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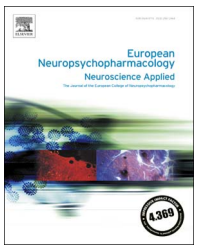

Bias in the reporting of harms in clinical trials of second-generation antidepressants for depression and anxiety: A meta-analysis

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Abstract
Previous research has shown that reporting bias has inflated the apparent efficacy of antidepressants. We investigated whether apparent safety was also affected. We included 133 trials, involving 31,296 patients, of second-generation antidepressants for the treatment of major depressive disorder (MDD) or anxiety disorders, obtained from Food and Drug Administration (FDA) reviews. We extracted data on overall discontinuation, discontinuation due to adverse events, and serious adverse events (SAEs). Meta-analysis was used to compare discontinuation rates between FDA reviews and matching journal articles, while SAEs were compared qualitatively. The odds ratio for overall discontinuation, comparing drug to placebo, was 1.0 for both sources, while that for discontinuation due to adverse events was 2.4 for both sources. Seventy-seven of 97 (79%) journal articles provided incomplete information on SAEs; sixty-one (63%) articles made no mention of SAEs at all. Of 21 articles which could be compared to the FDA, only 6 (29%) had full reporting without discrepancies. Nine (43%) articles reported a discrepant number of SAEs. Descriptions were absent or discrepant in 6 (29%) additional articles, even for important SAEs such as suicide attempts. In conclusion, reporting bias has not affected average discontinuation rates over trials. However, SAE reporting is not only very poor, with over half of articles failing to discuss SAEs altogether, but discrepancies between the FDA and articles were common and often led to a more favorable drug-placebo comparison.

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These findings suggest that journal articles are an unreliable source of data on SAEs in antidepressant trials.

1. Introduction

A significant fraction of all studies are never published in peer-reviewed journals (Dwan et al., 2013). Even within the subset of studies that are published, the (primary) analyses and outcomes reported in journal articles frequently deviate from the protocol (Chan et al., 2004; Dwan et al., 2014). As a consequence, statistically significant (positive) studies or outcomes are more likely to be published than non-significant (negative) studies (Dwan et al., 2013) or outcomes (Chan et al., 2004). While it is often difficult to assess the presence of reporting bias, the United States Food and Drug Administration (FDA) maintains an independent results database for drug trials, which can be used to examine the presence of reporting bias within a set of trials (Turner, 2004). This database has previously been used to assess reporting bias in trials of antipsychotics for schizophrenia (Turner et al., 2012) and antidepressants for major depressive disorder (MDD) (Turner et al., 2008) and anxiety disorders (Roest et al., 2015).

Second-generation antidepressants have been found to be effective for MDD (Turner et al., 2008) and anxiety disorders (Hidalgo et al., 2007; Blanco et al., 2013; Soomro et al., 2008; Andrisano et al., 2013; Stein et al., 2006; Bandelow et al., 2015). They are considered to have a favorable risk-benefit profile and hence are widely prescribed (Olfson and Marcus, 2009). While both studies examining the FDA database of antidepressant trials confirmed their efficacy for MDD and anxiety disorders, they also revealed substantial reporting bias (Turner et al., 2008; Roest et al., 2015). Although nearly all published trials (94–96%) reported positive results, only 51% of all submitted trials for MDD, and 72% of those for anxiety disorders, were judged to be positive by the FDA. As a consequence of reporting bias, the effect size of antidepressant treatment was overestimated by 32% and 15% for MDD and anxiety disorders, respectively.

An accurate assessment of the risk-benefit ratio of antidepressants requires an unbiased understanding of safety as well as efficacy, but this other side of the coin has not, thus far, been examined as comprehensively. Previous research has indicated that reporting of harms in journal articles is incomplete and inadequate in various medical fields (Ioannidis and Lau, 2001; Wieseler et al., 2013; Loke and Derry, 2001), including psychiatry (Papanikolaou et al., 2004). The case of reboxetine demonstrates the impact that reporting bias can have on apparent safety as well as efficacy: inclusion of unpublished data not only shifted the difference in efficacy between reboxetine and placebo from significant to non-significant, but it also showed that reboxetine was significantly inferior to placebo in terms of selected harm outcomes, while the published trials suggested they were equivalent (Eyding and Lelgemann, 2010). Poor reporting of harms has also been found in trials of two other antidepressants (sertraline and duloxetine) and several antipsychotics with serious adverse events (SAEs) not always reported fully or accurately in journal articles (Maund et al., 2014; Hughes et al., 2014).

The work on antidepressant trials was limited to relatively recent trials of three antidepressants, and only the reboxetine study quantified the possible impact of bias on an important harm outcome, discontinuation from the trial. In the present study, we assessed the presence of reporting bias, and its impact on several harm outcomes, within a comprehensive set of trials of second-generation antidepressants for both MDD and anxiety disorders.

2. Experimental procedures

2.1. Data from FDA reviews and journal articles

We previously obtained FDA reviews of second-generation antidepressants approved for MDD (Turner et al., 2008) and/or anxiety disorders (Roest et al., 2015) (specifically generalized anxiety disorder (GAD), social anxiety disorder (SAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD) and panic disorder (PD)). We defined second-generation antidepressants as including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), as well as other antidepressants (specifically mirtazapine, bupropion, and nefazodone) approved between 1987 and 2008. From these, we identified all phase 2/3 short-term clinical trials registered with the FDA and conducted in pursuit of marketing approval. For MDD, we identified 74 trials of 12 drugs; for GAD, 11 trials of 4 drugs; for SAD, 11 trials of 5 drugs; for OCD, 13 trials of 5 drugs; for PTSD, 7 trials for 2 drugs; and for PD, 17 trials for 5 drugs. Two of the PD trials were not included in our previous analysis (Roest et al., 2015), as we did not receive the FDA review containing these trials in time. Hence, we included a total of 133 trials, consisting of data from 31,296 participants, of whom 18,904 were treated with antidepressants and 12,392 with placebo.

We conducted an extensive search of the published literature to identify journal articles corresponding to these FDA-registered trials, as described previously (Turner et al., 2008; Roest et al., 2015). A total of 97 publications were identified, covering 102 (77%) of 133 trials: 51 for MDD (including 1 publication covering 2 trials), 9 for GAD (1 publication covering 2 trials), 11 for SAD, 9 for OCD (1 publication covering 2 trials), 5 for PTSD, and 12 for PD (1 publication covering 3 trials).

For each trial, we extracted the following data from FDA reviews and corresponding journal articles, separately for each treatment group: sample size, number and proportion of patients discontinuing, number and proportion of patients discontinuing due to adverse events specifically, and the number and nature of serious adverse events (SAEs). SAEs are defined as any adverse event that results in death, hospitalization, disability or permanent damage, a birth defect, or any other life-threatening situation. Individual trial protocols may, however, define additional adverse events as serious adverse events. Both SAEs occurring during the administration of a

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