placebo in all five PANSS factor domains, suggesting that it may have broad-spectrum efficacy in patients with acute schizophrenia."

One of the three schizophrenia trials was a relapse prevention study.²⁹ Only those who stabilized and remained stable on cariprazine for 20 weeks were randomized into the double-blind study. The relapse rate was 25% in the cariprazine-maintained group and 48% in the drug-withdrawn "placebo" group. The authors concluded that, "Long-term cariprazine treatment was significantly more effective than placebo for relapse prevention in patients with schizophrenia."

However, of the 765 patients enrolled into the study, only 200 successfully stabilized on cariprazine and were randomized. Only 18 of those randomized to cariprazine completed the 72-week relapse study; the remaining 89 in the drug arm either relapsed, discontinued due to adverse events, withdrew their consent, or were lost to follow-up. Thus, the documented stay-well rate for the cariprazine-treated group was only 3% (18 of 765).

In three pivotal studies of cariprazine for depression in bipolar 1,³⁰⁻³² cariprazine provided a statistically significant benefit in only four of the seven comparisons in which the difference in symptom reduction ranged from 2.4 to 4.0 points on the 60-point MADRS scale, which would likely not be clinically relevant. The least recognizable effect on a similar scale, the 52-point Hamilton depression scale, is 5-6.³³ The researchers concluded that cariprazine "was effective, generally well-tolerated, and relatively safe in reducing

depressive symptoms in adults with bipolar 1 depression."

Sales to Medicaid and Medicare amounted to \$1.2 billion for 2016-2019.

Austedo (deutetrabenazine)

Austedo is a treatment for tardive dyskinesia.

In a pivotal study, patients suffering from tardive dyskinesia were allowed to continue taking the psychiatric medications they were on.^{34,35} The investigators used the Abnormal Involuntary Movement Scale (AIMS), which assesses motor function in seven areas, with scores of zero to four in each domain. A total score of 7 on the 28-point scale tells of minimal symptoms, with abnormal movements being "infrequent and not easy to detect." Researchers have determined that there needs to be at least a 2-point difference on AIMS for it to be clinically meaningful,³⁶ but there was only a 1.4-point difference between deutetrabenazine and placebo in the trial.

On two secondary efficacy scales, the Clinical Global Impression of Change and the Patient Global Impression of Change, the differences were not statistically significant. Furthermore, when asked to give their impression of whether the patients had improved, stayed the same, or become worse, neither the investigators nor the patients noticed a difference. Nonetheless, the authors concluded that, "deutetrabenazine was well tolerated and significantly reduced abnormal movements."

Teva's speakers list featured four psychiatrists from the million-dollar club: Richard Jackson, Rakesh Jain, Arvinder Walia, and Andrew Cutler.

Sales to Medicaid and Medicare amounted to \$399 million in 2019.

Ingrezza (valbenazine)

Valbenazine was also approved for tardive dyskinesia. In the pivotal study, the 80 mg dose led to a 3.1-point drop in symptoms on the AIMS scale compared to placebo, and the 40 mg dose to a 1.8-point drop.^{37,38} The researchers concluded that "valbenazine significantly improved tardive dyskinesia in participants with underlying schizophrenia, schizoaffective disorder, or mood disorder."

However, the mean AIMS baseline score was 10.0, which means minimal to mild symptoms, and only the 80 mg dose exceeded the 2-point criterion for a minimal clinically relevant difference. Moreover, there were no significant differences between either drug dose or placebo on the Clinical Global Impression of Change scale.

Ingrezza generated sales of \$1.2 billion to Medicaid and Medicare in its first two full years on the market.

Discussion

In our review of seven psychiatric drugs approved from 2013 through 2017, we found that the pharmaceutical companies controlled every aspect of the drug testing process. Their marketing of their drugs regularly involved substantial payments to psychiatrists who wrote review articles and served as their speakers.

We found that the trials of the seven drugs were designed not to inform, but to produce a "message" that could be used to market the drugs. Trials were biased by design; the pivotal trials of the depression pills and the psychosis pills were fatally flawed by their use of drug-withdrawal groups as "placebo" controls; and the abstracts and the main text in the published reports did not discuss the lack of clinically important

differences between the medication and drug-withdrawn placebo groups.

Subsequent review articles then provided a rationale for prescribing the new drugs, and CME lectures repeated the praise from the review articles.

Prior to the passage of the 2013 Open Payments legislation, there was widespread recognition that published reports of pivotal clinical trials, which serve as the foundation for promotion of "safe and effective" new drugs, were ghostwritten.^{39,40} Our review showed that the ghostwriting aspect has disappeared, but for a reason that further compromises the possible merits of the published results. The company's control of the reported results is now visibly present. All the published studies that we reviewed had company employees as authors, and nearly all of the non-employee authors were paid to serve as consultants or speakers for the sponsoring drug company. The 27 US psychiatrists and neurologists named as authors on the 22 reports of clinical trials were collectively paid \$4.8 million by the study sponsors, and collectively earned \$17.5 million in industry payments from 2014 through 2020.

Industry payments to psychiatrists were then a central component of their marketing of their new drugs. Money went to authors of positive reviews of the drug; money went to the officers and board members of the American Society of Clinical Psychopharmacology, which is the publisher of the *Journal of Clinical Psychiatry*; money went to those who gave CME lectures on the drugs (laundered through CME organizations that hired the speakers); and money went to speakers on the dinner circuit.

This corruption of science led to success in the marketplace for the manufacturers of these drugs. Medicare and Medicaid alone spent more than \$5 billion on these newly approved agents through 2019. This corruption also seems particular endemic in psychiatry. In 2013, ProPublica detailed how 22 physicians, based on disclosures from the 15 largest pharmaceutical companies, had earned more than \$500,000 from 2009 to 2012 for their speaking and consulting activities.⁴¹ Twelve of the 22 were psychiatrists. All 12 show up prominently in the Open Payments database, and 5 of them are in top 10 in psychiatry's million-dollar list.

This is only the visible part of an "iceberg" of corruption. Unpublished trials tend to have worse results than published ones. Scrutiny of internal clinical study reports – those the companies send to drug regulators to get their drugs approved – have consistently revealed that psychiatric drugs are less effective than the published reports claim and have far more serious harms than those published.^{19,42} As just one example, about half of the deaths and half of the suicides in clinical trials of psychiatric drugs are never published,⁴³ and suicidal thoughts or acts in depression trials are downplayed, e.g. by calling them something else like lack of effect, emotional lability, or hospital admission without revealing the reason.^{19,39}

Most of the patients recruited into the trials we reviewed were harmed by the study design. The trials of the four psychosis pills and the depression pill all led to placebo groups of patients quickly withdrawn from the medications they had been on, and thus exposed to withdrawal harms. If a psychiatrist in everyday practice abruptly withdrew patients from depression pills or psychosis pills and left them untreated for weeks or months, this would be seen as malpractice. Yet, that very act of clinical malpractice stands at the heart of randomised controlled trials of psychiatric drugs, and everyone turns a blind eye to this fact and pretends the withdrawn group reflects the "untreated" course of depression or schizophrenia.

One of the worst withdrawal symptoms is akathisia, which increases the risk of suicide and homicide.^{19,20,39} Although akathisia is often described with the euphemism "agitation,"³⁹ those suffering from it tell of being tortured by inner turmoil, and of being unable to sit still and pacing frantically around. For instance, the Product Monograph for paroxetine warns that, "There are clinical trial and post-marketing reports with SSRIs and other newer depression pills, in both pediatrics [sic] and adults, of severe agitation-type adverse events coupled with self-harm or harm to others. The agitation-type events include: akathisia, agitation, disinhibition, emotional lability, hostility, aggression, and depersonalization."²⁰

In the trials conducted during the 1990s, the cold turkey drug withdrawal design proved lethal. RW reviewed FDA reviews of four drugs and found that one in every 138 patients who entered the trials for risperidone (Janssen), olanzapine (Eli Lilly), quetiapine (AstraZeneca) and sertindole (Lundbeck) died, but none of these deaths were mentioned in the scientific literature, and the FDA didn't require them to be mentioned.⁴⁴ Many of these patients killed themselves; the suicide rate in the trials was two to five times the usual rate for patients with schizophrenia, and a major reason was the withdrawal-induced akathisia.⁴⁴

The studies of seven drugs approved from 2013 to 2017 were riddled with elements of bad science, and we have discussed only the most egregious elements. It is important to note that the exclusion of first-episode patients from several of the psychosis pill trials reveals that the manufacturers deliberately avoided addressing the efficacy question that, if the trials were a scientific enterprise, they would focus on. Psychosis pill-naïve patients are the very group that could provide a real test of whether a psychosis pill was better than placebo. Thousands of trials of psychosis pills have been carried out, but as of 2019, only one placebo-controlled trial in psychosis had been published that only included patients who had not received such a drug earlier. It was from China⁴⁵ and appeared to be fraudulent.⁴⁶ In 2020, another such trial was published, in 90 patients with a first-episode psychosis.⁴⁷ The researchers found that "group differences were small and clinically trivial, indicating that treatment with placebo medication was no less effective than conventional psychosis pill treatment." The authors of a 2011 systematic review of psychosis pills for early episode schizophrenia pointed out that the available evidence doesn't support a conclusion that psychosis pill treatment in an acute early episode of schizophrenia is effective.⁴⁸

The maintenance studies appear to provide evidence for longer-term use of the medications, but they are flawed by withdrawal effects present in the "placebo" cohorts, which render their short-term results unreliable. A large meta-analysis of the placebo-controlled trials showed that the apparent effect of continued treatment with psychosis pills on relapse prevention decreases over time and is close to zero after three years.⁴⁹

To our knowledge, only one maintenance study exists that has a sufficiently long follow-up.⁵⁰ This trial randomised 128 remitted first-episode patients with schizophrenia to dose reduction or discontinuation, or to maintenance therapy, for two years, after which the clinicians were free to choose the treatments they felt the patients needed. Two years after randomisation, more patients had relapsed in the dose reduction/discontinuation group than in the maintenance group (43% vs 21%). However, after seven years, there was no difference (62% vs 69%). More patients had recovered in the dose reduction/discontinuation group

than in the maintenance group (40% versus 18%), and recovery was the study's primary outcome.

Our review of the four psychosis pills approved from 2013 to 2017 reveals flaws that taint the whole evidence base for this class of drugs. There is no good evidence that they are effective over the short term in psychosis pill-naïve patients while there is good evidence that they markedly impair long-term recovery rates.⁵¹ They also increase mortality substantially in all patient groups.^{19,52}

The two new drugs for tardive dyskinesia, while marketed as effective treatments for this adverse effect of psychosis pills, in fact were found to do little to reduce that harm. They appear to affect brain chemistry in the same way that psychosis pills do. Tardive dyskinesia is seen in 5% of patients within the first year of treatment with a psychosis pill and increases by an additional 5% with each additional year of exposure,^{44,53} which explains why about half the patients in long-term facilities have it.⁵⁴ It can be difficult to spot, particularly because ongoing treatment with psychosis pills can mask the symptoms. When drugs are given at equivalent doses, there seems to be little or no difference in the occurrence of tardive dyskinesia on newer psychosis pills and on older ones.⁵³ It can be argued that the new drugs for tardive dyskinesia are simply another way of increasing the dose of a psychosis pill for masking purposes, as both types of drugs reduce dopamine in the brain, albeit by different mechanisms.⁵⁵

For depression pills, the story is very much the same. Virtually all trials are flawed by their drug-withdrawal design, and yet their effect on the Hamilton depression scale is only about 2,^{56,57} or less than the minimal clinically relevant effect of 5-6.³³

The findings from the key trials we reviewed were published multiple times and there was a flurry of secondary papers and review articles as well that we have not assessed.

Our review tells of a research enterprise, driven by commerce, that utterly fails to provide prescribers and the public with an "evidence" base for assessing the benefits and harms of psychosis pills. Critiques of the evidence base for depression pills reveal a similar failure. The trials were designed not to inform, but to deceive, with that deception central to the successful marketing of the drugs.

Conclusions

The testing of psychiatric drugs is best described as a charade, one that can turn drugs that fail to provide a meaningful clinical benefit into "safe and effective" medications that generate billions in revenues for the drug companies.

Conflicts of interest

None.

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