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Review article

# Obsessive-compulsive disorder has a reduced placebo (and antidepressant) response compared to other anxiety disorders: A meta-analysis

Michael A. Sugarman[a,*], Irving Kirsch[b], Jonathan D. Huppert[c]

[a] Department of Psychology, Bedford Veterans Affairs Medical Center, United States
[b] Harvard Medical School, United States
[c] Department of Psychology, The Hebrew University of Jerusalem, Israel

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ABSTRACT

*Background:* Previous studies have indicated that obsessive-compulsive disorder (OCD) might have a reduced placebo response compared to other anxiety-related disorders including generalized anxiety disorder, panic disorder, post-traumatic stress disorder, and social anxiety disorder. No previous analysis has directly compared antidepressant and placebo responses between OCD and these conditions.

*Method:* We analyzed pre-post change scores within drug and placebo groups as well as between-groups change scores (i.e., drug compared to placebo) for all FDA-approved antidepressants for the treatment of these five anxiety-related disorders. Antidepressants included duloxetine, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine. Random effects meta-analysis was used to examine all trials submitted to the FDA, plus additional post-approval trials available from manufacturer-sponsored clinical trial registers. Clinician-rated symptom inventories were the outcome measures for all conditions to facilitate comparisons across diagnoses.

*Results:* Fifty-six trials met inclusion criteria. OCD had significantly lower pre-post effect sizes ($ps < 0.003$) for both placebo (Hedges' $g = 0.49$) and antidepressants ($g = 0.84$) compared to the other four conditions ($gs$ between 0.70 and 1.10 for placebo and 1.11 and 1.40 for antidepressants). However, the drug-placebo effect sizes did not significantly differ across diagnoses ($Q(4) = 6.09$, $p = 0.193$, $I^2 = 34.3\%$ [95% CI: −7.0,59.7]), with $gs$ between = 0.26 and 0.39.

*Conclusions:* Overall pre-post change scores were smaller for OCD compared to other anxiety disorders for both antidepressants and placebo, although drug-placebo effects sizes did not significantly differ across disorders. Theoretical and clinical implications for the understanding and treatment of OCD are discussed.

## 1. Introduction

Previous studies (Huppert et al., 2004; Khan et al., 2005) have indicated that the placebo response is lower in obsessive-compulsive disorder (OCD) compared to other psychiatric conditions including panic disorder, social anxiety disorder (SAD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), and major depressive disorder. Huppert et al. (2004) analyzed 70 individuals who received placebo across three studies evaluating treatment of OCD, panic disorder, and generalized social phobia. Upon examining the magnitude of change on the respective symptom inventories, they observed that the patients with OCD experienced about half as much improvement ($d = 0.50$) compared to panic disorder ($d = 0.91$) and generalized social phobia ($d = 1.08$). These differences could not be accounted for by differences in treatment expectancy. Khan et al. (2005) is the only previous meta-analysis examining drug and placebo group improvements across multiple psychiatric diagnoses. They found that patients with OCD given placebo experienced on average about a 10% improvement in their symptoms, whereas patients with other diagnoses (including GAD, PTSD, depression, and panic disorder) experienced a 25% or greater improvement while on placebo. However, comparisons between the drug-treated groups in this analysis were confounded by the inclusion of several classes of medications, including antidepressants (tricyclics and second-generation), antipsychotics, mood stabilizers, and benzodiazepines. The inclusion of these multiple classes of medications could have also impacted the comparison among placebo-treated groups, as there may have been differing placebo effects between drug classes and disorders due to differences in unblinding and/or expectancy effects.

A recent meta-analysis (Roest et al., 2015) examined all trials that

* Correspondence to: Department of Psychology, 116B, 200 Springs Rd, Bedford, MA 01730, United States.
*E-mail address:* Mike.Sugarman@wayne.edu (M.A. Sugarman).

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were submitted to the FDA for the approval of nine antidepressants for the treatment of OCD, GAD, panic disorder, PTSD, and SAD. They found that all five conditions had mean drug-placebo benefits between *Hedges' g* = 0.27 and 0.39. A subsequent analysis (de Vries et al., 2016) examined the role of baseline severity on treatment efficacy and found no significant relationship between baseline severity and the drug-placebo difference for any of the five conditions. This analysis included pre-post effect sizes for each treatment group (drug and placebo) separately. The placebo and drug responses for OCD appeared to be lower than for the other conditions, although this analysis did not directly compare the effect sizes across conditions. Additionally, these analyses were limited to trials submitted to the FDA for drugs that were approved and did not include industry-sponsored trials that were conducted after approval.

An analysis comparing single-group treatment effect sizes across conditions could yield valuable clinical insights. For example, take a hypothetical situation in which patients with OCD showed a drug-placebo effect size of 0.3 with effect sizes of 0.8 and 0.5 for drug and placebo responses, respectively, and patients with depression had an equivalent drug-placebo effect size of 0.3 but with larger effect sizes for drug (e.g., 1.2) and placebo (e.g., 0.9) responses. In such a situation, one interpretation could be that the medication was equivalently efficacious in the treatment of both conditions. However, the overall expected pre-post response to both placebo and medication would be substantially different across diagnoses, due to differential placebo effects.

The goals of the current study were two-fold: 1) to analyze the magnitude of placebo and antidepressant benefits in the treatment of OCD compared to other conditions using an unbiased sample of clinical trials (through FDA approval documents and manufacturer-sponsored comprehensive trial databases); and 2) to compare the magnitude of antidepressant-placebo benefits across anxiety-related psychiatric diagnoses, based on DSM-IV criteria. It is widely believed that large placebo responses reduce drug-placebo differences, rendering it difficult to establish drug effectiveness (Chen et al., 2011). If this is the case, diagnoses showing higher placebo responses should show diminished drug-placebo differences. This study will examine this hypothesis to determine if there is a relationship between the placebo response and drug-placebo effect sizes across psychiatric diagnoses.

## 2. Methods

### 2.1. Study retrieval

This meta-analysis included published and unpublished manufacturer-sponsored, placebo-controlled double blind trials for second-generation antidepressants that were approved for the treatment of OCD, GAD, SAD, PTSD, and panic disorder. These drugs included escitalopram, paroxetine, duloxetine, venlafaxine, fluvoxamine, sertraline, and fluoxetine. Our search included both trials that were submitted to the FDA for the approval of the medications as well as post-marketing trials made available from select manufacturers that provide comprehensive online registries of all trials, regardless of whether the trials were published. This type of approach minimizes the possibility of publication bias, which is important because trials with favorable outcomes for antidepressants in the treatment of anxiety disorders are about five times more likely to be published (Roest et al., 2015). The use of trials submitted to the FDA also guarantees a high study quality because the FDA reviewers apply rigorous standards for antidepressant efficacy trials (Center for Drug Evaluation and Research, 1977) and they are the basis for clinical practice. Thus, all drug approval trials that were deemed acceptable by FDA standards were included in our analyses.

FDA drug approval packages were obtained through the FDA's website (http://www.accessdata.fda.gov/scripts/cder/daf/) or, if not available for download, requested through the FDA's Freedom of Information Office (http://www.accessdata.fda.gov/scripts/foi/FOIRequest/requestinfo.cfm). All drugs were approved between 1994 and 2008. It is possible that other trials and submissions were conducted for other drugs and/or indications with these drugs and were not approved, and thus, these trials were not available or included in our analyses. We supplemented these trials with further post-approval trials available through each drug's manufacturer, where available. Specifically, we searched the GlaxoSmithKline Clinical Trial Register (http://www.gsk-clinicalstudyregister.com) for additional paroxetine trials, the Lilly Clinical Trial Registry (http://www.lillytrials.com) for duloxetine trials, and the Forest Laboratories Clinical Trial Registry (http://www.forestclinicaltrials.com) for escitalopram trials.

Trials were included in the current analyses if they met the following criteria: 1) they were double-blind, placebo-controlled trials available through the sources described above, 2) they included pre-post change scores for both drug and placebo-treated individuals on the clinician-rated symptom inventories described in the next Section, 3) the drug was approved by the FDA for the condition being treated, and 4) the dose levels for the drug were in the ranges recommended by FDA treatment guidelines.

### 2.2. Meta-analytic data synthesis

For each disorder, we analyzed ratio-level clinician-rated symptom inventory outcome measures. These inventories were the primary outcome measure for every condition but panic disorder. For OCD, this measure was the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman et al., 1989). PTSD trials utilized the Clinician-Administered PTSD Scale-2 (CAPS-2; Blake et al., 1995). SAD trials utilized the Leibowitz Social Anxiety Scale (LSAS; Heimberg et al., 1999). Panic disorder and GAD trials both utilized the Hamilton Rating Scale for Anxiety (HRSA; Hamilton, 1959). The change scores for each trial were converted to a common metric of the standardized mean difference by dividing the pre-post change by the standard deviation of change, with the Hedges' *g* correction for positive bias (Hedges, 1981).

We opted to analyze the HRSA for panic disorder rather than the reduction in the number of panic attacks (which was the primary outcome measure in these studies) to more readily facilitate comparisons across diagnoses and ensure that all outcome measures were clinician-rated symptom inventories. Additionally, there was considerable inconsistency across studies regarding the manner in which the reduction in panic attacks was reported, presumably because the distributions within the patient samples had high positive skews. Only 6 out of 17 trials reported the mean reduction and the standard deviation of the change score within each group, whereas several other trials only reported the median change from baseline (with no within-group variance estimates). Others reported the change as the percentage of patients in remission (a $\geq$50% reduction in the number of panic attacks) and/or the percentage of patients with zero panic attacks; these methods create artificial dichotomies in patient outcomes that essentially eliminates about one-third of the variance in each study and increases the risk of false positive trial outcomes (Altman and Royston, 2006). Thus, the mean change score on the HRSA was the most appropriate cross-study outcome measure for panic disorder in these analyses.

For each disorder, we conducted two types of meta-analyses: 1) we analyzed the primary study objective of within-group pre-post responses by calculating the standardized mean difference for each treatment group (placebo and drug) separately; and 2) we conducted more traditional analyses for the drug-placebo effect size as a comparison between groups by calculating the difference in change score divided by the pooled standard deviation. For trials that included multiple treatment groups compared to one placebo group (e.g., trials comparing multiple dosage levels), the initial severity and change scores were combined across groups, weighted by the respective group sample sizes times the inverse of the change score variance. All analyses