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Differential Outcomes of Placebo Treatment Across 9 Psychiatric Disorders
A Systematic Review and Meta-Analysis

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IMPORTANCE Placebo is the only substance systematically evaluated across common psychiatric diagnoses, but comprehensive cross-diagnostic comparisons are lacking.

OBJECTIVE To compare changes in placebo groups in recent high-quality randomized clinical trials (RCTs) across a broad spectrum of psychiatric disorders in adult patients.

DATA SOURCES MEDLINE and the Cochrane Database of Systematic Reviews were systematically searched in March 2022 for the latest systematic reviews meeting predetermined high-quality criteria for 9 major psychiatric diagnoses.

STUDY SELECTION Using these reviews, the top 10 highest-quality (ie, lowest risk of bias, according to the Cochrane Risk of Bias tool) and most recent placebo-controlled RCTs per diagnosis (totaling 90 RCTs) were selected, adhering to predetermined inclusion and exclusion criteria.

DATA EXTRACTION AND SYNTHESIS Following the Cochrane Handbook, 2 authors independently carried out the study search, selection, and data extraction. Cross-diagnosis comparisons were based on standardized pre-post effect sizes (mean change divided by its SD) for each placebo group. This study is reported following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.

MAIN OUTCOME AND MEASURE The primary outcome, pooled pre-post placebo effect sizes (d_{av}) with 95% CIs per diagnosis, was determined using random-effects meta-analyses. A *Q* test assessed statistical significance of differences across diagnoses. Heterogeneity and small-study effects were evaluated as appropriate.

RESULTS A total of 90 RCTs with 9985 placebo-treated participants were included. Symptom severity improved with placebo in all diagnoses. Pooled pre-post placebo effect sizes differed across diagnoses (Q = 88.5; df = 8; P < .001), with major depressive disorder (d_{av} = 1.40; 95% CI, 1.24-1.56) and generalized anxiety disorder (d_{av} = 1.23; 95% CI, 1.06-1.41) exhibiting the largest d_{av}. Panic disorder, attention-deficit/hyperactivity disorder, posttraumatic stress disorder, social phobia, and mania showed d_{av} between 0.68 and 0.92, followed by OCD (d_{av} = 0.65; 95% CI, 0.51-0.78) and schizophrenia (d_{av} = 0.59; 95% CI, 0.41-0.76).

CONCLUSION AND RELEVANCE This systematic review and meta-analysis found that symptom improvement with placebo treatment was substantial in all conditions but varied across the 9 included diagnoses. These findings may help in assessing the necessity and ethical justification of placebo controls, in evaluating treatment effects in uncontrolled studies, and in guiding patients in treatment decisions. These findings likely encompass the true placebo effect, natural disease course, and nonspecific effects.

Multimedia

Supplemental content

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Placebo is arguably the most extensively investigated therapeutic agent worldwide. In psychiatry, a placebo is deemed ethically acceptable for research in nearly all indications, serving as the sole intervention that has been studied for all psychiatric disorders.

In studies of psychiatric conditions, even patients in placebo groups typically show improvement, making it sometimes challenging to discern a verum-placebo contrast.[1-3] Also, placebo effects have increased over the years in studies on major depression[4-6] and schizophrenia and schizoaffective disorder.[7]

A genuine placebo effect, by definition, encompasses improvements induced by suggestion, hope for effective treatment, and conditioning effects through the administration of medications. However, other factors might improve psychopathology: psychiatric disorders often have episodic courses. Contextual factors, such as attentive study personnel, compassionate care, supportive conversations, and psychoeducation, can influence outcomes positively.[8] Life circumstances may change during a study, and regression to the mean is a statistical factor in symptom improvement.[9] Consequently, all observable changes under a placebo medication are referred to as the *placebo response*.

Placebo response is not equally distributed across different disorders, with limited comprehensive comparisons in psychiatry. Khan and coauthors[10] compared 6 disorders in a 2005 study, which is still the most comprehensive study to date, to our knowledge; however, significant conditions, like mania or social phobia, were not included. Other reviews have focused on depressive disorders[1,3,6,10-16] or a few other diagnoses.[7,17-20]

Understanding differential outcomes observed in placebo groups may enrich our knowledge of these conditions, aid clinical trial interpretation, assist treatment decisions, and improve treatments. Therefore, in this systematic review and meta-analysis, we compared placebo responses among a wide spectrum of psychiatric disorders in adults.

Key Points

Question Which psychiatric disorder exhibits the strongest improvement associated with placebo treatment in randomized clinical trials (RCTs)?

Findings This systematic review and meta-analysis of 90 high-quality RCTs with 9985 participants found significant improvement under placebo treatment for all 9 disorders, but the degree of improvement varied significantly among diagnoses. Patients with major depressive disorder experienced the greatest improvement, followed by those with generalized anxiety disorder, panic disorder, attention-deficit/hyperactivity disorder, posttraumatic stress disorder, social phobia, mania, and OCD, while patients with schizophrenia benefited the least.

Meaning These findings may inform planning of RCTs, interpreting of uncontrolled studies, and advising patients for or against a specific treatment.

Methods

This study aimed to quantify differences in the change of psychopathological symptoms within placebo groups of high-quality randomized clinical trials (RCTs) across major psychiatric diagnoses. We compared pooled pre-post effect sizes of placebo groups by diagnosis. The study protocol has been registered in advance on Open-Science-Foundation (identifier: u469a). This study is reported following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline.

We selected 9 prevalent and clinically significant psychiatric conditions commonly subject to pharmacological treatment: major depressive disorder (MDD; unipolar recurrent or single episode), mania, schizophrenia, obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD), generalized anxiety disorder (GAD), panic disorder, posttraumatic stress disorder (PTSD), and social phobia. We included the 10 most recent high-quality RCTs per diagnosis due to feasibility constraints, using a 2-stage systematic selection process.

Stage 1

In stage 1, we identified the most recent high-quality systematic review pertaining to psychopharmacological acute therapy for each of the diagnoses through systematic literature searches in MEDLINE via PubMed and in the Cochrane Database of Systematic Reviews (search history as well as quality, inclusion, and exclusion criteria are provided in eAppendix 1 in Supplement 1). In this initial step, we restricted the search to 2 databases, as we intended on finding a recent high-quality systematic review rather than all systematic reviews.

Screening for and selection of reviews was carried out in duplicate and independently by 2 of the authors (T.B., L.N., J.U., and C.B.) for each diagnosis. Any discrepancies were resolved by discussion among the entire group of authors. Originally, we aimed to include 10 diagnoses; however, we could not identify a systematic review adhering to stage 1 inclusion criteria for agoraphobia.

Stage 2

In stage 2, the 10 highest-quality RCTs (lowest risk of bias [ROB]) with placebo groups were selected from each of the 9 systematic reviews,[21-29] totaling 90 RCTs reported in 86 publications.[30-115] The selection was carried out independently by 2 authors (L.N. and J.U.).

All 9 systematic reviews used the Cochrane Risk of Bias tool (first or second version)[116,117] for ROB analysis of each RCT. The tool categorizes various ROB domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting of outcomes, and other sources of bias, eg, enriched design). RCTs with the highest number of domains rated as low ROB were included, so that the 10 RCTs per diagnosis with the highest total score were included for analysis. If this process led to more than 10 RCTs we selected the most recent RCTs. Inclusion and exclusion criteria for RCTs are provided in eAppendix 2 in Supplement 1.

Data Collection

Two authors (L.N. and J.U.) independently extracted predefined core data from each study into a standardized spreadsheet (Excel version 1808; Microsoft). Discrepancies were resolved through group discussion. Extracted data included quality ratings, study details (location, duration), active study group intervention, diagnosis confirmation method, and likelihood of receiving placebo. For placebo groups, initial and final participant numbers, age, gender or sex distribution, and psychopathology ratings of changes in the selected outcome or of baseline and follow-up scores, each with corresponding measures of dispersion, were extracted. Where available, Clinical Global Impression (CGI) scores were also extracted. Intention-to-treat data were prioritized (80 studies[30-35,37-58,60-65,67-74,76-78,80,81,83-96,98,99,101,102,104-112,114,115]); if not available, data from observed patients were used.[36,59,66,75,79,82,97,100,103,113] Dropout rates will be presented in a separate publication.

Outcomes Per RCT

Of 90 included RCTs,[30-115] only placebo groups were considered. Because RCTs for the different diagnoses used various established psychopathology rating scales, standardized pre-post effect sizes[118] were used to compare outcomes across diagnoses. Formulae are provided in eAppendix 3 in Supplement 1. We opted against calculating response rates, as these are directly dependent on the response definition, which varied significantly among diagnoses.

In panic disorder, most RCTs used panic attacks per time period as the main outcome. Owing to the nonparametric distribution of rate data and consistent with earlier research,[10,18,19] we resorted to including RCTs presenting an established outcome scale, such as the Hamilton Anxiety Rating Scale.

Statistical Analysis

Pre-Post Effect Sizes per Diagnosis

The main outcome was pooled pre-post placebo effect sizes per diagnosis (Cohen *d* for within-participant designs using mean SD, d_{av}[118,119]). In random-effects meta-analyses (method-of-moments-estimator DerSimonian and Laird), pooled pre-post placebo effect sizes and 95% CIs were calculated by diagnosis. With intention-to-treat data, we followed the imputation methods chosen by trial authors (eg, last observation carried forward or mixed-effects model analysis). For calculations, we used the Magnitude of Effect Size calculator, version 2 (MOTE),[120] as well as Comprehensive Meta-Analysis version 4 (Biostat). Statistical significance of the difference across pooled effects of all diagnoses was set at 2-sided α = .05 and calculated in a *Q* test.

Small Study Effects and Heterogeneity

To find evidence of small study effects or publication bias, we used funnel plots and calculated Egger test. Heterogeneity was explored using *Q* statistics and I^2 values, showing variance in excess of random error. Following the Cochrane Handbook,[121] I^2 values between 50% and 90% were classified as substantial heterogeneity and values above 75%, considerable heterogeneity. We also calculated prediction intervals, indicating the possible spread of outcomes in studies similar to those included, whereas CIs provide an estimate of the precision of d_{av} calculated.

Table 1. Systematic Reviews Identified Through the Search Process

Diagnosis	Review
Major depression	Cipriani et al, 2018[21]
Mania	Kishi et al, 2021[22]
Schizophrenia	Huhn et al, 2019[23]
Obsessive-compulsive disorder	Skapinakis et al, 2016[24]
Attention-deficit/hyperactivity disorder	Elliott et al, 2020[25]
Generalized anxiety disorder	Kong et al, 2020[26]
Social phobia	Williams et al, 2020[27]
Agoraphobia	None
Panic disorder	Chawla et al, 2022[28]
Posttraumatic stress disorder	Williams et al, 2022[29]

Secondary Outcome

In most of the included RCTs, symptom severity was also assessed with the CGI scale. Since CGI is a validated and established transdiagnostic scale, we decided post hoc to repeat our main analysis with CGI severity scores as a validation of the primary outcome. Although a meta-analysis of CGI suggests itself for calculating a nonstandardized mean change, for ease of comparison with the main analysis, we present standardized values.

Regression Analyses

We investigated potential confounders, including age, gender or sex, study duration and size, placebo randomization probability, ROB, and year of publication, in bivariable meta-regressions (considering the weights of RCTs included), with diagnoses as second factor to account for clustering by diagnoses. In multivariable meta-regression (mixed-effects, method-of-moments estimator), we included all possible confounders with $P < .10$ in bivariable analysis and also, on theoretical grounds, diagnosis and study duration. Data were analyzed from October 10 to December 15, 2023.

Results

Stage 1

The literature search (stage 1) was conducted on March 19, 2022, and yielded the results shown in the eTable in Supplement 1. A total of 9 high-quality systematic reviews[21-29] were selected (**Table 1**).

Stage 2

An overview of the 90 RCTs[30-115] included in the meta-analysis is provided in **Table 2**. A total of 9985 placebo-treated study participants were included, distributed across the 9 diagnoses as follows: 1598 participants with MDD,[30-39] 967 participants with mania,[40-46] 888 participants with schizophrenia,[47-56] 803 participants with OCD,[57-66] 1189 participants with ADHD,[67-76] 1457 participants with GAD,[77-85] 1180 participants with social phobia,[86-95] 1248 participants with

Table 2. Randomized Clinical Trials Included in Analyses

Source	Patients in placebo group, No.	Age, mean (SD or range), y	Women, %	Probability of receiving placebo, %	Active drugs	Study duration, wk	Selected outcome (psychopathology scale)
MDD							
Alvarez et al,[30] 2012	105	42.0 (10.9)	65.7	25	Vortioxetine, venlafaxine	6	MADRS
Bakish et al,[31] 2014	185	42.3 (13.2)	62.4	33.3	Levomilnacipran	8	MADRS
Baldwin et al,[32] 2012	145	43.4 (12.5)	69.6	20	Vortioxetine, duloxetine	8	MADRS
Jain et al,[33] 2013	286	42.4 (12.7)	54.7	50	Vortioxetin	6	HAM-D-24
Kennedy et al,[34] 2006	105	42.2 (12.0)	55.2	50	Agomelatine	6	HAM-D-17
Liebowitz et al,[35] 2013	223	42 (13)	62	33.3	Desvenlafaxine	8	HAM-D-17
Mahableshwarkar et al,[36] 2015	126	46.2 (11.8)	67.5	33.3	Vortioxetine	8	MADRS
McIntyre et al,[37] 2014	194	45.6 (12.1)	65.8	33.3	Vortioxetine	8	MADRS
Oakes et al,[38] 2012	110	43.9 (11.9)	66.4	33.3	Duloxetine	8	HAM-D Maier subscale
Olie et al,[39] 2007	119	45.6 (11.2)	75	50	Agomelatine	6	HAM-D-17
Overall MDD, mean (SD)	159.8 (57.7)	43.6 (1.6)	64.4 (5.9)	36.2 (10.0)	NA	7.2 (1.0)	NA
Mania							
Berwaerts et al,[40] 2012	115	41.0 (11.2)	45	25	Paliperidone	3	YMRS total score
Kushner et al,[41] 2006; cohort A	111	42 (13)	49	25	Topiramate, lithium	3	YMRS total score
Kushner et al,[41] 2006; cohort B	98	37 (10)	60	33.3	Topiramate	3	YMRS total score
Kushner et al,[41] 2006; cohort C	106	40 (11)	37	50	Topiramate	3	YMRS total score
Kushner et al,[41] 2006; cohort D	112	41 (12)	60	33.3	Topiramate, lithium	3	YMRS total score
Landbloom et al,[42] 2016	126	44.6 (11.5)	57.1	33.3	Asenapine	3	YMRS total score
Potkin et al,[43] 2005	65	39 (11.5)	45.5	33.3	Ziprasidone	3	MRS score
Tohen et al,[44] 2008	99	40.6 (12.8)	46.5	20	Olanzapine, valproate	3	YMRS total score
Vieta et al,[45] 2010	104	38 (10)	47	20	Paliperidone quetiapine	3	YMRS total score
Yildiz et al,[46] 2008	31	36[a] (18-54)	52	50	Tamoxifen	3	YMRS total score
Overall mania, mean (SD)	96.7 (26.6)	39.9 (2.4)	49.9 (7.0)	32.3 (10.2)	NA	3.0 (0.0)	NA
Schizophrenia							
Coppola et al,[47] 2011	63	36.5 (11.6)	28.1	33.3	Paliperidone	6	PANSS total score
Egan et al,[48] 2013	78	36.4 (8.5)	36.1	40	Mk-8998, olanzapine	4	PANSS total score
Kane et al,[49] 2015	145	36.7 (11.3)	25.2	33.3	Cariprazine	6	PANSS total score
Kane et al,[50] 2016	93	38.8 (11.4)	38.9	20	Brexpiprazole, aripiprazole	6	PANSS total score
Litman et al,[51] 2014	39	40.2 (11.6)	4.9	40	Pavinetant, olanzapine	4	PANSS total score
Loebel et al,[52] 2016	112	40.7 (11.6)	30.4	25	Lurasidone	6	PANSS total score
Meltzer et al,[53] 2011	114	37 (11.3)	23	25	Lurasidone olanzapine	6	PANSS total score
Nasrallah et al,[54] 2013	124	38.2 (9.9)	27.4	25	Lurasidone	6	PANSS total score
Ogasa et al,[55] 2012	49	38.1 (9.7)	16	33.3	Lurasidone	6	BPRS score
Potkin et al,[56] 2015	71	41 (9.7)	23.6	20	Lurasidone, haloperidol	6	BPRS score
Overall schizophrenia, mean (SD)	88.8 (32.8)	38.4 (1.7)	25.4 (9.2)	29.5 (7.1)	NA	5.6 (0.8)	NA
OCD							
GlaxoSmithKline,[57] 2005a	75	36.3 (10.7)	29.9	33.3	Paroxetine, clomipramine	12	Y-BOCS total score
Goodman et al,[58] 1996	78	36.6 (19-69)	50	50	Fluvoxamine	10	Y-BOCS total score
Hollander et al,[59] 2003a	73	43.1 (12.3)	33	25	Paroxetine	12	Y-BOCS total score
Hollander et al,[60] 2003b	120	36.7 (1.1[b])	67	50	Fluvoxamine	12	Y-BOCS total score
Kamijima et al,[61] 2004	94	38.5 (12.2)	58.5	50	Paroxetine	12	Y-BOCS total score
Kobak et al,[62] 2005	30	38.38 (10.6)	43.3	50	St. John's wort	12	Y-BOCS total score
Kronig et al,[63] 1999	79	38.1 (12.0)	47	50	Sertraline	12	Y-BOCS total score

(continued)

Table 2. Randomized Clinical Trials Included in Analyses (continued)

Source	Patients in placebo group, No.	Age, mean (SD or range), y	Women, %	Probability of receiving placebo, %	Active drugs	Study duration, wk	Selected outcome (psychopathology scale)
Montgomery et al,[64] 1993	56	36.3 (11.2)	41.1	25	Fluoxetine	8	Y-BOCS total score
Montgomery et al,[65] 2001	101	38.6 (12.1)	50.1	25	Citalopram	12	Y-BOCS total score
Stein et al,[66] 2007	97	37.6 (11.8)	55.3	25	Escitalopram, paroxetine	12	Y-BOCS total score
Overall OCD, mean (SD)	80.3 (23.8)	38.0 (1.9)	47.5 (10.7)	38.3 (11.9)	NA	11.4 (1.3)	NA
ADHD							
Adler et al,[67] 2013	75	34.9 (11.0)	46.3	50	Lisdexamfetamine	10	BRIEF-A GEC
Casas et al,[68] 2013	97	35.5 (8.8)	46.4	33.3	Methylphenidate	13	CAARS-O:SV
Frick et al,[69] 2020	103	35.6 (9.8)	44.2	25	Triple-bead mixed amphetamine salts	6	ADHD-RS-IV total score
Goodman et al,[70] 2017	172	34.7 (11.6)	45.1	50	Methylphenidate	6	AISRS
Goto et al,[71] 2017	195	31.7 (7.8)	51.3	50	Atomoxetine	10	CAARS-Inv:SV total score
Huss et al,[72] 2014	161	36.8 (12.2)	44.2	25	Methylphenidate	9	*DSM-IV* ADHD RS
Medori et al,[73] 2008	95	34.5[a] (32.5-36.4[c])	38.5	25	Methylphenidate	5	CAARS:O-SV
Takahashi et al,[74] 2014	140	34.1 (9.0)	51.8	50	Methylphenidate	8	CAARS-O:SV *DSM-IV* symptom score
Weisler et al,[75] 2012	65	33.4 (10.3)	41.1	16.67	Bavisant, atomoxetine	6	ADHD-RS-IV total score
Weisler et al,[76] 2017	86	34.5 (10.8)	52.8	33.3	Triple-bead mixed amphetamine salts	4	ADHD-RS-AP total score
Overall ADHD, mean (SD)	118.9 (42.5)	34.6 (1.3)	46.2 (4.4)	35.8 (12.4)	NA	7.7 (2.6)	NA
GAD							
Bidzan et al,[77] 2012	148	45.3 (13.5)	61.6	50	Vortioxetine	8	HAM-A total score
Kasper et al,[78] 2014	135	44.6 (12.3)	73.3	25	Lavender oil extract, paroxetine	10	HAM-A total score
Mahableshwarkar et al,[79] 2014	120	36.8 (12.1)	65	20	Vortioxetine, duloxetine	8	HAM-A total score
Nicolini et al,[80] 2009	163	42.8 (NA)	57.1	28.6	Duloxetine, venlafaxine	10	HAM-A total score
Pollack et al,[81] 2008; cohort 2	226	39.9 (12)	61	50	Tiagabine	10	HAM-A total score
Pollack et al,[81] 2008; cohort 3	223	40.8 (11.5)	58	50	Tiagabine	10	HAM-A total score
Rothschild et al,[82] 2012	113	41.4 (12.8)	63.8	50	Vortioxetine	8	HAM-A total score
Stein et al,[83] 2008	58	41.7 (6.9)	68.8	50	Agomelatine	12	HAM-A total score
Stein et al,[84] 2014	131	43 (12.2)	71.8	33.3	Agomelatine escitalopram	12	HAM-A total score
Stein et al,[85] 2017	140	44.1 (13.1)	63.4	33.3	Agomelatine	12	HAM-A total score
Overall GAD, mean (SD)	145.7 (47.4)	42.0 (2.4)	64.4 (5.2)	39.0 (11.6)	NA	10.0 (1.6)	NA
Social phobia							
Allgulander et al,[86] 2004	132	38.9 (10.6)	62	33.3	Venlafaxine, paroxetine	12	LSAS total score
Asakura et al,[87] 2016	196	33 (18-63)	55.6	33.3	Escitalopram	12	LSAS-J total score
Baldwin et al,[88] 1999	151	37.3 (11.4)	54.3	50	Paroxetine	12	LSAS total score
Davidson et al,[89] 1993	33	37.3 (9.5)	42	50	Clonazepam	10	LSAS total score
Davidson et al,[90] 2004	126	37.2 (0.9[b])	31	50	Fluvoxamine	12	LSAS total score
Lepola et al,[91] 2004	184	39 (11.5)	47	50	Paroxetine	12	LSAS total score
Schneier et al,[92] 1998	37	34.1 (8.2)	32.4	50	Moclobemide	8	LSPDS overall severity
Stein et al,[93] 1998	92	36.7 (18-76)	60.2	50	Paroxetine	12	LSAS total score
Stein et al,[94] 2005	126	37.7 (11.9)	43	33.3	Venlafaxine	28	LSAS total score
Stein et al,[95] 2010	103	35.8 (11.9)	35.8	50	Levetiracetam	12	LSAS total score
Overall social phobia, mean (SD)	118 (51.5)	36.7 (1.8)	46.3 (10.8)	45.0 (7.7)	NA	13.0 (5.2)	NA
Panic disorder							
Asnis et al,[96] 2001	92	36.7 (9.8)	64.1	50	Fluvoxamine	8	CAS item 7
Ballenger et al,[97] 1988	234	37.5 (10.2)	68	50	Alprazolam	8	HAM-A total score

(continued)

Table 2. Randomized Clinical Trials Included in Analyses (continued)

Source	Patients in placebo group, No.	Age, mean (SD or range), y	Women, %	Probability of receiving placebo, %	Active drugs	Study duration, wk	Selected outcome (psychopathology scale)
Ballenger et al,[98] 1998	69	37.3 (10.4)	68.1	25	Paroxetine	10	HAM-A total score
Caillard et al,[99] 1999	51	37 (10)	58.8	33.3	Clomipramine	8	HAM-A total score
Liebowitz et al,[100] 2009	105	36.7 (12.0)	59	50	Venlafaxine	10	HAM-A total score
Michelson et al,[101] 1998	74	37.9 (11.5)	67.9	33.3	Fluoxetine	10	HAM-A total score
Noyes et al,[102] 1996	79	36.6 (10.5)	65.2	33.3	Alprazolam, diazepam	8	HAM-A total score
Pohl et al,[103] 1998	73	37.5 (11.5)	57	50	Sertraline	10	Multicenter Panic Anxiety Scale
Pollack et al,[104] 1998	87	34.9 (9.6)	61	50	Sertraline	10	HAM-A total score
Sheehan et al,[105] 2005	384	37.8 (10.6)	56.4	50	Paroxetine	10	HAM-A total score
Overall panic disorder, mean (SD)	124.8 (99.0)	37.0 (0.8)	62.6 (4.4)	42.5 (9.5)	NA	9.2 (1.0)	NA
PTSD							
Connor et al,[106] 1999	26	38 (33-41[d])	93	50	Fluoxetine	12	Duke Global Rating for PTSD
Davidson et al,[107] 2006	168	40.5 (13.0)	53	50	Venlafaxine	24	CAPS-SX17 score
Davis et al,[108] 2008	41	55.2 (6.8)	2	50	Divalproex	8	CAPS total
Davis,[109] 2017	44	36.6 (10.5)	8.7	50	Nepicastat	6	CAPS total
Davis et al,[110] 2020	34	38.1 (9.5)	7.7	50	Mirtazapine	8	SIP
Friedman et al,[111] 2007	82	37.8 (8.4)	19.3	50	Sertraline	12	CAPS-2 total score
Li et al,[112] 2017	36	44.9 (5.8)	11.1	50	Sertraline	12	IES-R
Raskind et al,[113] 2018	136	51.4 (13.8)	0.7	50	Prazosin	10	CAPS total
Rasmusson et al,[114] 2017	50	37.7 (10.9)	17	50	Ganaxolone	6	CAPS total
Villarreal et al,[115] 2016	38	54 (10)	3	50	Quetiapine	12	CAPS total
Overall PTSD, mean (SD)	65.5 (46.1)	43.4 (7.0)	21.5 (27.8)	50.0 (0.0)	NA	11.0 (4.9)	NA

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ADHD-RS-AP, ADHD Rating Scale with Adult Prompts; ADHD-RS-IV, ADHD Rating Scale, version IV; AISRS, Adult ADHD Investigator Symptom Rating Scale; BPRS, Brief Psychiatric Rating Scale; BRIEF-A GEC, Behavior Rating Inventory of Executive Function–Adult Version, Global Executive Composite; CAARS-Inv:SV, Conners' Adult ADHD Rating Scale-Investigator Rated: Screening Version; CAARS-O:SV, Conners' Adult ADHD Rating Scales–Observer: Screening Version; CAPS, Clinician-Administered PTSD Scale for *DSM-5*; CAPS-2, Part 2 of the Clinician-Administered PTSD Scale; CAPS-SX17, Clinician-Administered PTSD Scale, abbreviated 1-Week Symptom Status Version; CAS, Clinical Anxiety Scale; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HAM-D-17, Hamilton Depression Rating Scale, 17-item version; HAM-D-24, Hamilton Depression Rating Scale, 24-item version; IES-R, Impact of Event Scale–Revised; LSAS, Liebowitz Social Anxiety Scale; LSAS-J, Liebowitz Social Anxiety Scale, Japanese version; LSPDS, Liebowitz Social Phobic Disorders Scale–Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; MRS, Mania Rating Scale; NA, not applicable; OCD, obsessive-compulsive disorder; PANSS, Positive and Negative Syndrome Scale for Schizophrenia; SIP, Structured Interview for PTSD; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; YMRS, Young Mania Rating Scale.

[a] Expressed as median instead of mean.

[b] Expressed as SE.

[c] Expressed as 95% CI.

[d] Expressed as quartiles.

panic disorder,[96-105] and 655 participants with PTSD.[106-115] There was no indication of small-study effects or publication bias based on findings from a funnel plot (eFigure in Supplement 1) or from Egger test (P = .95).

There was an overrepresentation of women in depression, GAD, and panic disorder studies and an underrepresentation of women in schizophrenia and PTSD studies, whereas age, on the study level, varied only moderately. The duration of the studies also differed based on the diagnosis, with a relatively long duration of up to 12 weeks for OCD, social phobia, and GAD, and a shorter duration of 3 weeks for mania (Table 2).

Main Outcome

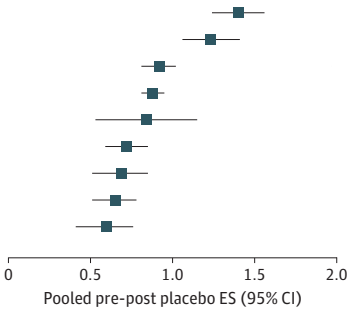
In all diagnoses, there were improvements in symptom severity during placebo treatment (ie, the lower limit of the 95% CIs of the pooled pre-post placebo effect sizes were >0). As indicated by the Q test, the pooled pre-post placebo effect sizes differed statistically significantly among the disorders (Q = 88.5; df = 8; $P \leq .001$) (**Figure 1**). The largest effect size was observed in MDD (d_{av} = 1.40; 95% CI, 1.24 to 1.56), followed by GAD (d_{av} = 1.23; 95% CI, 1.06 to 1.41). Schizophrenia had the smallest effect size (d_{av} = 0.59; 95% CI, 0.41 to 0.76) and OCD had the second weakest (d_{av} = 0.65; 95% CI, 0.51 to 0.78). There were no overlaps of the 95% CIs of GAD and depression with the 95% CIs of panic disorder, ADHD, social phobia, mania, OCD, and schizophrenia (Figure 1).

The placebo response varied substantially from study to study, as indicated by heterogeneity values (I^2>75% for GAD, mania, MDD, PTSD, and schizophrenia) (Figure 1). The prediction intervals were 0.84 to 1.96 for MDD, 0.60 to 1.87 for GAD, 0.60 to 1.23 for GAD, −0.31 to 1.99 for PTSD, 0.29 to 1.15 for social phobia, 0.06 to 1.30 for mania, 0.19 to 1.10 for OCD, and −0.02 to 1.19 for schizophrenia. For ADHD, a prediction interval was not assessed due to uniform effect sizes (I^2 = 0); thus,

Figure 1. Random-Effects Meta-Analysis Estimates of Pooled Pre-Post Placebo Effect Sizes

Diagnosis	Study participants, No.	Q	I^2, %	ES (95% CI)
MDD	1598	47.9	81	1.40 (1.24-1.56)
GAD	1457	61.4	85	1.23 (1.06-1.41)
Panic disorder	1307	20.8	57	0.92 (0.81-1.02)
ADHD	1189	7.3	0	0.88 (0.81-0.95)
PTSD	655	99.8	91	0.84 (0.53-1.15)
Social phobia	1180	34.7	74	0.72 (0.59-0.85)
Mania	967	53.1	83	0.68 (0.51-0.85)
OCD	819	29.6	70	0.65 (0.51-0.78)
Schizophrenia	888	50.0	82	0.59 (0.41-0.76)

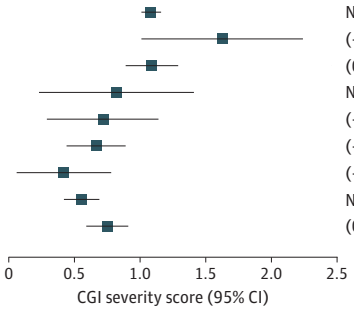
Heterogeneity: $\chi^2_8 = 88.50$ ($P < .01$)



Random-effects meta-analysis estimates of Cohen d_{av} pooled pre-post placebo effect sizes (ES) and 95% CIs of placebo groups in randomized clinical trials by diagnosis (90 studies; 10 for each diagnosis). ADHD indicates attention-deficit/hyperactivity disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; and PTSD, posttraumatic stress disorder.

Figure 2. CGI Severity Score Based Random-Effects Meta-Analysis Estimates of Pooled Pre-Post Placebo Effect Sizes

Diagnosis	Studies, No.	Q	I^2, %	CGI severity score–based effect size	(95% PI)
MDD	6	5.3	5	1.08 (1.01-1.16)	NA
GAD	6	164.9	97	1.63 (1.01-2.24)	(-0.64 to 3.89)
Panic disorder	6	21.5	77	1.09 (0.89-1.29)	(0.43 to 1.75)
ADHD	2	17.2	94	0.82 (0.23-1.41)	ND
PTSD	6	65.4	92	0.72 (0.29-1.14)	(-0.04 to 1.47)
Social phobia	6	36.1	86	0.67 (0.44-0.89)	(-0.42 to 1.75)
Mania	4	27.0	89	0.42 (0.06-0.78)	(-1.27 to 2.11)
OCD	3	1.6	0	0.55 (0.42-0.69)	NA
Schizophrenia	8	28.5	76	0.75 (0.59-0.91)	(0.21 to 1.29)



Pooled pre-post effect sizes (Cohen d_{av}), 95% CIs, and 95% prediction intervals (PIs) in random-effects meta-analysis in randomized clinical trials of 9 different psychiatric diagnoses. $Q = 71.2$; $df = 8$; $P < .001$. ADHD indicates attention-deficit/hyperactivity disorder; GAD, generalized anxiety disorder; MDD, major depressive disorder; NA, not assessed (all studies share a common effect size; thus I^2 was very low and there was no difference between CI and PI); ND, not done (number of studies too small for valid determination [ie, <3 studies]); OCD, obsessive-compulsive disorder; and PTSD, posttraumatic stress disorder.

there was no difference between CI and prediction interval results.

Clinical Global Impression

In 47 studies,[32-35,37,39,42-44,46,48-50,52-57,60,64,70,73,78,79,82-91,96,98-100,104,105,107,108,110-112,115] CGI severity score (CGI-S) results allowed a transdiagnostic comparison on the same scale. Results of standardized comparisons corroborated main analysis findings, highlighting pronounced placebo responses in GAD, panic disorder, and MDD (**Figure 2**). Diagnoses differed significantly ($Q = 71.2$; $df = 8$; $P < .001$). Again, substantial heterogeneity across studies was apparent (I^2>75%), except for MDD ($I^2 = 5\%$) and OCD ($I^2 = 0\%$). Summary outcomes based on mean differences, as opposed to standardized mean differences, of CGI-S supported standardized-based results for both the CGI-S–related and the primary analyses.

Bivariable and Multivariable Meta-Regressions

Bivariable meta-regressions indicated potential associations of pre-post effect sizes with gender or sex (slope point estimate, 0.0084; 95% CI, 0.0036 to 0.0133), study duration (slope point estimate, 0.0202; 95% CI, 0.0002 to 0.0402), and probability of placebo assignment (slope point estimate, −0.0047; 95% CI, −0.0103 to 0.0008). In multivariable analysis, apart from diagnosis, only gender or sex remained statistically significantly associated with pooled pre-post effect sizes (slope point estimate, 0.0076; 95% CI, 0.0026 to 0.0126; $P = .003$), indicating that with each percentage point of women in the study, the effect size increased by 0.0076, or by 0.19 with 25% more women ($R^2 = 51\%$; goodness of fit [residual heterogeneity]: $Q = 354.97$; $df = 78$; $P < .001$). Bivariable and multivariable analyses based on CGI-S supported this finding.

Discussion

This systematic review and meta-analysis of placebo groups of RCTs for 9 psychiatric diagnoses had 5 main findings. First, symptom improvement occurred in all conditions under placebo treatment. Second, the improvements were of considerable magnitude. Third, improvement varied significantly among disorders and was particularly strong in MDD and GAD, while schizophrenia, OCD, and mania had comparatively modest improvements. Fourth, for most diagnoses, there was substantial

or considerable variability in the improvements across RCTs. Fifth, alongside diagnoses, an increasing proportion of women was associated with larger improvements in placebo groups.

First, symptom improvement in all disorders is in line with previous studies,[10,13,19,20] but our study expands insight toward a broader range of diagnoses. A secondary CGI-S analysis supported our findings. Second, even without systematic treatment, such as psychotherapy, meaningful improvements were evident. The more pronounced the improvement in the placebo groups, the more the treatment could at least initially be justified by the omission of medication. The significant improvements under placebo treatment justify placebo controls in psychiatric research. Of note, pre-post effect sizes, whether for placebo or active treatments, are in a different order of magnitude than effect sizes resulting from the comparison of an intervention group with a control group, at least in psychiatry.

Third, previous studies have already reported a particularly large effect of placebo in MDD[4,6,11,12,14-16] and GAD,[10,19] with a comparatively smaller effect in OCD.[13,17-20] Schizophrenia,[7] mania,[17,20] ADHD, and PTSD have been comparatively less studied.

To date, depression studies have been investigated the most extensively. Some investigators submit that more than three-quarters[122] or two-thirds[6] of the positive outcomes observed under a treatment with an antidepressant may be attributed to nonspecific and placebo effects, although it should be noted that the diagnosis of depression encompasses a wide range of disorders, rather than being a specific entity.[123] This appears counterintuitive, given depression's impact on hope and confidence. However, affective disorders commonly follow an episodic course. Additionally, interpersonal support, psychoeducation, inspiring of hope, and the conveyance of medical concepts constitute fundamental components of antidepressant psychotherapy but are also often evident in placebo groups.

The large and robust improvements observed in ADHD studies have not been reported to our knowledge. Notable differences among anxiety disorders exist. GAD studies presented the largest improvements, and social phobia studies presented relatively modest improvements. Panic disorder again showed a moderate effect size, and OCD, often classified as an anxiety disorder, showed relatively small improvements in the placebo group.

We found that patients with schizophrenia had the least benefit associated with placebo treatment, possibly due to episodic relapses and an unfavorable prognosis.[124] Impaired interpersonal functioning might reduce the impact of personal attention and nonspecific effects in placebo groups. Distorted reality perception and limited insight into illness may hinder the development of hope and belief in effective treatment. However, these hypotheses cannot be proven with our approach. Furthermore, the relatively small improvement observed in mania studies is reasonable with regard to impaired illness awareness and little desire for treatment.

Uncontrolled studies often gauge treatment effectiveness using pre-post findings or historical control comparisons. In this regard, our analyses highlight the importance of understanding symptom trajectories without specific treatment, underscoring the crucial role of placebo controls, especially for diagnoses with substantial placebo effects.

Fourth, the high heterogeneity, with I^2 values greater than 75% for MDD, GAD, PTSD, mania, and schizophrenia, indicates significant variation within diagnoses across RCTs. This suggest prudence in drawing conclusions but is also unsurprising, considering internal and external influences, like study design and illness characteristics. Notably, active treatment group pre-post effect sizes also vary, such as in MDD studies.[122] Meta-analyses of single study groups typically exhibit greater between-study heterogeneity than pairwise analyses under the same conditions.[125] In multivariable meta-regression, we found no association of pre-post effect sizes with study duration or the likelihood of receiving placebo. This latter differs from previous analyses of depression studies.[126] Overall, diagnosis differences in our study were not solely explained by study design variations.

Fifth, the positive association of response and proportion of women participants cannot be explained by higher female participation in MDD and GAD studies alone and requires further investigation. Our study cannot determine whether this signifies a generally better prognosis in women, as seen in schizophrenia,[127,128] or if women particularly benefit from nonspecific factors in clinical studies.

Limitations

This study has several limitations. Our analysis cannot precisely attribute measured changes to the placebo effect in the strict sense. Assessments would require studies with a group receiving no study medication or treatment at all, a rarity in psychiatry. A 2023 review provides an overview of contextual effects in general medicine.[129] A 1998 depression study indirectly compared placebo groups with psychotherapy waiting-list groups, estimating the placebo effect's contribution to the overall improvement with an antidepressant to be approximately 50%.[122] However, the study did not account for potential nocebo effects associated with waiting-list assignment.[130]

Our study, limited to adults, encountered variations in study designs both among and within diagnostic groups, affecting multiple factors, like study duration and placebo likelihood. Reassuringly, regression analyses yielded no positive signal regarding these potential confounders. Nevertheless, the heterogeneity in most disorders suggests prudence in drawing firm conclusions at this point. We see the association of gender or sex and placebo response found in our multivariable analyses as preliminary. These analyses are hypothesis generating and must be interpreted with caution. For example, this association is prone to an ecological fallacy, and individual patient data are necessary to uncover a true association.

Furthermore, it was not possible to analyze all placebo-controlled studies conducted on the 9 disorders, but our sample is reliable, systematically including high-quality and current RCTs through a preregistered protocol. Excluding low-quality RCTs (ie, high ROB) is particularly relevant in the analysis of placebo effects, which strongly depend, for example, on the success of blinding.[131] However, ROB primarily pertains to

comparing different treatment groups within a study and can only indirectly be applied to the pre-post analysis of just 1 study group (placebo). Variability in psychopathology scales used for placebo group effects measurement might limit comparability. Comparing pre-post effect sizes is the best statistical approach for this purpose, as seen in prior analyses across diagnoses.[10,19] Using the CGI-S, we were able to confirm our results with a transdiagnostic scale. However, this was possible for only slightly more than half of the RCTs.

Conclusions

This systematic review and meta-analysis of placebo groups from high-quality RCTs covering a spectrum of 9 core psychiatric disorders found considerable improvements, with significant interdisorder differences not primarily linked to study design variations. Insights into the course of illness under placebo may aid in judging the urgency of specific treatments and help to understand the illness course in the absence of a specific intervention. A better understanding of placebo responses may improve treatments, especially in psychiatric disorders where confidence, conditioning, and belief play a significant role. Our findings could inform the interpretation of placebo-controlled trials, where the medication-placebo difference typically is the primary outcome.

For all disorders in our analysis, a multifactorial etiology encompassing psychogenic and biological determinants, intricately linked and interactive, is postulated. Over the past decades, diverse research paradigms, including genetic examinations and functional imaging, have been diligently used to assess individual factors.[132] Comparing the courses of different disorders under placebo indirectly may assist in understanding disease etiology, possibly providing insights into the proportionate influence of organic and psychogenic factors.[10] Conditions with presumed substantial hereditary and biological components, such as schizophrenia,[133] exhibited modest placebo responses in our analysis. Conversely, disorders with potentially less biological contribution, eg, depression and GAD, showed stronger responses. Our study may serve as an initial framework for incorporating the comprehensive insights derived from placebo groups of controlled trials into the etiopathogenetic exploration of mental illnesses.

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