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Impact Of Fdaaa On Registration, Results Reporting, And Publication Of Clinical Trials Evaluating New Neuropsychiatric Drugs Approved Between 2005 And 2014

Constance Xuanyi Zou

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Impact of FDAAA on Registration, Results Reporting, and Publication of Clinical Trials Evaluating New Neuropsychiatric Drugs Approved between 2005 and 2014

A Thesis Submitted to the Yale University School of Medicine in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

by

Constance Xuanyi Zou

Class of 2019
Abstract

IMPACT OF FDAAA ON REGISTRATION, RESULTS REPORTING, AND PUBLICATION OF CLINICAL TRIALS EVALUATING NEW NEUROPSYCHIATRIC DRUGS APPROVED BETWEEN 2005 AND 2014

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Evidence-based medicine (EBM) promotes the use of randomized controlled trials (RCTs) published in peer reviewed medical journals as the “gold standard”. However, up to 50% of the completed clinical trials are never published and trials with results in favor of studied interventions are 2-4 times more likely to have been published then those with non favorable results. Publication bias seems to be a particularly severe problem for RCTs evaluating newly approved brand-name neuropsychiatric drugs. Mandatory trial registration, and later results reporting, were proposed to mitigate selective clinical trial publication and outcome reporting. Congress enacted the FDA Amendments Act (FDAAA) on September 27, 2007 requiring the registration of all non-phase I clinical trials involving FDA-regulated medical interventions and results reporting for FDA approved drugs. It’s been 10 years since FDAAA enactment, the impact of FDAAA on the selective publication of clinical trials has not been studied. Our objective is to determine whether FDAAA enactment is associated with improvements in trial
registration and results reporting, as well as with decreased publication bias of clinical trials evaluating new neuropsychiatric drugs. We conducted a retrospective cohort study of all efficacy trials supporting FDA new drug approval between 2005 to 2014 for neuropsychiatric indications. Trials were categorized as pre- or post-FDAAA based on initiation and/or completion dates as outlined by the statute. The main outcomes were the proportions of trials registered, proportions reported results in ClinicalTrials.gov, and the degree of publication bias. Publication bias was estimated using the relative risks pre- and post-FDAAA of both the publication of positive vs non-positive trials, as well as of publishing positive vs. non-positive trials without misleading interpretations. Registration and results reporting proportions were compared pre- and post-FDAAA using two-tailed Fisher Exact Test and the degrees of publication bias were compared by calculating the ratio of relative risks (RRR) for each period. Our study sample included 101 Pre-FDAAA and 41 Post-FDAAA efficacy trials supporting the FDA approval of 37 new drugs for neuropsychiatric indications between 2005 and 2014. Post-FDAAA trials were significantly more likely to be registered (100% vs 64%; P<0.001) and report results (100% vs 10%; P<0.001) than pre-FDAAA trials. Pre-FDAAA, positive trials were more likely to be published (RR=1.52; 95% Confidence Interval [CI]=1.17-1.99; P=0.002) and published without misleading interpretations (RR=2.47; CI=1.57-3.73; p<0.001) than those with non-positive results. In contrast, post-FDAAA positive trials were equally likely to have been published (RR=1; CI=1-1, p=NA), and published without misleading interpretations (RR=1.20; CI=0.84-1.72; p=0.30). The likelihood of publication bias pre-FDAAA vs. post-FDAAA was greater for publication of positive vs. non-positive trials (RRR=1.52; CI=1.16-1.99; p=0.002) and for publication without misleading interpretations (RRR=2.06, CI=1.17-3.61, p=0.01). The enactment of FDAAA was followed by significantly higher proportions of trials that were registered and reported
results on ClinicalTrials.gov, and with significantly lower degrees of publication bias among trials supporting recent FDA approval of drugs for neuropsychiatric indications.
Acknowledgement

We would like to thank Dr. Vinay Rathi (Yale University School of Medicine Class of 2015) for his outstanding peer mentorship. We thank the organizers of the Eighth International Peer Review Congress (PRC) for giving us the opportunity to present our work,\(^1\) and the editors and reviewers who helped us publish our manuscripts in Trials.

\(^1\) Video recording of Ms. Zou’s presentation has been made available by the meeting organizer through Youtube. [https://youtu.be/yDKwxE81Tk4](https://youtu.be/yDKwxE81Tk4)

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Introduction

The Role of Randomized Controlled Trials in Modern Medicine

Randomized controlled trials (RCT) started to have profound impacts on the practice of medicine today since the rise of evidence-based medicine (EBM), which has been defined as “the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.” (1) However, it is difficult, to put one’s finger on what made EBM the haute couture, based on its name and such a definition. Some find it difficult to distinguish the phrase EBM from the word medicine itself. (2, 3) (4–7)If one were to summarize the teaching of how-to-EBM textbooks and guides(14–18), EBM method describes an RCT based formula to answer hypothetical questions involving hypothetical patients with hypothetical diseases related to clinical care. The main agenda of the EBM campaign is to make sure that RCTs are the best evidence and that only the RCT are good enough to rely on as the “gold standard” for “judging whether a treatment does more good than harm” (19) because they are “so much more likely to inform clinicians and so much less likely to mislead them” (than the alternatives).(20)(3)(21)

The success of EBM campaign has resulted in many parts of medicine being governed by RCTs through the Practice Guidelines, which are usually issued by medical professional societies outlining best practices. These practice guidelines are welcomed by physicians who are believers of the power of RCT but find themselves incapacitated by the complexity of the method and the volume of the work involved in full EBM style investigation and calculation. The proponents of EBM may object to the idea that EBM encourages mindless following of practice guidelines, after all, the physician can and should
learn to speak the EBM fluently themselves and use it to guide their day to day practice. That could happen if the United States suddenly required graduate degrees in statistics for all medical school graduates; if the physicians have at least days between each appointment to perform one round of rituals in full as outlined by the 500-hundred page long EBM bible; (21) and if there is a sudden change of US malpractice law. The truth is the physicians cannot afford the time or the effort to perform EBM on their own. When they do try, it usually means a quick PubMed search followed by skimming through the abstracts of a few randomly selected publications of RCTs. They could not afford the luxury sometimes to disobey the order of the “best practice” as outlined in the practice guidelines, even when they have good reasons to believe it inappropriate for a given setting. They may lose bonuses tied to meeting “quality measures”, which are frequently based on guidelines, or worse, they can be sued for transgressing the norm as defined by their professional societies even though it was suppose to be a suggestion.

Practice guidelines are being used in the malpractice arena to define a credible standard of care to measure the accused physician for an alleged problem addressed. This may occur despite a medical society’s disclaimer that they are not intended, nor devised, for that purpose. (22)

**RCT, Gold Standard with an Achille’s Heel**

The EBM formula relies on RCTs published in the literature. The problem is as many as 50% of completed clinical studies were never published (23–42) What’s more, trials with non-positive results were significantly more likely to remain unpublished than trials with positive results and negative results were often manipulated to appear positive. (39, 43–46)

Experience has shown that such study reports do not always contain a complete, or entirely accurate, representation of study plans, conduct and outcomes. Outright fraud (i.e.,
deliberate deception) is unusual. However, incompleteness, lack of clarity, unmentioned deviation from prospectively planned analyses, or an inadequate description of how critical endpoint judgments or assessments were made are common flaws. (47)

Because studies were usually considered positive when whatever proposed new intervention works better than a control, publication bias leads to perceived efficacy. EBM informed clinical practice based on half of the whole truth can result in inappropriate enthusiasms for what’s new. Many considered the problems of nonpublication and untruthful publication to be particularly severe among trials evaluating newly approved brand name neuropsychiatric drugs. (48) Clinical studies supporting approved drugs for neuropsychiatric indications, such as paroxetine (Paxil) (49), reboxetine (Edronax) (50), gabapentin (Neurontin) (51), and lamotrigine (Lamictal) (52), have been identified as being subject to underreporting. Data demonstrating these drugs to be potentially ineffective for approved indications or suggesting harm were not publicly disclosed until the pharmaceutical companies’ internal documents were reviewed during legal proceedings (53, 54).

Ten years ago, if a psychiatrist were to use the EBM method to calculate and compare the effect size of any of the one dozen antidepressants approved in the previous several decades, he or she would find only good news—all of the published trials showed the drugs to be effective, but in fact only half of the completed trials were. The physician would overestimate the effect size of each drug for about 30%. (28) Take one of these antidepressants Serzone (nefazodone) for example, which was approved by the FDA in 1994. When the drug was just approved, Bristol-Myers called it a "significant" addition to the numerous antidepressants with an “additional boost, fewer side-effects—and a lower price.” (55) It was speculated that the sales of this drug contributed to the fact that Bristol-Myers Squibb “posted record results for 1996.” (56) While its effective size based
on FDA documents was only 0.26. Effect size measures the magnitude of difference between a given drug and the placebo. 0.2-0.5 is small difference, 0.5-0.8, medium, and 0.8-1, high. 0.26 means the difference between nefazodone and sugar pills are small. Because its effective size based on the published trials was 69% higher, EBM practice based on published RCTs would conclude that the drug seem to have a moderate effect. (28) It is also worth noting this drug was associated with severe liver toxicity and death and was pulled from the market in 2004. (57–59)

Similarly, among trials evaluating drugs indicated for anxiety (23), and psychotic disorders (60) that were first approved by the U.S. Food and Drug Administration (FDA) in recent decades, 80-90% of trials with negative or equivocal results were either not published or were published in a misleading manner to suggest a positive result, while nearly 100% of trials with positive results were published.

**RCT, Gold Standard or Gold Trojan Horse?**

Many feel that this new paradigm brought by EBM based on RCT is doomed to fail because the industry can and will harness the power of RCT for the benefit of the few. (2, 3, 61–73)

In the perfect world pictured by the proponents of EBM, RCTs are performed by disinterested researchers who are driven only by the desire to further truth, to improve care, and to reduce waste. In reality, most large RCT are sponsored by the industry as business strategy. It is unrealistic to expect that they will always choose to protect the public interest even at the cost of getting a smaller share of the $3 Trillion that United
States spends on healthcare each year, of which 17% were for prescription drugs. (74)

Because of high cost of new drug development, high risk of failure, and high potential financial gain, conflicts of interest is a particularly serious problem for RCT evaluating new drugs. With few exceptions, for profit industry are the primary funders of clinical trials because of the high cost associated with conducting early phase clinical trials to evaluate drugs that had never been used in humans: Phase II trials can cost up to $20 million dollars, while Phase III, up to $50 million each. On average, the cost to run clinical trials to support the FDA approval of a new drug for a single indications is about 200 millions dollars. In order for the drug company to profit, not only they need to recover the astronomical cost invested in the drug target that received approval, but also those that did not, which happens 2 to 50 times more often. (75, 76) (77)

**FDAAA: Mandatory Registration and Results Reporting**

What can be done to prevent the results of completed trials from being swept under the rug? Publication has always been and will likely remain voluntary, but if the protocols and results of all clinical trials can be found through a publicly accessible, centralized trial registry, it would be difficult for the sponsors to withhold trials with unfavorable results or to introduce post hoc analysis to encourage positive interpretations of the results. Additionally, Journal editors, peer reviewers, and interested members of the public could cross reference the results submitted by the sponsors and investigators for publication.

In 1997, Congress passed the FDA Modernization Act (FDAMA), which mandated the first U.S.-based public registry ClinicalTrials.gov in 2000 by the National Institute of Health (NIH). In 2005, the International Committee of Medical Journal Editors (ICMJE)
issued a policy requiring trial registration as a condition of publication in member journals. De Angelis et al., 2009, #257) Nonetheless, FDAMA only required registration of a small number of trials, while the ICMJE recommendation was only followed on a voluntary basis and still permitted publication of unregistered trials. (78) (79)

In 2007, Congress passed the FDA Amendments Act (FDAAA). At the time FDAAA was applicable to essentially all non-phase I interventional studies involving FDA-regulated drugs, biological products, or devices with manufacture site or trial site based in the United States. FDAAA mandated that sponsors and investigators register all applicable trials in ClinicalTrials.gov prior to subject enrollment, and report results to ClinicalTrials.gov within 30 days post approval of the indication being studied. FDAAA is applicable to trials that began after September 27th, 2007 and to earlier trials that were still ongoing as of December 26th, 2007. Inappropriately delayed registration and results reporting, as well as reporting of false results, are punishable by fines of up to $10,000 per day and can lead to withholding of funding from studies receiving federal support.

It has now been ten years since FDAAA was enacted. Its impact on clinical trial registration, results reporting, and publication bias has largely remained undetermined. (41) Recently we demonstrated that FDAAA was associated with increased registration and publication of clinical studies in another study involving new drugs approved to treat cardiovascular disease and diabetes (CXZ performed data validation and contributed to the final editing of the manuscript for publication). (80) However, no study has focused on trials involving drugs treating neurological and psychiatric conditions, an area for which concern for selective publication and outcome reporting remain.
Statement of Purpose

We conducted a retrospective cohort study using efficacy trials that were submitted to and reviewed by the FDA for the approval of new drug applications (NDA) between 2005 and 2014 for the treatment of neurologic and psychiatric conditions. Our objective is to compare the rate of registration, results reporting, and the degree of publication bias for efficacy trials involving newly approved drugs treating neurologic and psychiatric conditions before and after the enactment of FDAAA. For each trial, we determined whether a trial is pre- or post-FDAAA based on trial initiation and/or completion dates, as well as their registration, results reporting, and publication status. Prior to conducting this study, we put forth the following hypotheses:

1. There is an association between the FDAAA status, and the likelihood of trial registration on ClinicalTrials.gov.
2. There is an association between the FDAAA status, and the likelihood of trial results reported to ClinicalTrials.gov.
3. There is an association between the FDAAA status and the degree of publication bias.

The aim of this study was three fold: (1) to assess the impact of FDAAA on selective registration and publication of efficacy trials supporting new drugs approved by the FDA to treat neurologic and psychiatric conditions, (2) to assess the degree of publication bias
among trials evaluating newly approved neuropsychiatric drugs, and (3) to inform ongo-
ing efforts to regulate clinical trials registration and results reporting.
Method

Data Sources

Data were obtained from three sources: Drugs@FDA, ClinicalTrials.gov and PubMed’s listing of Medline-indexed journals. Drugs@FDA is a public database maintained by the FDA, providing access to regulatory actions and documents issued for each drug approved by the agency. ClinicalTrials.gov is a public clinical trial registry database maintained by the National Library of Medicine at the NIH (U.S. National Library of Medicine 2018). PubMed’s list of Medline-indexed journals includes more than 5,500 biomedical journals.

Novel Therapeutics Approved for Treating Neurological and Psychiatric Disorders, 2005-2014

The Center of Drug Evaluation and Research (CDER), which is part of the FDA, provides annual reports summarizing all New Drug Applications (NDAs) approved in each year (U.S. Food and Drug Administration). We downloaded the reports from 2005 to 2014, when available, and otherwise searched Drugs@FDA for those NDAs that were approved to treat neurologic and psychiatric disorders. Our study sample began with drugs approved in 2005 to align with our prior work (Downing, Aminawung et al. 2014) and because an earlier seminal study on the topic examined all antidepressants approved through 2004 (Turner, Matthews et al. 2008); we chose to exclude drugs approved after December 2014 to ensure that at least 24 months had passed between drug approval date and the date when we concluded the final search for the registration record, reported results and publication, which was March 2017. For each NDA, we recorded its
indication, orphan status, priority review status, accelerated approval status, sponsor, and approval date.

CXZ performed all of the above data collection in the summer of 2016. JSR, as the principle investigator, reviewed with CXZ the lists of approved NMEs and BLAs between 2005 and 2014 to ensure that all new drugs approved with neuropsychiatric indications were included in our sample. JSB, randomly selected 4 drugs using an online randomizer and validated the data collected for those 4 drugs.

_Efficacy Trials Supporting FDA New Neuropsychiatric Drug Approval_

As described in a comprehensive tutorial for how to use the Drugs@FDA (Turner 2013), we downloaded the relevant FDA files for each NDA from Drugs@FDA, including the approval letters, summary reviews, clinical reviews, and statistical reviews. Among these files, we searched for clinical trials evaluating the efficacy of the drugs under review. We included only trials for which the FDA discussed and characterized results, based on the assumption that these trials influenced the FDA’s decision to approve the study drug for the proposed indication. We excluded ongoing trials, phase I/safety-only trials, expanded access trials, terminated and withdrawn trials without enrollment, and trials evaluating indications different than that for which the drugs were originally approved. We also excluded failed trials. Failed trials were determined by the FDA and the results of failed trials are invalid. For each included trial, we recorded the following characteristics: pivotal status, phases, sponsors, study sites, trial length, randomization, blinding, types of control, description of the treatments, arms of the investigational drugs, enrollment numbers, and the primary efficacy endpoints. A pivotal study is defined by the FDA as “a definitive study in which evidence is gathered to
support the safety and effectiveness evaluation of the medical product for its intended use” (2013). Pivotal status was frequently assigned prospectively by FDA, occasionally assigned retrospectively by the FDA, or at times not assigned by FDA and thus determined using a previously described method. (Downing, Aminawung et al. 2014) All searches and data collection were done by CXZ between June 2015 and October 2015. JSB validated the data collected associated with previously randomly selected 4 NDAs.

_Determination of FDAAA Status_

At the time when FDAAA was enacted in 2007, it applied to trials that were initiated after September 27th, 2007, as well as to trials initiated earlier but still ongoing as of December 26th, 2007. Based on this, FDAAA applicable trials were categorized as post-FDAAA, while trials that were initiated or completed prior to the cut-off dates were categorized as pre-FDAAA. All coding was done by CXZ in the summer of 2015. JSB validated the data collected associated with previously randomly selected 4 NDAs.

_Determination of Registration and Results Reporting Status on ClinicalTrials.gov_

To determine whether trials were registered and reported results on ClinicalTrials.gov, one investigator (CXZ) performed the initial search using the following terms and their combination: generic, or brand names of the study drugs, drug indications, trial IDs, trial acronyms, numbers of participants randomized, comparators, and study time frames. All searches were done by CXZ between the summer of 2015. JSB validated the data collected associated with previously randomly selected 4 NDAs. For trials that were not able to be matched with any registration record, a second
investigator (JEB) independently performed a second round of searches. No new records were identified.

**Determination of Publication Status**

To determine whether trials were published, we searched PubMed for full-length publications using the same terms as we did for the registration record. Among identified publications, abstracts and conference reports were excluded. Publications reporting multiple trials, such as reviews and meta-analyses were also excluded unless the results of each trial were analyzed and discussed individually in the level of detail as one would expect from a full-length publication. When the search terms returned too many similar entries in PubMed, we used Google Scholar to narrow the results. Google Scholar has the advantage that it can search among the full texts of publications hosted by a variety of online database or platforms, while for many journals, especially those that require paid access, PubMed searches only among the title and abstracts. All searches were done by CXZ between the summer of 2015 and the spring of 2016. JSB validated the data collected associated with previously randomly selected 4 NDAs. For trials that were not able to be matched with any registration record, a second investigator (JEB) independently performed a second round of searches. No new records were identified.

**Interpretation of Trial Results: Publication vs. FDA**

Trials were classified as positive, negative, or equivocal based on the FDA’s interpretation of the results as described in **Additional File 1**. The classification was based on whether the primary outcome(s) achieved statistical significance while taking into consideration the summary statements made by the FDA medical reviewers
regarding whether or not the findings provide support for the efficacy claim of the study drugs. Published trial results were categorized similarly based on whether the primary outcomes achieved statistical significance according to the authors’ analysis while taking into considerations the authors’ conclusions in the abstract section. Trials with equivocal or negative results were grouped together as non-positive trials for purposes of calculating publication bias.

All data collection was done by CXZ between the summer of 2015 and the spring of 2016. JSB validated the data collected associated with previously randomly selected 4 NDAs. For trials that were not able to be matched with any registration record, a second investigator (JEB) independently performed a second round of searches. No new records were identified.

*Validating the Published Interpretations*

We validated the interpretations of the trial results made by the study investigators for each publication using the interpretations made by the FDA medical reviewers found in the FDA approval package as the gold standard. Both the conclusions in the abstract and the main text of the publications were validated. The two were considered in agreement if the interpretations were both categorized as positive, negative or equivocal, and no major contradictions existed between the two statements. As an example of contradiction between two sources: the published interpretation of trial 02 of milnacipran (Savella) concluded that “both doses (100 and 200 mg/d) were associated with significant improvements in pain and other symptoms.” (81) This was considered different from the statement made by the FDA in the summary review documents, which stated that “[the] analysis of the ‘pain only’ responders does not indicate that there is a significant effect of MLN
(Savella) on pain…. (treatment effect) was driven by the patient global response outcome rather than the pain or function outcome… when studied in isolation, statistically significant treatment effects for pain and function were not demonstrated.” (82) All coding was done by CXZ in the summer and fall of 2016. JSB validated the coding associated with the previously selected 4 drugs. Due to the interpretive nature of this comparison, two additional investigators (JEB and JSR) reviewed all instances where there was disagreement between the FDA’s and the authors’ interpretation.

Calculating the Degree of Publication Bias

We calculated and compared two different measures of publication bias between pre- and post-FDAAA trials. First, we estimated the relative risk of publication of positive vs non-positive trials in each period. Second, we estimated the relative risk of publishing positive vs non-positive trials without misleading interpretations in each period. Thus, publication bias was calculated as the ratio of relative risks (RRR) pre-FDAAA vs post-FDAAA. CXZ completed the data analysis in fall 2017 and JSR performed validation of the analysis.

Data Collection and Data Validation

Registration status, results reporting status, publications status, and publication-FDA interpretation agreement were validated as described previously. We performed a quality control for the rest of the data set, many of which were collected but not reported for purposes of this study. A second investigator (JEB) re-collected all data elements obtained for a random 10% sample of the included new drug approvals, using an online randomization tool to randomly select 4 out of the 37 drugs. Among the 676 unique data
elements collected by the two investigators, the rate of agreement was 99.6% and disagreements were resolved through consensus.

Data Analysis

We used descriptive statistics to characterize the proportions of trials that were registered and reporting results on ClinicalTrials.gov. We used two-tailed Fisher Exact tests to compare the proportions among pre- and post-FDAAA trials. Analysis was performed using Epi Info Companion App for iOS (3.1.1) (Centers for Disease Control and Prevention [CDC]; Atlanta, GA), as well as with MedCalc online statistical software (2016), supplemented using an online program written by Hutchon (Hutchon 2015) to calculate the RRRs to estimate both measures of publication bias.

All data analysis was completed by CXZ, JSR independently validated the analysis.
Results

Characteristics of the Neuropsychiatric Drugs Approved between 2005-2014

Between January 1st, 2005 and December 31st, 2014, 37 new drugs were approved by the FDA for the treatment of neuropsychiatric conditions, of which 23 (62%) were approved for neurological conditions and 14 (38%) for psychiatric disorders, which included 3 drugs for substance-use related conditions (Table 1). Among the 37 approved drugs, 34 (92%) were pharmacologic therapies, 3 (8%) were biologics; orphan status was granted for 9 (24%), priority review status for 6 (17%), and accelerated approval for 1 (3%)

Table 1. New Drug Applications (NDA) Approved by the FDA between 2005 and 2014 with Indications for Neurologic and Psychiatric Conditions.

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>INN Name</th>
<th>NDA Applicant</th>
<th>Indication</th>
<th>Approval Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rozerem</td>
<td>Ramelteon</td>
<td>Takeda Global</td>
<td>Insomnia</td>
<td>2005</td>
</tr>
<tr>
<td>Chantix</td>
<td>Varenicline Tartrate</td>
<td>Pfizer</td>
<td>Smoking cessation</td>
<td>2006</td>
</tr>
<tr>
<td>Azilect</td>
<td>Rasagiline Mesylate</td>
<td>Teva</td>
<td>Parkinson’s disease</td>
<td>2006</td>
</tr>
<tr>
<td>Invega</td>
<td>Paliperidone</td>
<td>Janssen, L.P.</td>
<td>Schizophrenia</td>
<td>2006</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Lisdexamfetamine Dimesylate</td>
<td>New River</td>
<td>Attention deficit hyperactivity disorder</td>
<td>2007</td>
</tr>
<tr>
<td>Neupro</td>
<td>Rotigotine</td>
<td>Schwarz Biosciences</td>
<td>Parkinson’s disease</td>
<td>2007</td>
</tr>
<tr>
<td>Pristiq</td>
<td>Desvenlafaxine Succinate</td>
<td>Wyeth</td>
<td>Major depressive disorder</td>
<td>2008</td>
</tr>
<tr>
<td>Relistor</td>
<td>MethylNaltrexone Bromide</td>
<td>Progenics</td>
<td>Opioid-induced constipation</td>
<td>2008</td>
</tr>
<tr>
<td>Xenazine</td>
<td>Tetrabenazine</td>
<td>Prestwick</td>
<td>Huntington's disease</td>
<td>2008</td>
</tr>
<tr>
<td>Vimpat</td>
<td>Lacosamide</td>
<td>Schwarz Biosciences</td>
<td>Partial-onset seizure disorder</td>
<td>2008</td>
</tr>
<tr>
<td>Brand Name</td>
<td>Active Ingredient</td>
<td>Manufacturer</td>
<td>Indication</td>
<td>Year</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
<td>--------------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Banzel</td>
<td>Rufinamide</td>
<td>Eisai INC</td>
<td>Seizures associated with Lennox-Gastaut syndrome</td>
<td>2008</td>
</tr>
<tr>
<td>Nucynta</td>
<td>Tapentadol Hydrochloride</td>
<td>Ortho McNeil Janssen</td>
<td>Acute Pain</td>
<td>2008</td>
</tr>
<tr>
<td>Lusedra</td>
<td>Fospropofol Disodium</td>
<td>Eisai Medical</td>
<td>Anesthesia</td>
<td>2008</td>
</tr>
<tr>
<td>Savella</td>
<td>Milnacipran Hydrochloride</td>
<td>Cypress Biotechnology INC</td>
<td>Fibromyalgia</td>
<td>2009</td>
</tr>
<tr>
<td>Dysport</td>
<td>Abobotulinumtoxina</td>
<td>Ipsen Biopharm Limited</td>
<td>Cervical dystonia</td>
<td>2009</td>
</tr>
<tr>
<td>Fanapt</td>
<td>Iloperidone</td>
<td>Vanda Pharmaceuticals Inc</td>
<td>Schizophrenia</td>
<td>2009</td>
</tr>
<tr>
<td>Saphris</td>
<td>Asenapine Maleate</td>
<td>Organon USA INC</td>
<td>Bipolar I disorder</td>
<td>2009</td>
</tr>
<tr>
<td>Sabril</td>
<td>Vigabatrin</td>
<td>Lundbeck Inc</td>
<td>Complex partial seizure disorder</td>
<td>2009</td>
</tr>
<tr>
<td>Qutenza</td>
<td>Capsaicin</td>
<td>Neurogesx Inc</td>
<td>Neuropathic pain</td>
<td>2009</td>
</tr>
<tr>
<td>Ampyra</td>
<td>Dalfampridine</td>
<td>Acorda Therapeutics Inc</td>
<td>Multiple sclerosis</td>
<td>2010</td>
</tr>
<tr>
<td>Xeomin</td>
<td>Incobotulinumtoxina</td>
<td>Merz Pharmaceuticals GMBH</td>
<td>Cervical dystonia and Blepharospasm</td>
<td>2010</td>
</tr>
<tr>
<td>Gilenya</td>
<td>Fingolimod</td>
<td>Novartis Pharmaceuticals Corp</td>
<td>Multiple sclerosis</td>
<td>2010</td>
</tr>
<tr>
<td>Latuda</td>
<td>Lurasidone Hydrochloride</td>
<td>Sunovion Pharmaceuticals INC</td>
<td>Schizophrenia</td>
<td>2010</td>
</tr>
<tr>
<td>Viibryd</td>
<td>Vilazodone Hydrochloride</td>
<td>Trovis Pharmaceuticals LLC</td>
<td>Major depressive disorder</td>
<td>2011</td>
</tr>
<tr>
<td>Horizant</td>
<td>Gabapentin Enacarbil</td>
<td>Glaxo Group LTD DBA GlaxoSmithKline</td>
<td>Restless legs syndrome</td>
<td>2011</td>
</tr>
<tr>
<td>Potiga</td>
<td>Ezogabine</td>
<td>GlaxoSmithKline</td>
<td>Partial seizure disorder</td>
<td>2011</td>
</tr>
<tr>
<td>Onfi</td>
<td>Clobazam</td>
<td>Lundbeck INC</td>
<td>Seizures associated with Lennox-Gastaut syndrome</td>
<td>2011</td>
</tr>
<tr>
<td>Aubagio</td>
<td>Teriflunomide</td>
<td>Sanofi Aventis US LLC</td>
<td>Multiple sclerosis</td>
<td>2012</td>
</tr>
<tr>
<td>Fycompa</td>
<td>Perampanel</td>
<td>Eisai INC</td>
<td>Partial seizure disorder</td>
<td>2012</td>
</tr>
<tr>
<td>Dotarem</td>
<td>Dimethyl Fumarate</td>
<td>Biogen Idec INC</td>
<td>Multiple sclerosis</td>
<td>2013</td>
</tr>
<tr>
<td>Drug Name</td>
<td>INN*</td>
<td>Company Name</td>
<td>Disease</td>
<td>Year</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>--------------</td>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>Trintellix (formerly Brintelix)</td>
<td></td>
<td></td>
<td>Major depressive disorder</td>
<td>2013</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td></td>
<td>Takeda Pharmaceuticals USA INC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aptiom</td>
<td>Eslicarbazine-</td>
<td>Sunovion Pharmaceuticals INC</td>
<td>Partial seizure disorder</td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>pine Acetate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hetlizoz</td>
<td>Tasimelteon</td>
<td>Vanda Pharmaceuticals Inc</td>
<td>Non-24-hour sleep-wake disorder</td>
<td>2014</td>
</tr>
<tr>
<td>Northera</td>
<td>Droxidopa</td>
<td>Chelsea Therapeutics Inc</td>
<td>Neurogenic orthostatic hypotension</td>
<td>2014</td>
</tr>
<tr>
<td>Belsomra</td>
<td>Suvorexant MK4305</td>
<td>Merck Sharp and Dohme Corp</td>
<td>Insomnia</td>
<td>2014</td>
</tr>
<tr>
<td>Plegidy</td>
<td>Peginterferon Beta-1A</td>
<td>Biogen Idec INC</td>
<td>Multiple sclerosis</td>
<td>2014</td>
</tr>
<tr>
<td>Movantik</td>
<td>Naloxegol</td>
<td>Astrazeneca Pharmaceuticals LP</td>
<td>Constipation s/p opioids</td>
<td>2014</td>
</tr>
</tbody>
</table>

Note: INN= International nonproprietary name; NDA=New Drug Application; ADHD=Attention deficient hyperactivity disorder; please refer to the drug label for full description of each drug indication.

**Clinical Trials Supporting FDA Approval**

There were 142 efficacy trials that supported the approval of these 37 neuropsychiatric drugs (Figure 1), of which 101 (71%) were categorized as pre-FDAAA and 41 (29%) as post-FDAAA. All 142 trials were funded by industry and 105 (74%) were phase III, 33 (23%) phase II, and 4 (3%) phase II/III. In addition, the results of 107 (75%) of the trials were interpreted by the FDA to be positive, 17 (12%) as equivocal, and 18 (13%) as negative (Table 2).

**Clinical Trial Registration and Results Reporting**

FDAAA was followed by significantly greater proportions of trial registration and results reporting. Pre-FDAAA, 64% (65 of 101) of clinical trials were registered on
ClinicalTrials.gov, while 100% (41 of 41) of post-FDAAA trials were registered (P<0.001; Figure 2). Similarly, pre-FDAAA, 10% (10 of 101) of clinical trials reported results on ClinicalTrials.gov, while 100% (41 of 41) of post-FDAAA trials reported results (P<0.001; Figure 2); the results of 32 of 41 (78%) FDAAA trials were reported within 30 days of drug approval.

Publication and Published Interpretations

Pre-FDAAA, among 72 positive trials, none were unpublished nor published with misleading interpretation. In contrast, among 29 non-positive trials, 10 (34%) were not published and 7 (24%) were published with misleading interpretations. Post-FDAAA, among 35 positive trials, again none were unpublished and none were published with a misleading interpretation. In addition, among 6 non-positive trials, none were unpublished and only 1 was published with a misleading interpretation. (Figure 3) The publications of the following new drugs had misleading interpretations: Droxidopa (Northera) of Chelsea Therapeutics, Dalfampridine (Ampyra) of Acorda Therapeutics, Iloperidone (Fanapt) of Vanda Pharmaceuticals, Milnacipran Hydrochloride (Savella) of Forest Research and Cypress Bioscience, and Rulfinamide (Banzel) of Novartis (Box 1).

Table 2. Characteristics of 142 Efficacy Trials Supporting FDA Approval of NDA for Neuropsychiatric Conditions, 2005-2014.

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
<th>No. Registered (%)</th>
<th>No. Results Reported (%)</th>
<th>No. Published (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=142)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDAAA Applicability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-FDAAA</td>
<td>101 (71%)</td>
<td>65 (64%)</td>
<td>10 (10%)</td>
<td>91 (90%)</td>
</tr>
<tr>
<td></td>
<td>Pre-FDAAA</td>
<td>Post-FDAAA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------</td>
<td>------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pivotal Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pivotal</td>
<td>92 (65%)</td>
<td>78 (85%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Pivotal</td>
<td>50 (35%)</td>
<td>28 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All United States</td>
<td>65 (46%)</td>
<td>50 (77%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some United States</td>
<td>54 (38%)</td>
<td>41 (76%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None United States</td>
<td>23 (16%)</td>
<td>15 (65%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Study Phase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>33 (23%)</td>
<td>17 (52%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td>105 (74%)</td>
<td>87 (83%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II/III</td>
<td>4 (3%)</td>
<td>2 (50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NA (single-group)</td>
<td>5 (4%)</td>
<td>2 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomized</td>
<td>136 (96%)</td>
<td>103 (76%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonrandomized</td>
<td>1 (1%)</td>
<td>1 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double-Blinded</td>
<td>135 (95%)</td>
<td>102 (76%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open-Label</td>
<td>7 (5%)</td>
<td>4 (57%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comparators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo Only</td>
<td>94 (66%)</td>
<td>70 (74%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Comparator Only</td>
<td>8 (6%)</td>
<td>5 (63%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo and Active Comparator</td>
<td>29 (20%)</td>
<td>23 (79%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower-Dose Comparator Only</td>
<td>4 (3%)</td>
<td>4 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comparator</td>
<td>7 (5%)</td>
<td>4 (57%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** FDAAA=Food and Drug Administration Amendments Act

**Table 3.** Publication and Publication-FDA Agreement of Trials Supporting FDA Approval of NDAs with Neuropsychiatric Indications with Positive, Equivocal, and Negative Results.
Notes: Trials were classified as positive, negative, or equivocal based on the FDA’s interpretation of the results. Published interpretation of the trial with the FDA’s interpretation for each trial. The two were considered in agreement if the interpretations were both categorized as positive, negative or equivocal, and no major contradictions existed between the two statements. Negative and equivocal trials were combined into a single group as non-positive trials when calculating publication bias.

Box 1 Examples of Trials Published with Interpretations Disagreeing with the Interpretations of the FDA medical reviewers

<table>
<thead>
<tr>
<th>FDA and Published Interpretations Not in Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example #1</strong></td>
</tr>
<tr>
<td><em>Trial ID:</em> Droxidopa (Northera) 301</td>
</tr>
<tr>
<td><em>FDAAA Status:</em> Post-FDAAA</td>
</tr>
<tr>
<td><em>Sponsor:</em> Chelsea Therapeutics</td>
</tr>
</tbody>
</table>

  *FDA interpretation:* Equivocal. "These results were considered to be implausible, and quite remarkable, different from all other data....1) If data from Site 507 were deemed acceptable, that would mean that the dossier included a single positive study. But with only 1 positive study and one site disproportionately responsible for the favorable treatment effect, the data would not constitute sufficient evidence of efficacy upon which to base an approval action. 2) If data from Site 507 were deemed inadmissible, then Study 301 was not positive; none of the studies were positive.” (83)

  *Published interpretation:* Positive. “In patients with symptomatic nOH, droxidopa improved symptoms and symptom impact on daily activities, with an associated increase in standing systolic BP, and was generally well tolerated published the analysis per protocol.” (84)

| **Example of Contradicting Interpretation #2** |
| *Trial ID:* Milnacipran Hydrochloride (Savella) 02 |
| *FDAAA Status:* Pre-FDAAA |
Sponsor: Forest Research Institute and Cypress Bioscience

FDA interpretation: Negative “[The] analysis of the ‘pain only’ responders does not indicate that there is a significant effect of MLN (Savella) on pain…. (treatment effect) was driven by the patient global response outcome rather than the pain or function outcome…when studied in isolation, statistically significant treatment effects for pain and function were not demonstrated.” (82)

Published interpretation: Positive. “both doses (100 and 200 mg/d) were associated with significant improvements in pain and other symptoms.” (81)

Example of Contradicting Interpretation #3

Trial ID: Rufinamide (Banzel) AE/ET1

FDAAA Status: Pre-FDAAA

Sponsor: Novartis

FDA interpretation: Equivocal. FDA conclusion in summary review “Dr. Siddiqui noted that the sponsor had included the placebo group in its dose response analyses. Further, he noted that the dose groups were coded inappropriately (non-proportional to the actual dose). When the doses were coded proportionally to the actual dose in his dose-response analysis, and placebo was excluded, the p-value for the dose response slope was 0.086, implying none of the dose differed materially.” (85)

Published interpretation: Positive. The author concluded in the abstract of the publication that “in the linear trend of dose response for seizure frequency per 28 days in the double-blind treatment phase was statistically significant in favor of rufinamide (p=0.003).” (86)

Example of Contradicting Interpretation #4

Trial ID: Milnacipran Hydrochloride (Savella) 031

FDAAA Status: Pre-FDAAA

Sponsor: Forest Research Institute and Cypress Bioscience

FDA interpretation: Equivocal. The FDA medical reviewer in more than one places in the review emphasized that this trial fail to demonstrate effect as far as pain is concerned: “analysis of the ‘pain only’ responders does not indicate that there is a significant effect of MLN(Savella) on pain” and the treatment effect is “driven by the patient global response outcome rather than the pain or function outcome, when studied in isolation, statistically significant treatment effects for pain and function were not demonstrated”. In the risk benefit section of the summary review, the FDA again stated that "an unusual finding in this application is that, while the product appears to be effective when measured according to a prespecified responder definition, the results on the individual components of that responder definition, pain, function and a patient global evaluation, were not consistently statistically significant in the post-hoc analyses performed by the clinical/statistical review team. In particularly, the dominant feature of FM is pain and the results of the team's analyses of the individual pain endpoints did not demonstrate a
statistically significant treatment effect for Savella (milnacipran), on the pain endpoint in either of the clinical trials." (82)

Published interpretation: Positive. For trial 02 of milnacipran (Savella), the author of the publication concluded in the abstract that "both doses (100 and 200 mg/d) were associated with significant improvements in pain and other symptoms." (87)

Example of Contradicting Interpretation #5

Trial ID: Iloperidone (Fanapt) 3000

FDAAA Status: Pre-FDAAA

Sponsor: Vanda Pharmaceuticals Inc

FDA interpretation: Negative. “Thus, either approach to defining the sample for this study (whether it's FDA preferred or sponsor preferred) yields a negative result for iloperidone. With the sponsor's preferred analysis including all randomized patients, the superiority of haloperidol (active comparator) over the primary iloperidone (study drug) group (8+12mg) is statistically significant. This study, therefore, provides no support for iloperidone (study drug) but does suggest the statistically significant superiority of haloperidol (active control) over iloperidone (study drug).” FDA reviewer also pointed out that the protocol of 3000 specified that no comparison of individual doses against placebo can be done unless the combined group 12mg+8mg are shown to be significant, since the combined dose was not significant, then no individual dose comparison can be done, and the study is negative.” (88)

Published interpretation: Positive. Publication concluded that 3000, 3004 and 3005 are all positive. The positive conclusion for 3000 was partially supported by comparing the outcomes of individual doses against placebo, a practice not supported by the protocol as pointed out the FDA reviewer Publication also did not comment on the fact that the study drug was less effective than the active control. Also, in the abstract session is the mentioning of other analysis. "Additional analysis in patients who received active treatment for at least 2 weeks indicated comparable efficacy score reductions at 6 weeks for patients receiving iloperidone 20 to 24 mg/d versus those receiving haloperidol or risperidone". The publication stated, at the end of the abstract that "These trials indicate that iloperidone is effective for the treatment of schizophrenia." (89)

Example of Contradicting Interpretation #6

Trial ID: Iloperidone (Fanapt) 3004

FDAAA Status: Pre-FDAAA

Sponsor: Vanda Pharmaceuticals Inc

FDA interpretation: Equivocal. "........ we still do not find this study an acceptable source of evidence. Although the results for both dose groups in the all-randomized patients' analysis are positive, there is a striking difference in outcomes for the schizophrenic (intended indication) and the schizoaffective (not intended indication) subgroups. The analysis focusing only on the schizophrenic subgroup is not even close to positive for either dose group (p=0.306 for 10-16mg/day and p=0.581 for 4-8mg/day).” Following this conclusion, the FDA reviewer stated " I
think the data for that trial are fatally pathological, and one cannot reasonably pool data from the schizophrenic and schizoaffective subgroups. It is not that I fundamentally object to polling data from schizophrenic and schizoaffective patients (we have accepted this approach many times in the past), but for this study, where the positive findings in the schizoaffective patients is by the sponsor's own admission an 'anomaly,' there is no justification for such a pooling. Thus, I find this study uninterpretable.” (88)

*Published interpretation:* Positive. Same as 3000. "These trials indicate that iloperidone is effective for the treatment of schizophrenia." (89)

**Example of Contradicting Interpretation #7**

*Trial ID:* Iloperidone (Fanapt) 3005

*FDAAA Status:* Pre-FDAAA

*Sponsor:* Vanda Pharmaceuticals Inc

*FDA interpretation:* Equivocal. FDA noted that” the effect size observed in Study 3005 was greater in active control than in both doses of iloperidone”. And that” the observation in study 3005 that the positive effect for iloperidone over placebo was coming almost entirely from the non-US sites.” The reviewer, in summarizing the findings in study 3005, pointed out that stated that the data collected from the US sites for study 3005 were uninterpretable I am persuaded by the sponsor's argument that the lack of efficacy in the US sites for study 3005 should not rule out this study as a source of evidence. As they point out, risperidone also failed in the US sites, and thus, data from these sites is simply uninterpretable.” The conclusion of the FDA was “For study 3005, only the analysis focused on the schizophrenic subgroup shows superiority of iloperidone over placebo. In the sponsor's preferred analysis, iloperidone fails to show superiority to placebo and, at the same time, risperidone appears to be statistically significantly superior to iloperidone.” (88)

*Published interpretation:* Positive. Publication concluded that one of the doses in study 3005, 20–24 mg/d [P = 0.010]). "Active controls were also significantly more effective than placebo in each trial, thus validating the trials... These trials indicate that iloperidone is effective for the treatment of schizophrenia." No comparison was drawn between the active control with iloperidone. No statement was made regarding the data from the US study sites were uninterpretable.” (89)

**Example of Contradicting Interpretation #8**

*Trial ID:* Dalfampridine (Ampyra) 202

*FDAAA Status:* Pre-FDAAA

*Sponsor:* Acorda Therapeutics Inc

*FDA interpretation:* Negative. "There were no statistically significant differences between any dose and placebo. Independent analyses by Dr. Joo-Yeon Lee of Pharmacometrics has shown no dose response in the range studied for the percent change from baseline in walking speed.” (90)
Published interpretation: Equivocal. “This phase 2 study suggests that a subgroup of patients, when treated with fampridine, experiences a clinically relevant improvement in walking ability, which is sustained for at least 14 weeks.” (91)

Publication Bias

Pre-FDAAA, positive trials were more likely to be published (RR=1.52; 95% Confidence Interval [CI]=1.17-1.99; P=0.002) and published without misleading interpretations (RR=2.47; CI=1.57-3.73; p<0.001) than those with non-positive results. In contrast, post-FDAAA, positive trials were equally likely to have been published (RR=1; CI=1-1, p=NA) and published without misleading interpretations (RR=1.20; CI=0.84-1.72; p=0.30). The likelihood of publication bias pre-FDAAA vs. post-FDAAA was greater for publication of positive vs. non-positive trials (RRR=1.52; CI=1.16-1.99; p=0.002) and for publication without misleading interpretations (RRR=2.06, CI=1.17-3.61, p=0.01).
Discussion

Study Findings & Prior literature

In this retrospective cohort study of 142 trials supporting the approval of 37 neuropsychiatric therapeutics approved by the FDA between 2005 and 2014, post-FDAAA trials were uniformly registered, reported results, published, and published without misleading interpretations. As compared to pre-FDAAA trials, proportions of trials that were registered and reporting results on ClinicalTrials.gov were significantly higher and the degree of publication bias was lower. Our results suggest that FDAAA likely contributed to improving the registration, results reporting, and publication of clinical trials supporting FDA approval of new drugs used to treat neuropsychiatric indications, although other factors may also have been in play.

Prior work examining similar clinical trials supporting FDA approval of new drugs in 2012, many of which were completed before FDAAA as enacted, found 57% were registered and 20% reported results on ClinicalTrials.gov. (41) Among trials supporting approval of neuropsychiatric drugs, we found similar rates among pre-FDAAA trials, 63% and 10%, but also show that among post-FDAAA trials, 100% were registered and reported results. A study involving trials supporting FDA approval of cardiovascular and diabetic drugs showed a similar association between FDAAA and trial registration and results reporting. (80)

As discussed previously, earlier studies have consistently demonstrated significant publication bias: positive trials are more likely to be published and published accurately or completely than non-positive trials. In our study, such publication bias was observed only among trials that were completed prior to FDAAA enactment, but not afterwards. In
addition, overall rates of clinical trial publication were quite high, challenging the assumption that selective publication is worse among clinical trials of neuropsychiatric drugs than for other types of drugs. Our findings have important implications for understanding the impact of FDAAA, for developing future strategies to improve selective publication and outcome reporting more broadly, and for the practice of evidence-based medicine.

*Implication for Understanding the Impact of FDAAA*

There is likely a causal relationship between the enactment of FDAAA and the improved rates of registration and results reporting given the strength of the association, consistency of the association across different types of trials, existence of a temporal relationship, and high degree of plausibility. When we examined the relationship between FDAAA status with registration status and the relationship between FDAAA status with results reporting status using the two tailed Fisher Exact test, the p-Value was less than 0.001 in both cases. Studies evaluating trials for cardiovascular and diabetic drugs showed the similar results. Considering that FDAAA explicitly required registration and results reporting and has the power to fine the sponsors $11,569 for each day a trial remains unreported following a 30-day notification period, it is reasonable to anticipate that there is high degree of compliance for trials that were initiated after the FDAAA enactment. Other changes might also be contributory. For example, trials involving patients with serious and life threatening illnesses and pediadiatric patients were required to register according to FDAMA1997 and according to guidelines issued by the FDA for the pharmaceutical industry practice as early as 2004. (92). The ICMJE recommendation issued in 2004 might also have had a small impact on trial registration, specifically
prospective trial registration. However, as previously discussed, only the 11 members of ICMJE were required to comply with ICMJE, while other journals follow the recommendation on a voluntary basis. When surveyed, editors were willing to consider the publication of unregistered trials due to many factors: “not wanting to lose out to rival journals, not wanting to reject otherwise sound articles or submissions from developing countries, and perceptions that such policies were not relevant to all journals.” (93)

The impact of FDAAA on reducing publication bias is less clear because FDAAA does not regulate medical journals directly. Our results at least provided a positive outlook. Post-FDAAA trials, regardless of the results, were all published. Publication bias was not detectable among the post-FDAAA trials and represents a significant improvement compared to the pre-FDAAA trials.

*Implications for Future Policy Development*

FDAAA applies only to trials of medical products regulated by the FDA. But the practice of medicine includes not only the use of medical products to improve patient outcomes, but also behavioral, surgical and other procedural interventions, as well as health system interventions. To ensure that the medical literature is as unbiased and representative as is possible, rules and regulations like FDAAA, which mandate registration and results reporting in a publicly accessible database but also apply to all clinical research and health system studies, may be an effective strategy to promote comprehensive registration, results reporting, and publication.

*Implications for the Practice of Medicine*
The sponsors and investigators have published all of the Post-FDAAA clinical trials supporting the FDA’s decision to approve new drugs treating neurologic and psychiatric conditions and there were no negative trials misleadingly published to encourage positive interpretation. Evidence-based practice regarding the use of these drugs will be less affected by publication bias. However, it is uncertain whether this will improve the practice of medicine for several reasons. One, the “effective publication rate,” as perceived by clinicians and patients, may be lower because the publications for some trials were difficult to locate and were only found using specific trial data in multiple search engines. Two, the pharmaceutical companies, supported usually by large marketing departments have other ways to “advertise” their expensively made products, to incentivize physicians to prescribe the newer and more expensive drugs over the older or cheaper drugs. Lastly, it is unclear that EBM is itself the appropriate framework for medical decision making. The chasm between the RCT-based formula to providing care to patients, each with their unique circumstances in resource-constrained environments, is vast.

Limitations

Several factors should be considered in the interpretation of our findings. First, our study is cross-sectional and can only establish associations, not causality. Other reasons beyond FDAAA, including academic advocacy for clinical trial data transparency, may have accounted for trial sponsors’ and investigators’ decision to register, report results and publish the findings of the clinical trials. More studies are needed to disentangle the impact of FDAAA on clinical trial registration, results reporting, and publication from other factors that may have contributed to these trends, especially the ICMJE clinical trial
registration policy, although it’s not clear that this policy would impact either results reporting or publication. Second, we limited our search of trial registration to ClinicalTrials.gov. It is possible that trials conducted pre-FDAAA used other registers. Third, for trials determined to be unregistered or unpublished, we did not contact sponsor companies for confirmation. Fourth, our sample is limited to phase II and III trials supporting neuropsychiatric drugs and the sample size of post-FDAAA trials, at 41, is relatively small. Fifth, our study was focused on pre-marketing phase II and III trials evaluating neuropsychiatric drugs successfully approved by the FDA. Our findings may not be generalized to phase I and phase IV post marketing trials, trials evaluating drugs that were not approved by the FDA, as well as trials for other types of drugs for which the registration and publication have yet to be characterized. Finally, our study was focused on the reporting and publication of trials’ primary results and did not examine reporting or publication of secondary and safety outcomes.

Conclusions

For clinical trials supporting the FDA approval of new drugs for neuropsychiatric indications, the proportions of trials that were registered and reporting results on ClinicalTrials.gov were significantly higher and publication bias was significantly lower after the passage of FDAAA in 2007, suggesting that FDAAA likely contributed to the reduction of selective registration and results reporting and to mitigating publication bias. These findings have important implications for understanding the potential impact of FDAAA, along with other initiatives that may have improved research reporting, and for developing future strategies to improve selective publication and outcome reporting more broadly.
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Figures, Titles, and Legends

Figure 1. Identification of Trials Reviewed by the FDA for New Drug Applications with Neuropsychiatric Indications, 2005-2014

Legend: Flow chart depicting the process of selecting efficacy trials reviewed by the FDA for the approval of new drug with neuropsychiatric indications between 2005-2014. Trials can be excluded for satisfying one or more exclusion criteria.
Figure 2 Registration and Results Reporting Status of Trials Supporting FDA Indications by FDAAA applicability, 2005-2014

Legend: Post-FDAAA trials were significantly more likely to be registered (100% vs 64%; P<0.001) and report results (100% vs 10%; P<0.001) than pre-FDAAA. Outcomes were compared by two-tailed Fisher Exact tests.
Figure 3. Publication Status and Publication-FDA Agreement of Neuropsychiatric Trials by FDAAA applicability and by Trial Results

Legend: Overall, more Post-FDAAA trials were published (100% vs 90%; P=0.06) and the publication were in agreement with the FDA’s interpretation (98% vs. 93%; P=0.28), but neither the outcomes were significant. When stratified by results, trials with positive were all published during both pre- (72 of 72) and post-FDAAA (35 of 35). When trials with negative results were examined in isolation, the publication rate was significantly higher after FDAAA as compared to before (5 of 5 vs 5 of 13; P=0.04). There were not enough equivocal trials to draw comparison. All comparisons were based on two-tailed Fisher Exact tests.