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Original Investigation

Reporting Bias in Clinical Trials Investigating the Efficacy of Second-Generation Antidepressants in the Treatment of Anxiety Disorders

A Report of 2 Meta-analyses

Annelieke M. Roest, PhD; Peter de Jonge, PhD; Craig D. Williams, PharmD; Ymkje Anna de Vries, MSc; Robert A. Schoevers, MD, PhD; Erick H. Turner, MD

IMPORTANCE Studies have shown that the scientific literature has overestimated the efficacy of antidepressants for depression, but other indications for these drugs have not been considered.

OBJECTIVE To examine reporting biases in double-blind, placebo-controlled trials on the pharmacologic treatment of anxiety disorders and quantify the extent to which these biases inflate estimates of drug efficacy.

DATA SOURCES AND STUDY SELECTION We included reviews obtained from the US Food and Drug Administration (FDA) for premarketing trials of 9 second-generation antidepressants in the treatment of anxiety disorders. A systematic search for matching publications (until December 19, 2012) was performed using PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials.

DATA EXTRACTION AND SYNTHESIS Double data extraction was performed for the FDA reviews and the journal articles. The Hedges *g* value was calculated as the measure of effect size.

MAIN OUTCOMES AND MEASURES Reporting bias was examined and classified as study publication bias, outcome reporting bias, or spin (abstract conclusion not consistent with published results on primary end point). Separate meta-analyses were conducted for the 2 sources, and the effect of publication status on the effect estimates was examined using meta-regression.

RESULTS The findings of 41 of the 57 trials (72%) were positive according to the FDA, but 43 of the 45 published article conclusions (96%) were positive ($P < .001$). Trials that the FDA determined as positive were 5 times more likely to be published in agreement with that determination compared with trials determined as not positive (risk ratio, 5.20; 95% CI, 1.87 to 14.45; $P < .001$). We found evidence for study publication bias ($P < .001$), outcome reporting bias ($P = .02$), and spin ($P = .02$). The pooled effect size based on the published literature (Hedges *g*, 0.38; 95% CI, 0.33 to 0.42; $P < .001$) was 15% higher than the effect size based on the FDA data (Hedges *g*, 0.33; 95% CI, 0.29 to 0.38; $P < .001$), but this difference was not statistically significant ($\beta = 0.04$; 95% CI, -0.02 to 0.10; $P = .18$).

CONCLUSIONS AND RELEVANCE Various reporting biases were present for trials on the efficacy of FDA-approved second-generation antidepressants for anxiety disorders. Although these biases did not significantly inflate estimates of drug efficacy, reporting biases led to significant increases in the number of positive findings in the literature.

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There is strong evidence¹ that significant results from randomized clinical trials are more likely to be published than are nonsignificant results. As a consequence, published studies, including meta-analyses, may overestimate the benefits of treatments while underestimating their harms, thus misinforming physicians, policy makers, and patients.²

Different types of reporting biases can be present. *Study publication bias* occurs when studies with positive results are more likely to be published than studies with negative results.³ *Outcome reporting bias* involves publishing outcomes from a study that are “positive” (eg, statistically significant) without publishing “negative” outcomes or switching the status of primary and secondary outcomes based on results.⁴ Finally, *spin* occurs when treatments are described by investigators as beneficial, even though published results for primary outcomes are nonsignificant.⁵

The registry and results database of the US Food and Drug Administration (FDA) can be used to assess the degree to which published trial results may overestimate efficacy.^{6–8} Pharmaceutical companies must register all trials they intend to use in support of an application for US marketing approval with the FDA; information on these trials is compiled in this database. A previous study⁶ found that 51% of the trials on antidepressants used in the treatment of major depressive disorder were deemed positive by the FDA compared with 94% of those in the literature; in addition, a meta-analysis⁶ of only published data overestimated the effect of antidepressants by 32%. This finding was followed by debate and additional research on the efficacy of antidepressants for depression.^{2,9,10}

Antidepressants are widely prescribed for conditions other than depression.¹¹ However, research on reporting biases for these other indications is lacking. Anxiety disorders are common in the general population, with an estimated year prevalence of 12%.¹² Second-generation antidepressant drugs, namely selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors, are the primary pharmacologic treatments for generalized anxiety disorder (GAD),^{13,14} panic disorder (PD),^{14,15} social anxiety disorder (SAD),¹⁶ post-traumatic stress disorder (PTSD),¹⁷ and obsessive-compulsive disorder (OCD).¹⁸ Several meta-analyses have reported that second-generation antidepressants are superior to placebo in the treatment of GAD,¹⁹ PD,^{20,21} SAD,²² PTSD,²³ and OCD.²⁴ Some of these meta-analyses^{20,22} suggested the existence of study publication bias based on funnel plot asymmetry. However, such methods cannot prove the existence of publication bias; for that, one must access and analyze unpublished data as well.⁷ A recent study²⁵ examined the efficacy of one selective serotonin reuptake inhibitor in the treatment of GAD and PD using a complete data set of trials sponsored by the manufacturer. This study showed that published trials had significantly larger effect sizes than did the unpublished trials.

In the present study, the first objective was to examine reporting bias in the scientific literature on the efficacy of second-generation antidepressants approved by the FDA for the treatment of anxiety disorders. By comparing published articles with corresponding FDA reviews, we examined the presence of study publication bias, outcome reporting bias, and spin. The second objective was to compare the magnitude of the

overall effect based on published trial data from premarketing trials with the effect based on the full cohort of such trials registered with the FDA.

Methods

Selection of Trials and Journal Articles and Data Extraction

We began by identifying the inception cohort of premarketing trials for the indications of interest, then conducted a literature search for those trials. This process was similar to that of other studies.^{6,7}

Data from FDA Reviews

We identified the phase 2 and 3 clinical, double-blind, placebo-controlled trials registered with the FDA and conducted in pursuit of marketing approval of second-generation antidepressants for the treatment of GAD, PD, SAD, PTSD, and OCD. Nine drugs approved by the FDA for these indications were examined: 7 selective serotonin reuptake inhibitors (paroxetine hydrochloride, paroxetine controlled release [CR], sertraline hydrochloride, fluoxetine hydrochloride, fluvoxamine maleate, fluvoxamine CR, and escitalopram oxalate) and 2 serotonin norepinephrine reuptake inhibitors (venlafaxine hydrochloride extended release [ER] and duloxetine hydrochloride). We retrieved the FDA Drug Approval Packages (hereafter termed *FDA reviews*) from the FDA's website (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>); if these packages were not available for download, we requested them from the FDA's Freedom of Information Office (<http://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm>). We extracted the results the FDA used to decide whether the trial was positive (ie, whether it could be used to support marketing approval). Data were extracted preferably from the statistical review but also from the medical review and administrative correspondence (eg, memos by team leaders). In cases in which multiple primary end points were identified in a trial, results were extracted for the end point that was most consistent with the primary end point identified in other trials for the same indication. In accordance with previous publications,^{6,7} the FDA's regulatory decisions were classified as (1) positive (clearly supporting efficacy) or (2) not positive, with the latter including both questionable (neither clearly positive nor clearly negative) and negative (not supportive of efficacy) trials. The questionable category included trials characterized by the FDA as “marginally” or “borderline” positive. These trials had nonsignificant *P* values for 1 or more of the primary end points but were considered by the FDA to be supportive of other positive trials because of significant findings on secondary variables. The questionable category also included “failed” trials (in which neither the study drug nor the active comparator demonstrated statistical superiority to placebo). For multiple-dose trials, we used the FDA's overall decision. For purposes of meta-analysis, we extracted data only for approved dosages, thus excluding subtherapeutic dosages.⁶ Data extraction, classification, and entry were performed independently by 2 investigators (A.M.R. and C.D.W.) with discrepancies resolved by consensus (A.M.R., C.D.W., and E.H.T.).

Data from Journal Articles

Having identified the inception cohort of premarketing trials registered with the FDA, we systematically searched for matching publications using PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials without language restrictions, with a search cutoff date of December 19, 2012. We searched the title field for the name of the drug and the type of anxiety disorder and any field for the word *placebo*. For example, when searching PubMed for relevant escitalopram trials for GAD, the search syntax was *escitalopram* [title] and (*generalized* [title] or *generalised* [title]) and *anxiety* [title] and *disorder* [title] and *placebo*. Publication matches for trials registered with the FDA were identified using the following information: drug name, name of the active comparator (if applicable), dosage groups, sample sizes, trial duration, and names of the investigators. Stand-alone publications (ie, a full-length article devoted to reporting the results of a single trial) were preferred. If no stand-alone publication could be found, pooled analyses were sought in which multiple trials were addressed in a single article. Data from journal articles that pooled data from multiple trials that were not identical in design according to the FDA were excluded from the present study. Pooled-trials publications were also excluded when 1 or more of the included trials had been published earlier as a stand-alone publication and the pooled-trials publication did not present separate results for the included trials. Finally, data published only in abstract form were excluded.

Several steps were taken to minimize the possibility that we missed matching publications. If no publication was found via the electronic database search, PubMed was used to identify the 3 most recent review articles focusing on the efficacy of the trial drug for the condition treated in the trial. The reference lists for those publications were hand searched. In addition, the drug sponsor's website was searched for bibliographic information on the trials in question.

To assess drug efficacy according to published journal articles, we used the primary end point specified in the publication. If a primary end point was not specified or no end point was clearly emphasized, we extracted the drug-placebo comparison reported first in the text of the results section or in the Table or Figure first cited in the text.⁷ If multiple end points were identified as primary in a single study, results were extracted for the end point reviewed as primary by the FDA. Data extraction and entry were done independently (A.M.R. and R.A.S.) with discrepancies resolved through consensus (A.M.R., Y.A.d.V., and R.A.S.).

In addition, each article's conclusion was classified as positive or not positive (including questionable and negative) based on the sentence in the abstract reporting the authors' overall conclusion regarding study outcome. Conclusions were classified independently by 2 authors (A.M.R. and P.d.J.); one (P.d.J.) was blinded to the results of the FDA review.

This study was approved by the research and development committee of the Portland Veterans Affairs Medical Center. Because of the nature of the study, informed consent from individual participants was not required.

Statistical Analysis

Trial Outcome vs Published Results

The binomial probability test was used to assess whether the proportion of positive conclusions in journal articles was significantly different from the proportion of positive trials according to the FDA. In addition, using the Fisher exact test, we examined whether not-positive trials (according to the FDA) were more likely to be unpublished, or published in a positive manner, compared with positive trials. The presence of study publication bias (trial results not published), outcome reporting bias (changes in analysis or primary end point affecting the significance of findings), and spin (abstract conclusion not consistent with published results on primary end point) were also compared for positive and not-positive trials.

Meta-analysis

We conducted 2 meta-analyses: one using data from the FDA reviews and another using the corresponding published data.^{6,7} The Hedges *g* value was used as a measure of effect size and was calculated with the following equation in which *t* represents the *t* test statistic and *n*₁ and *n*₂ are the numbers of study participants in the drug and placebo groups, respectively:

$$g = t \sqrt{\frac{n_1 + n_2}{n_1 n_2}} = t \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$$

The values for *g* were adjusted using Hedges correction for small sample size.^{6,7} The *t* statistic was calculated from the precise *P* value and the trial sample size using Microsoft Excel's TINV function (Microsoft Corporation), multiplying *t* by -1 when the study drug was inferior to placebo. If a precise *P* value was not available because it was reported as a range (eg, $P < .05$), the *t* statistic was calculated from other summary statistics (ie, SDs, SEs, and 95% CIs around the mean difference). When the data were presented as dichotomized statistics, the Hedges *g* value was calculated from χ^2 analysis.²⁶ If none of these data were available and FDA and journal data were otherwise congruent, data were imputed with information extracted from the other source. In addition, for 2 journal articles,^{27,28} the Hedges *g* value was calculated from the *F* statistic (analysis of variance).²⁶ Finally, *P* values and other efficacy data were not reported for 2 negative FDA trials that were, in one case, not published and, in the other case, published as positive (trial 95-003: sertraline for SAD and trial 495: sertraline for OCD). These *P* values were imputed with $P = .396$, which was derived from 16 nonsignificant but precise *P* values according to the method described by Turner et al⁶ in the appendix of their article. For each multiple-dose study, we computed a single study-level effect size using a fixed-effects model to pool the values from that trial's multiple treatment arms. When calculating the SE, we counted each trial's shared placebo *n* once, rather than redundantly, for each dose group to avoid a spuriously low SE. A limitation of this method is that it only partially addresses error due to correlation between the comparisons.³ Calculations of all effect sizes were performed independently by 2 authors (A.M.R. and Y.A.d.V.).

The random-effects pooling method was used to generate summary estimates of the Hedges *g*, and *I*² and 95% CIs around

I^2 were calculated to assess heterogeneity.²⁹ The I^2 value reflects the proportion of total variance explained by heterogeneity. Meta-regression, using the restricted maximum likelihood method, was conducted to examine the impact of publication status on the effect estimates. In addition, prespecified subgroup analyses were performed for each anxiety disorder. All statistical analyses were performed using Stata, version 11.0 (StataCorp).

Results

FDA Reviews

We analyzed 9 second-generation antidepressants for data related to the 5 anxiety disorders. Within those 45 possible drug indication combinations, 21 are FDA approved. Of those combinations, we were able to download 9 FDA approval packages through the FDA website; for the remaining 12 combinations, we made requests to the FDA Freedom of Information Office. Of these, the FDA Freedom of Information Office fulfilled 11 requests (the FDA informed us that the drug approval package for fluoxetine for panic disorder would not be available for at least 18 months). Twenty approval packages were available for the present study (eTable 1 in the Supplement). These drug approval packages, which were issued between 1994 and 2008, reviewed the results of 57 randomized, placebo-controlled short-term trials.

Journal Articles

For the 57 above-mentioned FDA-registered trials, we identified 48 publications presenting the results of 52 trials. Three of these articles were excluded from further analyses.³⁰⁻³² As a result, 3 additional trials (trials: 637 [paroxetine for GAD], 627 [paroxetine for PTSD], and 514 [sertraline for PD]) were judged to be not fully published. Two articles pooled trials that were not identical in design,^{30,31} and another pooled-trials article failed to present separate results for the included trials³² and included a trial that was previously published as a stand-alone publication.³³ A flow diagram of this process is shown in eFigure 1 in the Supplement, and characteristics of the included trials are presented in Table 1.

Trial Outcome vs Published Results

The proportion of positive findings was 72% (41 of 57) according to the FDA vs 96% (43 of 45) according to the published literature. This difference was statistically significant (binomial test, $P < .001$).

Of the 41 positive trials, 40 trials (98%) were published in agreement with the FDA. By contrast, of the 16 not-positive trials, only 3 (19%) were published in agreement with the FDA (Figure 1). This difference was statistically significant (Fisher exact test, $P < .001$). Overall, trials that the FDA judged as positive were 5 times more likely to be published in agreement with that decision than were FDA-determined not-positive trials (risk ratio, 5.20; 95% CI, 1.87-14.45; $P < .001$).

Study Publication Bias

Sixteen of the 57 trials (28%) were not positive according to the FDA. Seven of these 16 not-positive trials (44%) were not published, but only 1 of the 41 positive trials (2%) was not pub-

lished (Table 1). This difference was statistically significant (Fisher exact test, $P < .001$).

Outcome Reporting Bias

For 3 of the 16 not-positive trials (19%),^{33,43,61} results were published with a conclusion that conflicted with that in the FDA review, changing the effects from nonsignificant to statistically significant. By contrast, outcome reporting bias was found in none of the 41 FDA-positive trials (Table 1). The difference in proportions was statistically significant (Fisher exact test, $P = .02$).

One of the 3 above-mentioned publications (trial 120 [paroxetine for PD])⁴³ presented only observed-cases analyses for the primary outcome; according to the FDA, the primary analysis involved last-observation-carried-forward analyses, the results of which were not statistically significant. In the article³³ presenting the results of trial 529, data from participants with PD who were randomized to different dosages of sertraline were pooled and compared with the placebo group, yielding a significant result. The FDA review showed that the primary results for each of the dosage groups were nonsignificant. Finally, one article⁶¹ presenting the results of trial 95-003, which compared the effect of sertraline (with and without exposure therapy) with that of placebo (with and without exposure therapy) in patients with SAD, combined scores on 3 end points (disorder-specific Clinical Global Impression Scale [severity and improvement] and Social Phobia Scale) in response vs nonresponse categories. According to the FDA, the primary end point was the severity total score of the disorder-specific Clinical Global Impression Scale, and results for this end point were nonsignificant.

Spin

Spin was present in an additional 3 of 16 (19%) of the not-positive trials^{52,70,74} and not present for positive trials (Fisher exact test, $P = .02$) (Table 1). Each of these 3 articles reported that the primary end point was nonsignificant in the results section but, in the abstract, concluded that the trial was positive. The FDA classified these trials as questionable (trial 237/248: sertraline for OCD⁷⁴) or negative (trial E079: fluoxetine for OCD⁷⁰ and trial 391: venlafaxine ER for PD⁵²). Conclusions on study drug efficacy for these trials, according to the FDA and the authors of the journal articles, are included in eTable 2 in the Supplement.

Meta-analysis

FDA Data

The pooled effect size based on the FDA data was 0.33 (95% CI, 0.29-0.38; $P < .001$). Heterogeneity was moderate ($I^2 = 39%$; 95% CI, 15%-56%). For trials published in agreement with the FDA review results, the pooled effect size (Hedges $g = 0.38$; 95% CI, 0.34-0.42; $P < .001$) was larger than the pooled effect size of trials that were not published or published in disagreement with the FDA conclusion (Hedges $g = 0.17$; 95% CI, 0.09-0.26; $P < .001$). Meta-regression showed this difference to be statistically significant ($\beta = 0.21$; 95% CI, 0.12-0.30; $t = 4.61$; $P < .001$).

Journal Data and Comparison With FDA Data

The pooled effect size based on the literature was 0.38 (95% CI, 0.33 to 0.42; $P < .001$). Heterogeneity was low ($I^2 = 30%$; 95% CI, 0% to 51%). This effect size represented a 15% increase in

Table 1. Characteristics of Included Premarketing Trials According to FDA and Journal Match

Drug	Trial No.	Duration, wk	Dose, mg/d	No. of Participants		Primary End Point	FDA Conclusion	Publication ^a	Type of Bias
				Placebo	Drug				
GAD									
Escitalopram oxalate	MD-05	8	10-20	128	124	HAM-A	Positive	Goodman et al, ³⁴ 2005	NP
	MD-06	8	10-20	138	143	HAM-A	Positive	Goodman et al, ³⁴ 2005	NP
	MD-07	8	10-20	153	154	HAM-A	Positive	Davidson et al, ³⁵ 2004	NP
Paroxetine hydrochloride	641	8	20	180	188	HAM-A	Positive	Rickels et al, ³⁶ 2003	NP
			40	197					
	642	8	20-50	163	161	HAM-A	Positive	Pollack et al, ³⁷ 2001	NP
637	8	20-50	183	181	HAM-A	Negative	No full publication	Study publication bias	
Duloxetine hydrochloride	HMBR	9	60	173	165	HAM-A	Positive	Koponen et al, ³⁸ 2007	NP
			120	169					
	HMDT	10	60-120	158	161	HAM-A	Positive	Rynn et al, ³⁹ 2008	NP
HMDU	10	60-120	158	149	HAM-A	Positive	Hartford et al, ⁴⁰ 2007	NP	
Venlafaxine hydrochloride ER	210	8	75	96	86	HAM-A	Positive	Rickels et al, ⁴¹ 2000	NP
			150	81					
			225	86					
	214	8	75	98	87	HAM-A	Positive	Davidson et al, ⁴² 1999	NP
			150	87					
PD									
Paroxetine	120	10	40	69	72	% of Patients with no attacks	Questionable	Ballenger et al, ⁴³ 1998	Outcome reporting bias
	108	12	20-60	60	60	% of Patients with no or 1 attack	Positive	Oehrberg et al, ⁴⁴ 1995	NP
	187	12	20-60	123	123	% of Patients with no attacks	Positive	Leclubier et al, ⁴⁵ 1997	NP
	223	10	10-60	68	77	% of Patients with no attacks	Questionable	No full publication	Study publication bias
Paroxetine CR	494	10	25-75	129	122	% of Patients with no attacks	Positive	Sheehan et al, ⁴⁶ 2005	NP
	495	10	25-75	136	123	% of Patients with no attacks	Positive	Sheehan et al, ⁴⁶ 2005	NP
	497	10	25-75	130	132	% of Patients with no attacks	Negative	Sheehan et al, ⁴⁶ 2005	NP
Sertraline hydrochloride	629	10	50-200	87	79	No. of attacks	Positive	Pohl et al, ⁴⁷ 1998	NP
	630	10	50-200	88	88	No. of attacks	Positive	Pollack et al, ⁴⁸ 1998	NP
	529	12	50	44	42	No. of attacks	Questionable	Londborg et al, ³³ 1998	Outcome reporting bias
			100	41					
			200	44					
514	12	50	38	38	No. of attacks	Negative	No full publication	Study publication bias	
			100	38					
			200	36					
Venlafaxine ER	398	12	75	154	157	% of Patients with no attacks	Positive	Pollack et al, ⁴⁹ 2007	NP
			150	158					
	399	12	75	157	156	% of Patients with no attacks	Positive	Pollack et al, ⁵⁰ 2007	NP
			225	160					
353	10	75-225	155	155	% of Patients with no attacks	Questionable	Liebowitz et al, ⁵¹ 2009	NP	
391	10	75-225	168	160	% of Patients with no attacks	Negative	Bradwejn et al, ⁵² 2005	Spin	
SAD									
Fluvoxamine maleate CR	3107	12	100-300	125	110	LSAS	Positive	Davidson et al, ⁵³ 2004	NP
	3108	12	100-300	148	126	LSAS	Positive	Westenberg et al, ⁵⁴ 2004	NP
Paroxetine	502	12	20-50	145	136	LSAS	Positive	Baldwin et al, ⁵⁵ 1999	NP
	382	12	20-50	92	90	LSAS	Positive	Stein et al, ⁵⁶ 1998	NP
	454	12	20	92	89	LSAS	Positive	Liebowitz et al, ⁵⁷ 2002	NP
			40	88					
		60	91						

(continued)

Table 1. Characteristics of Included Premarketing Trials According to FDA and Journal Match

Drug	Trial No.	Duration, wk	Dose, mg/d	No. of Participants		Primary End Point	FDA Conclusion	Publication ^a	Type of Bias
				Placebo	Drug				
Paroxetine CR	790	12	12.5-37.5	184	185	LSAS	Positive	Lepola et al, ⁵⁸ 2004	NP
Sertraline	R-0601	12	50-200	196	205	LSAS	Positive	Liebowitz et al, ⁵⁹ 2003	NP
	94-004	20	50-200	69	134	BSPS	Positive	Van Ameringen et al, ⁶⁰ 2001	NP
	95-003	24	50-150	196	191	CGI-L	Negative	Blomhoff et al, ⁶¹ 2001	Outcome reporting bias
Venlafaxine ER	387	12	75-225	138	133	LSAS	Positive	Liebowitz et al, ⁶² 2005	NP
	393	12	75-225	135	126	LSAS	Positive	Rickels et al, ⁶³ 2004	NP
PTSD									
Sertraline	641	12	50-200	82	84	CAPS-2	Negative	Friedman et al, ⁶⁴ 2007	NP
	682	12	50-200	94	94	CAPS-2	Negative	No full publication	Study publication bias
	640	12	50-200	104	98	CAPS-2	Positive	Davidson et al, ⁶⁵ 2001	NP
	671	12	50-200	90	93	CAPS-2	Positive	Brady et al, ⁶⁶ 2000	NP
Paroxetine	651	12	20	167	166	CAPS-2	Positive	Marshall et al, ⁶⁷ 2001	NP
			40		156				
	648	12	20-50	133	136	CAPS-2	Positive	Tucker et al, ⁶⁸ 2001	NP
	627	12	20-50	159	154	CAPS-2	Questionable	No full publication	Study publication bias
OCD									
Fluoxetine hydrochloride	HCEP 1	13	20	47	47	Y-BOCS	Positive	Tollefson et al, ⁶⁹ 1994	NP
			40		45				
			60		47				
	HCEP 2	13	20	41	39	Y-BOCS	Positive	Tollefson et al, ⁶⁹ 1994	NP
			40		41				
			60		42				
E079	8	20	56	52	Y-BOCS	Negative	Montgomery et al, ⁷⁰ 1993	Spin	
		40		52					
		60		54					
Fluvoxamine	5529	10	100-300	80	79	Y-BOCS	Positive	No full publication	NP
	5534	10	100-300	77	78	Y-BOCS	Positive	Goodman et al, ⁷¹ 1996	NP
Fluvoxamine CR	3103	12	100-300	119	113	Y-BOCS	Positive	Hollander et al, ⁷² 2003	NP
Paroxetine	116	12	40	88	83	Y-BOCS	Positive	Hollander et al, ⁷² 2003	NP
			60		83				
	118	12	20-60	75	79	Y-BOCS	Negative	No full publication	Study publication bias
	136	12	20-60	99	198	Y-BOCS	Positive	Zohar et al, ⁷³ 1996	NP
Sertraline	237/248	8	50-200	44	43	Y-BOCS	Questionable	Chouinard et al, ⁷⁴ 1990	Spin
	371/372	12	50	84	79	Y-BOCS	Positive	Greist et al, ⁷⁵ 1995	NP
			100		81				
			200		80				
	546	12	50-200	79	85	Y-BOCS	Positive	Kronig et al, ²⁸ 1999	NP
495	16	50-200	87	83	Y-BOCS	Negative	No full publication	Study publication bias	

Abbreviations: BSPS, Brief Social Phobia Scale; CAPS-2, Clinician-Administered PTSD Scale, part 2; CGI-L, Clinical Global Impressions-Liebowitz; CR, controlled release; ER, extended release; FDA, US Food and Drug Administration; GAD, generalized anxiety disorder; HAM-A, Hamilton Rating Scale for Anxiety; LSAS, Liebowitz Social Anxiety Scale; NP, not present; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder;

SAD, social anxiety disorder; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

^a Information on all trials was also obtained from FDA websites: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm> and <http://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm>.

effect size compared with the value based on the FDA data. This difference was not statistically significant by meta-regression ($\beta = 0.04$; 95% CI, -0.02 to 0.10 ; $t = 1.36$; $P = .18$).

Anxiety Subgroup Analyses

Effect sizes based on data from the FDA reviews were 0.32 for GAD, 0.28 for PD, 0.27 for PTSD, and 0.39 for both OCD and SAD. For all disorders, the pooled effect sizes of trials published in agreement with the FDA review results were larger than the pooled effect sizes of trials that were not published or were published in disagreement with the FDA conclusion (Table 2). As a

result, forest plots for all disorders showed fewer nonsignificant trials according to the literature than according to the FDA, especially for PD and OCD (Figure 2 and Figure 3; see eFigure 2 in the Supplement for GAD, SAD, and PTSD).

Effect sizes based on the literature were larger for all disorders compared with effect sizes based on the FDA reviews, with the smallest increases for GAD (Hedges $g = 0.34$, 6% increase) and SAD (Hedges $g = 0.42$, 8% increase) and larger increases for OCD (Hedges $g = 0.45$, 15% increase), PTSD (Hedges $g = 0.32$, 19% increase), and PD (Hedges $g = 0.35$, 25% increase). However, the differences in effect estimates based on

the journal articles and the FDA reviews were not statistically significant for any of the individual disorders (Table 2).

Discussion

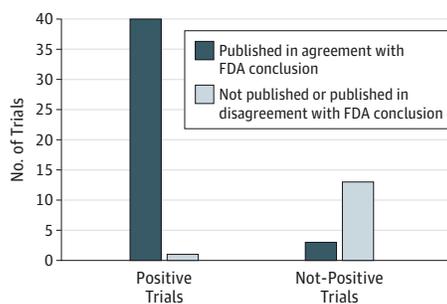
The present study shows the presence of reporting bias in randomized clinical trials on the efficacy of second-generation antidepressants for anxiety disorders. Trials that the FDA judged to be positive were greater than 5 times more likely to be published in agreement with the FDA analysis than were not-positive trials. As a result, 96% of the journal articles (43 of 45) were framed positively, but only 72% of the trials (41 of 57) were deemed positive by the FDA. All reporting biases examined (ie, study publication bias, outcome reporting bias, and spin) were present among the included trials.

In a previous study⁶ that examined reporting bias in trials on second-generation antidepressants for major depressive disorder, the overall effect size based on the FDA data was 0.31, which is comparable to the effect size of 0.33 found in the present study. After conducting 2 meta-analyses, one based on data from the FDA reviews and the other based on data from the corresponding journal articles, we found that reporting bias inflated the apparent effect size by 15%. This increase was not statistically significant, in contrast to the larger inflation factor (32%)

found earlier with major depressive disorder.⁶ For the individual anxiety disorders, the inflation factors ranged from 6% (GAD) to 25% (PD), indicating the importance of using unbiased data in meta-analyses on the efficacy of second-generation antidepressants for treatment of anxiety disorders.

In the main analyses we combined 5 disorders classified as anxiety disorders in the *DSM-IV*; however, in the *DSM-5*, OCD is now classified under *obsessive-compulsive and related disorders*, and PTSD is under *trauma- and stressor-related disorders*. Therefore, with the recent change in taxonomy, our grouping of these disorders could be viewed as a limitation, although the efficacy of the drugs was comparable across disorders. A clearer limitation of the present study is the small number of trials for the individual anxiety disorders, decreasing the power of the subgroup analyses. An additional limitation is that we did not examine biased reporting of harm outcomes, which figures into the overall risk-benefit ratio of a drug, but such an examination would have been beyond the scope of the present study. Certain data available only in pooled-trials publications were classified as unpublished, which could also be viewed as a limitation. However, a study⁷⁶ of antidepressant trials submitted to the Swedish drug regulatory authority showed that positive trials were more likely to be presented as stand-alone publications, and negative trials tended to be reported only within pooled-trials publications. Pooled analyses may not follow the predetermined analysis plan and power calculation and can therefore yield different conclusions than the original trials. Pooled analyses are also associated with “salami slicing” (publishing similar results from one study in multiple publications).⁷⁷ Therefore, although these publications may provide new information, especially on subgroups and secondary end points, they are susceptible to bias.⁷⁸ This bias can be reduced by first publishing the original trial results. Future research could assess the bias that is introduced by pooled-trials publications. Finally, we did not contact drug sponsors to ask whether specific trials were published in the scientific literature, so there is a small chance that trials could have been misclassified as unpublished. However, considering the extensive literature search methods, it seems unlikely that such publications would be discoverable by the typical health care professional.

Figure 1. Reporting Bias in Not-Positive Trials



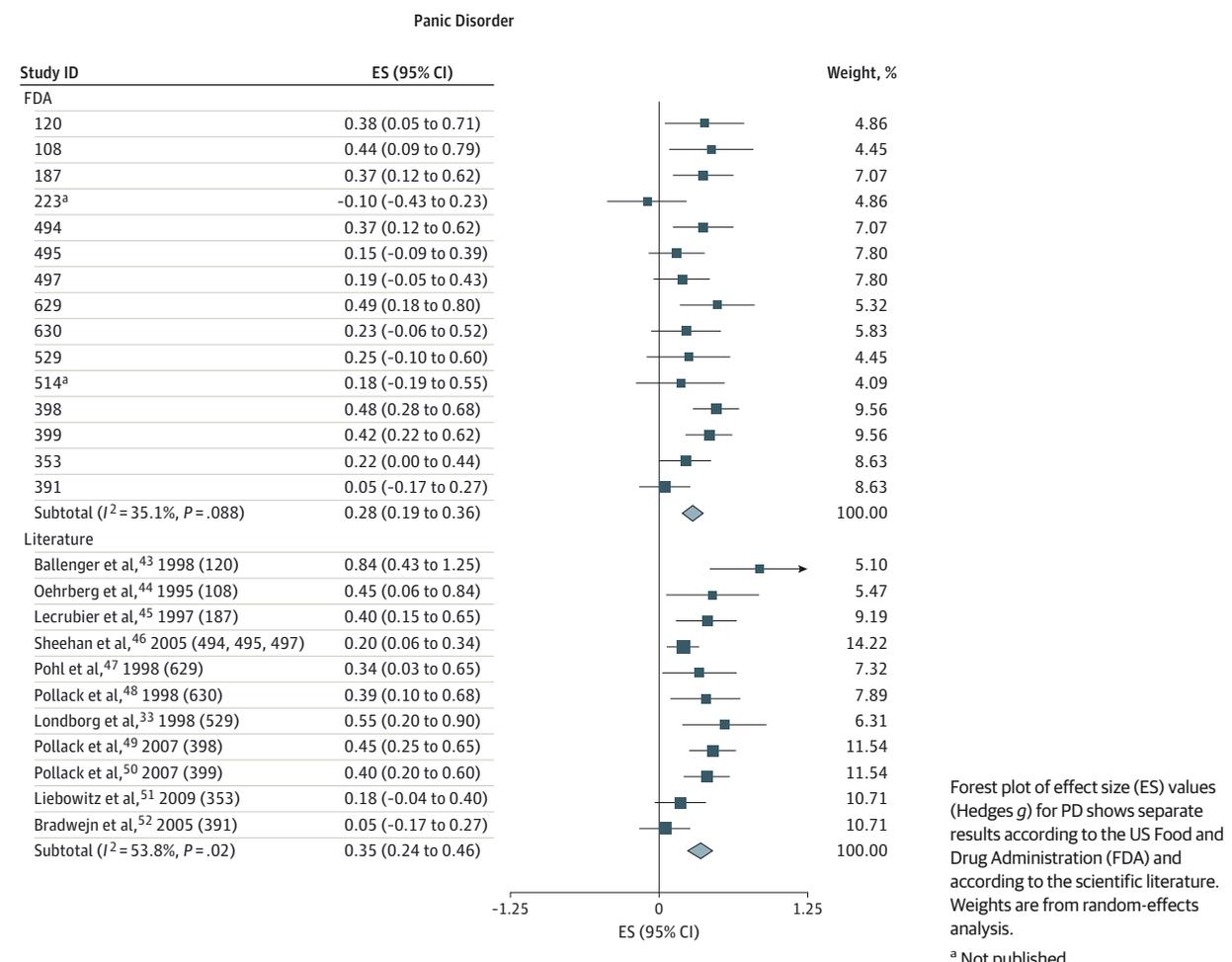
FDA indicates US Food and Drug Administration.

Table 2. Effect Estimates for Individual Anxiety Disorders

Disorder	FDA		Published in Agreement, Hedges <i>g</i> (95% CI)	Published Not in Agreement, Hedges <i>g</i> (95% CI)	Journal		Overestimation of Hedges <i>g</i> (Journal vs FDA Total), %	<i>P</i> Value Overestimation
	Total Hedges <i>g</i> (95% CI)	<i>I</i> ² (95% CI), %			Hedges <i>g</i> (95% CI)	<i>I</i> ² (95% CI), %		
GAD	0.32 (0.25 to 0.39)	17 (0 to 57)	0.34 (0.28 to 0.41)	0.11 (-0.09 to 0.31)	0.34 (0.27 to 0.41)	0 (0 to 62)	6	.65
PD	0.28 (0.20 to 0.36)	35 (0 to 65)	0.33 (0.25 to 0.41)	0.13 (-0.02 to 0.29)	0.35 (0.24 to 0.46)	54 (9 to 77)	25	.38
SAD	0.39 (0.30 to 0.49)	42 (0 to 71)	0.43 (0.35 to 0.50)	0.09 (-0.11 to 0.29)	0.42 (0.35 to 0.49)	0 (0 to 60)	8	.56
PTSD	0.27 (0.11 to 0.44)	66 (24 to 85)	0.33 (0.14 to 0.53)	0.13 (-0.12 to 0.38)	0.32 (0.14 to 0.50)	61 (0 to 85)	19	.76
OCD	0.39 (0.30 to 0.49)	27 (0 to 62)	0.44 (0.33 to 0.54)	0.30 (0.11 to 0.48)	0.45 (0.35 to 0.56)	16 (0 to 58)	15	.42
Overall	0.33 (0.29 to 0.38)	39 (15 to 56)	0.38 (0.34 to 0.42)	0.17 (0.09 to 0.26)	0.38 (0.33 to 0.42)	30 (0 to 51)	15	.18

Abbreviations: FDA, US Food and Drug Administration; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PD, panic disorder; PTSD, posttraumatic stress disorder; SAD, social anxiety disorder.

Figure 2. Forest Plot for Panic Disorder (PD)



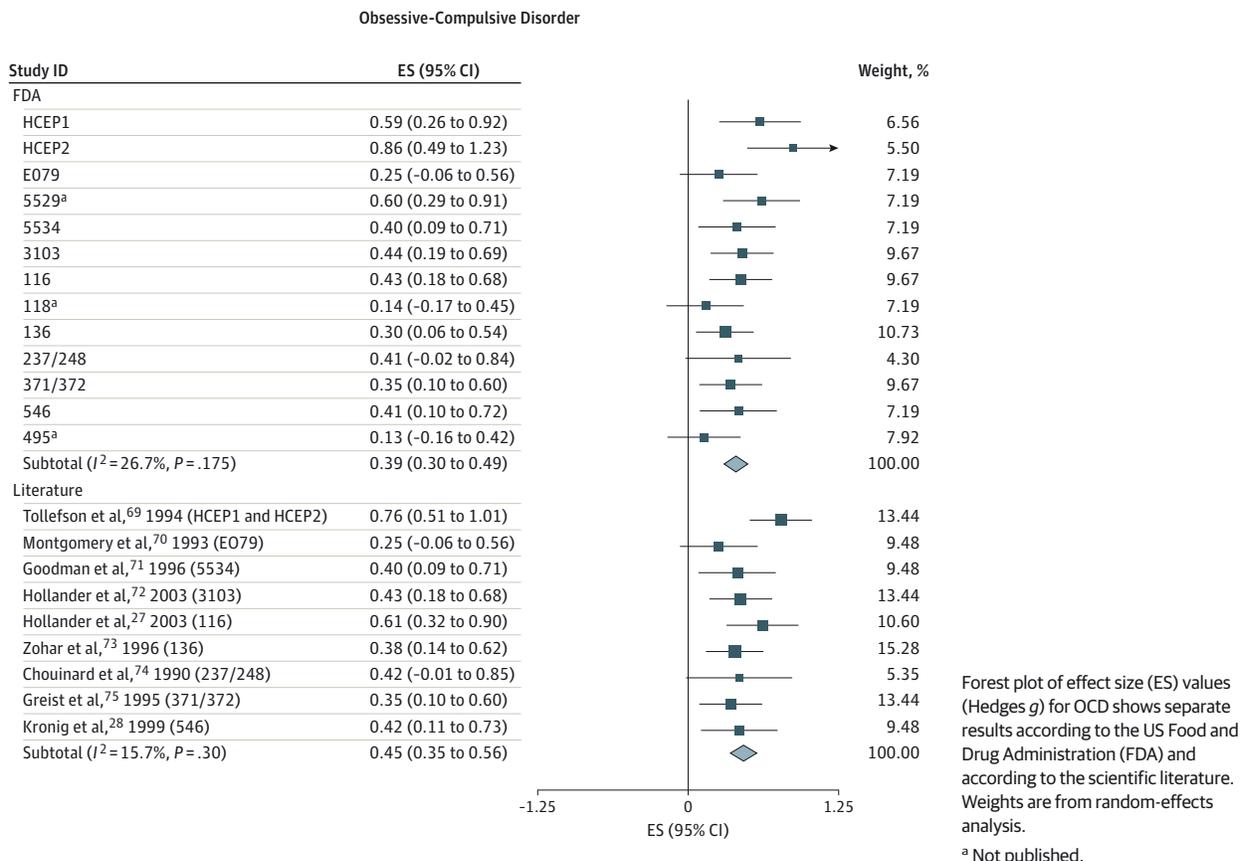
A strength of this study is that, for 20 of the 21 FDA-approved drug-indication combinations, we were able to include data from all premarketing randomized clinical trials, thereby allowing a reliable assessment of different reporting biases for these trials. However, we could not include data from rejected drug-indication applications because the FDA does not release these reviews.⁷⁹ It is likely that the amount of reporting bias that was found would increase if these trials were also examined. In addition, our estimation of the amount of reporting bias present might be influenced by the fact that all trials were sponsored by pharmaceutical companies. Yet reporting bias is not restricted to pharmacologic treatments sponsored by drug companies.⁷⁹ Since reporting bias has been shown⁸⁰ for the treatment of depression with psychotherapy, it should be worthwhile to systematically assess reporting bias in trials using psychotherapy for anxiety disorders.

Spin can result from different intentional or unintentional strategies, for example, by focusing on secondary end points for which significant results were obtained.⁸¹ Journal articles for which spin was identified also often reported “marginally significant results” (*P* values between .05 and .10) in the present study. Ideally, interpretation of trial results should not be based solely

on a *P* value indicating whether results are statistically significant.⁵ In addition to providing *P* values, future research could consider including Bayes factors as a measure of the strength of the evidence. Bayes factors stem from Bayesian statistics and have the advantage of expressing the strength of the evidence on a continuous scale.⁸²

Reporting bias significantly increased the number of positive vs negative publications in the literature in the present study. This outcome likely affects physicians’ perceptions of the efficacy of these drugs, which could reasonably be expected to affect prescribing behavior. In both Europe and the United States, use of antidepressants has been rising markedly during the past 2 decades, with much of that use appearing to be driven by nonspecialists in primary care settings.^{83,84} Although these studies could not take into account the indications for which the drugs were prescribed, a realistic view of the efficacy of these agents is important across all indications.^{83,84} Results of the present study and additional studies^{6,25} comparing published results with data from FDA reviews or other registries can perhaps assist physicians in gaining a more realistic view of the evidence for the efficacy of antidepressants in the short-term treatment of affective disorders.

Figure 3. Forest Plot for Obsessive-Compulsive Disorder (OCD)



This study adds to the growing body of literature establishing the pervasiveness of reporting bias.^{79,85} It also highlights the need to address this problem using various measures, as recently reviewed.⁸⁶ One suggested approach, which would address outcome reporting bias and spin (but not study publication bias), would require peer reviewers to make preliminary decisions based on the strength of the methods in the original trial protocol⁷⁹ so that their decisions are not influenced by the statistical significance of the study results.⁸⁷ Use of study registries, such as ClinicalTrials.gov, can also reduce reporting bias in the scientific literature,⁷⁹ but this registry does not function optimally.

For example, for most trials subjected to mandatory reporting within 1 year following trial completion, the results were not posted within this timeframe.⁸⁸

Conclusions

Although most trials on the efficacy of FDA-approved second-generation antidepressants for anxiety disorders evaluated in this meta-analysis were positive, various reporting biases were present. These reporting biases led to an overly positive representation of significant findings in the scientific literature.

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Study concept and design: Roest, de Jonge, Schoevers, Turner.

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Drafting of the manuscript: Roest, de Jonge.

Critical revision of the manuscript for important intellectual content: de Jonge, Williams, de Vries, Schoevers, Turner.

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(FDA). From 2001 to 2005, Dr Turner provided outside consulting to Bristol-Myers Squibb, Eli Lilly, and GlaxoSmithKline. From 2004 to 2005, Dr Turner was on the speakers bureaus of AstraZeneca, Bristol-Myers Squibb, and Eli Lilly. No other disclosures were reported.

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REFERENCES

- Dwan K, Gamble C, Williamson PR, Kirkham JJ; Reporting Bias Group. Systematic review of the empirical evidence of study publication bias and outcome reporting bias—an updated review. *PLoS One*. 2013;8(7):e66844. doi:10.1371/journal.pone.006684.
- Eyding D, Lelgemann M, Grouven U, et al. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and selective serotonin reuptake inhibitor controlled trials. *BMJ*. 2010;341:c4737.
- Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. <http://www.cochrane-handbook.org>. Published 2011. Accessed August 25, 2013.
- Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA*. 2004;291(20):2457-2465.
- Boutron I, Dutton S, Ravaud P, Altman DG. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *JAMA*. 2010;303(20):2058-2064.
- Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252-260.
- Turner EH, Knoopfmacher D, Shapley L. Publication bias in antipsychotic trials: an analysis of efficacy comparing the published literature to the US Food and Drug Administration database. *PLoS Med*. 2012;9(3):e1001189. doi:10.1371/journal.pmed.1001189.
- Turner EH. How to access and process FDA drug approval packages for use in research. *BMJ*. 2013;347:f5992.
- Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*. 2010;303(1):47-53.
- Ioannidis JP. Effectiveness of antidepressants: an evidence myth constructed from a thousand randomized trials? *Philos Ethics Humanit Med*. 2008;3:14.
- Olfson M, Marcus SC. National patterns in antidepressant medication treatment. *Arch Gen Psychiatry*. 2009;66(8):848-856.
- Baxter AJ, Scott KM, Vos T, Whiteford HA. Global prevalence of anxiety disorders: a systematic review and meta-regression. *Psychol Med*. 2013;43(5):897-910.
- Davidson JR. First-line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatry*. 2009;70(suppl 2):25-31.
- NICE clinical guideline 113. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. Issued January 2011. National Institute for Health and Clinical Excellence. <https://www.nice.org.uk/guidance/cg113>. Published 2011. Accessed October 22, 2014.
- Batelaan NM, Van Balkom AJ, Stein DJ. Evidence-based pharmacotherapy of panic disorder: an update. *Int J Neuropsychopharmacol*. 2012;15(3):403-415.
- Blanco C, Bragdon LB, Schneier FR, Liebowitz MR. The evidence-based pharmacotherapy of social anxiety disorder. *Int J Neuropsychopharmacol*. 2013;16(1):235-249.
- Ipser JC, Stein DJ. Evidence-based pharmacotherapy of post-traumatic stress disorder (PTSD). *Int J Neuropsychopharmacol*. 2012;15(6):825-840.
- Fineberg NA, Brown A, Reghunandan S, Pampaloni I. Evidence-based pharmacotherapy of obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2012;15(8):1173-1191.
- Hidalgo RB, Tupler LA, Davidson JR. An effect-size analysis of pharmacologic treatments for generalized anxiety disorder. *J Psychopharmacol*. 2007;21(8):864-872.
- Otto MW, Tuby KS, Gould RA, McLean RY, Pollack MH. An effect-size analysis of the relative efficacy and tolerability of serotonin selective reuptake inhibitors for panic disorder. *Am J Psychiatry*. 2001;158(12):1989-1992.
- Andrisano C, Chiesa A, Serretti A. Newer antidepressants and panic disorder: a meta-analysis. *Int Clin Psychopharmacol*. 2013;28(1):33-45.
- Hedges DW, Brown BL, Shwalb DA, Godfrey K, Larcher AM. The efficacy of selective serotonin reuptake inhibitors in adult social anxiety disorder: a meta-analysis of double-blind, placebo-controlled trials. *J Psychopharmacol*. 2007;21(1):102-111.
- Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database Syst Rev*. 2006;1(1):CD002795.
- Soomro GM, Altman D, Rajagopal S, Oakley-Browne M. Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD). *Cochrane Database Syst Rev*. 2008;1(1):CD001765.
- Sugarman MA, Loree AM, Baltes BB, Grekin ER, Kirsch I. The efficacy of paroxetine and placebo in treating anxiety and depression: a meta-analysis of change on the Hamilton Rating Scales. *PLoS One*. 2014;9(8):e106337. doi:10.1002/14651858.CD001765.pub3.
- Lipsey MW, Wilson D. *Practical Meta-Analysis (Applied Social Research Methods)*. Thousand Oaks, CA: Sage Publications; 2001:199-200.
- Hollander E, Allen A, Steiner M, Wheadon DE, Oakes R, Burnham DB; Paroxetine OCD Study Group. Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. *J Clin Psychiatry*. 2003;64(9):1113-1121.
- Kronig MH, Apter J, Asnis G, et al. Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. *J Clin Psychopharmacol*. 1999;19(2):172-176.
- Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
- Rickels K, Rynn M, Iyengar M, Duff D. Remission of generalized anxiety disorder: a review of the paroxetine clinical trials database. *J Clin Psychiatry*. 2006;67(1):41-47.
- Stein DJ, Davidson J, Seedat S, Beebe K. Paroxetine in the treatment of post-traumatic stress disorder: pooled analysis of placebo-controlled studies. *Expert Opin Pharmacother*. 2003;4(10):1829-1838.
- Sheikh JI, Londborg P, Clary CM, Fayyad R. The efficacy of sertraline in panic disorder: combined results from two fixed-dose studies. *Int Clin Psychopharmacol*. 2000;15(6):335-342.
- Londborg PD, Wolkow R, Smith WT, et al. Sertraline in the treatment of panic disorder: a multi-site, double-blind, placebo-controlled, fixed-dose investigation. *Br J Psychiatry*. 1998;173:54-60.
- Goodman WK, Bose A, Wang Q. Treatment of generalized anxiety disorder with escitalopram: pooled results from double-blind, placebo-controlled trials. *J Affect Disord*. 2005;87(2-3):161-167.
- Davidson JR, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety*. 2004;19(4):234-240.
- Rickels K, Zaninelli R, McCafferty J, Bellow K, Iyengar M, Sheehan D. Paroxetine treatment of generalized anxiety disorder: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2003;160(4):749-756.
- Pollack MH, Zaninelli R, Goddard A, et al. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62(5):350-357.
- Koponen H, Allgulander C, Erickson J, et al. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. *Prim Care Companion J Clin Psychiatry*. 2007;9(2):100-107.
- Rynn M, Russell J, Erickson J, et al. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. *Depress Anxiety*. 2008;25(3):182-189.
- Hartford J, Kornstein S, Liebowitz M, et al. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. *Int Clin Psychopharmacol*. 2007;22(3):167-174.
- Rickels K, Pollack MH, Sheehan DV, Haskins JT. Efficacy of extended-release venlafaxine in nondepressed outpatients with generalized anxiety disorder. *Am J Psychiatry*. 2000;157(6):968-974.
- Davidson JR, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *J Clin Psychiatry*. 1999;60(8):528-535.
- Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. *Am J Psychiatry*. 1998;155(1):36-42.
- Oehrberg S, Christiansen PE, Behnke K, et al. Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. *Br J Psychiatry*. 1995;167(3):374-379.

45. Lecrubier Y, Bakker A, Dunbar G, Judge R; Collaborative Paroxetine Panic Study Investigators. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. *Acta Psychiatr Scand*. 1997;95(2):145-152.
46. Sheehan DV, Burnham DB, Iyengar MK, Perera P; Paxil CR Panic Disorder Study Group. Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. *J Clin Psychiatry*. 2005; 66(1):34-40.
47. Pohl RB, Wolkow RM, Clary CM. Sertraline in the treatment of panic disorder: a double-blind multicenter trial. *Am J Psychiatry*. 1998;155(9):1189-1195.
48. Pollack MH, Otto MW, Worthington JJ, Manfro GG, Wolkow R. Sertraline in the treatment of panic disorder: a flexible-dose multicenter trial. *Arch Gen Psychiatry*. 1998;55(11):1010-1016.
49. Pollack MH, Lepola U, Koponen H, et al. A double-blind study of the efficacy of venlafaxine extended-release, paroxetine, and placebo in the treatment of panic disorder. *Depress Anxiety*. 2007; 24(1):1-14.
50. Pollack M, Mangano R, Entsuah R, Tzanis E, Simon NM, Zhang Y. A randomized controlled trial of venlafaxine ER and paroxetine in the treatment of outpatients with panic disorder [published correction appears in *Psychopharmacology (Berl)*. 2008 Feb;196(2):339]. *Psychopharmacology (Berl)*. 2007;194(2):233-242.
51. Liebowitz MR, Asnis G, Mangano R, Tzanis E. A double-blind, placebo-controlled, parallel-group, flexible-dose study of venlafaxine extended release capsules in adult outpatients with panic disorder. *J Clin Psychiatry*. 2009;70(4):550-561.
52. Bradwejn J, Ahokas A, Stein DJ, Salinas E, Emilien G, Whitaker T. Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry*. 2005;187:352-359.
53. Davidson J, Yaryura-Tobias J, DuPont R, et al. Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol*. 2004;24(2):118-125.
54. Westenberg HG, Stein DJ, Yang H, Li D, Barbato LM. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol*. 2004;24(1):49-55.
55. Baldwin D, Bobes J, Stein DJ, Scharwächter I, Faure M; Paroxetine Study Group. Paroxetine in social phobia/social anxiety disorder: randomised, double-blind, placebo-controlled study. *Br J Psychiatry*. 1999;175:120-126.
56. Stein MB, Liebowitz MR, Lydiard RB, Pitts CD, Bushnell W, Gergel I. Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. *JAMA*. 1998;280(8):708-713.
57. Liebowitz MR, Stein MB, Tancer M, Carpenter D, Oakes R, Pitts CD. A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. *J Clin Psychiatry*. 2002;63(1):66-74.
58. Lepola U, Bergtholdt B, St Lambert J, Davy KL, Ruggiero L. Controlled-release paroxetine in the treatment of patients with social anxiety disorder. *J Clin Psychiatry*. 2004;65(2):222-229.
59. Liebowitz MR, DeMartini NA, Weihs K, et al. Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. *J Clin Psychiatry*. 2003; 64(7):785-792.
60. Van Ameringen MA, Lane RM, Walker JR, et al. Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. *Am J Psychiatry*. 2001;158(2):275-281.
61. Blomhoff S, Haug TT, Hellström K, et al. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. *Br J Psychiatry*. 2001;179:23-30.
62. Liebowitz MR, Mangano RM, Bradwejn J, Asnis G; SAD Study Group. A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. *J Clin Psychiatry*. 2005;66(2):238-247.
63. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. *J Clin Psychopharmacol*. 2004;24(5):488-496.
64. Friedman MJ, Marmor CR, Baker DG, Sikes CR, Farfel GM. Randomized, double-blind comparison of sertraline and placebo for posttraumatic stress disorder in a Department of Veterans Affairs setting. *J Clin Psychiatry*. 2007;68(5):711-720.
65. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry*. 2001;58(5):485-492.
66. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2000;283(14):1837-1844.
67. Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry*. 2001;158(12):1982-1988.
68. Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry*. 2001;62(11):860-868.
69. Tollefson GD, Rampey AH Jr, Potvin JH, et al. A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1994;51(7):559-567.
70. Montgomery SA, McIntyre A, Osterheider M, et al; Lilly European OCD Study Group. A double-blind, placebo-controlled study of fluoxetine in patients with DSM-III-R obsessive-compulsive disorder. *Eur Neuropsychopharmacol*. 1993;3(2):143-152.
71. Goodman WK, Kozak MJ, Liebowitz M, White KL. Treatment of obsessive-compulsive disorder with fluvoxamine: a multicentre, double-blind, placebo-controlled trial. *Int Clin Psychopharmacol*. 1996;11(1):21-29.
72. Hollander E, Koran LM, Goodman WK, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 2003;64(6):640-647.
73. Zohar J, Judge R; OCD Paroxetine Study Investigators. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry*. 1996;169(4):468-474.
74. Chouinard G, Goodman W, Greist J, et al. Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. *Psychopharmacol Bull*. 1990;26(3):279-284.
75. Greist J, Chouinard G, DuBoff E, et al. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. *Arch Gen Psychiatry*. 1995;52(4):289-295.
76. Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence based medicine—selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ*. 2003;326(7400):1171-1173.
77. Spielmanns G, Biehn TL, Sawrey DL. A case study of salami slicing: pooled analyses of duloxetine for depression. *Psychother Psychosom*. 2010;79(2):97-106.
78. Thaler KJ, Morgan LC, Van Noord M, et al. A case study of pooled-studies publications indicated potential for both valuable information and bias. *J Clin Epidemiol*. 2013;66(10):1082-1092.
79. Turner EH. Publication bias, with a focus on psychiatry: causes and solutions. *CNS Drugs*. 2013; 27(6):457-468.
80. Cuijpers P, Smit F, Bohlmeijer E, Hollon SD, Andersson G. Efficacy of cognitive-behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. *Br J Psychiatry*. 2010;196(3):173-178.
81. Yavchitz A, Boutron I, Bafeta A, et al. Misrepresentation of randomized controlled trials in press releases and news coverage: a cohort study. *PLoS Med*. 2012;9(9):e1001308. doi:10.1371/journal.pmed.1001308.
82. Goodman SN. Toward evidence-based medical statistics: 2: the Bayes factor. *Ann Intern Med*. 1999; 130(12):1005-1013.
83. Lockhart P, Guthrie B. Trends in primary care antidepressant prescribing 1995-2007: a longitudinal population database analysis. *Br J Gen Pract*. 2011;61(590):e565-e572. doi:10.3399/bjgp11X593848.
84. Mojtabai R, Olfson M. National trends in long-term use of antidepressant medications: results from the U.S. National Health and Nutrition Examination Survey. *J Clin Psychiatry*. 2014;75(2): 169-177.
85. McGauran N, Wieseler B, Kreis J, Schüller YB, Kölsch H, Kaiser T. Reporting bias in medical research—a narrative review. *Trials*. 2010;11:37.
86. Ioannidis JP, Munafò MR, Fusar-Poli P, Nosek BA, David SP. Publication and other reporting biases in cognitive sciences: detection, prevalence, and prevention. *Trends Cogn Sci*. 2014;18(5):235-241.
87. Emerson GB, Warne WJ, Wolf FM, Heckman JD, Brand RA, Leopold SS. Testing for the presence of positive-outcome bias in peer review: a randomized controlled trial. *Arch Intern Med*. 2010;170(21):1934-1939.
88. Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ*. 2012;344:d7373.