**Placebo and Nocebo Responses in Randomized, Controlled Trials of Medications for ADHD: A Systematic Review and** **Meta-Analysis**

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**Running Title:** Placebo and Nocebo Responses in ADHD

**ABSTRACT**

**Background:** The nature and magnitude of placebo and nocebo responses to ADHD medications and the extent to which response to active medications and placebo are inter-correlated is unclear. **Aims:** To assess the magnitude of placebo and nocebo responses to ADHD and their association with active treatment response. **Methods:** We searched literature until June 26, 2019 for published/unpublished double-blind, randomised placebo-controlled trials (RCTs) of ADHD medication. Authors were contacted for additional data. We assessed placebo effects on efficacy and nocebo effects on tolerability using random-effects meta-analysis. We assessed the association of study design and patient features with placebo/nocebo response. **Results:** We analysed 128 RCTs (10,578 children/adolescents and 9,175 adults) and found significant and heterogenous placebo effects for all efficacy outcomes, with no publication bias. The placebo effect was greatest for clinician compared with other raters. We found nocebo effects on tolerability outcomes. Efficacy outcomes from most raters showed significant positive correlations between the baseline to endpoint placebo effects and the baseline to endpoint drug effects. Placebo and nocebo effects did not differ among drugs. Baseline severity and type of rating scale influenced the findings. **Conclusions:** Shared non-specific factors influence response to both placebo and active medication. Although ADHD medications are superior to placebo, and placebo treatment in clinical practice is not feasible, clinicians should attempt to incorporate factors associated with placebo effects into clinical care. Future studies should explore how such effects influence response to medication treatment. **Data set**: Upon publication data will be available in Mendeley Data. **Registration:** PROSPERO (CRD42019130292).

**Funding:** None

**INTRODUCTION**

Double-blind randomized, placebo-controlled trials (RCTs) have documented the efficacy of stimulant and non-stimulant medications for treating Attention-Deficit/Hyperactivity Disorder (ADHD) 1. The effects of stimulant medications for ADHD are among the highest in psychiatry and other areas of medicine 2. However, all RCTs of ADHD medications show improvements in some patients receiving placebo, i.e., placebo responses. They also show some adverse events in patients receiving placebo, i.e., nocebo responses. We use 'placebo/nocebo effect' and 'placebo/nocebo response' to refer to any improvements in symptoms/adverse events that cannot be attributed to an active treatment.

Little is known about whether factors that contribute to placebo response also influence the outcome of clinical care rendered to patients with ADHD. Knowing how to leverage factors that influence placebo response could be useful for improving outcomes because, for many interventions, placebo and active treatment effects can work synergistically to improve outcomes 3. Clinicians can create a psychosocial context that boosts the effect of medications 4. For some conditions, such as pain-related disorders, open-label placebo treatment has been found to be effective 5-7. Thus, determining if placebo effects improve active treatment outcomes in ADHD would provide guidance for clinicians about increasing the benefits of treatment. Additionally, learning about nocebo effects could help reduce adverse outcomes.

Although a number of previous studies have assessed predictors of placebo response to ADHD medications 8-13, they have not addressed whether placebo effects impact active treatment outcomes. Moreover, no meta-analysis is available on possible nocebo effects in RCTs of ADHD medications and predictors of placebo/nocebo effects in trials of ADHD medications remain unclear.

To fill these gaps, we used data from published and unpublished RCTs of medications for ADHD to assess: 1) to what extent placebo and nocebo effects exist; 2) whether the nature and magnitude of placebo and nocebo effects in clinical trials are correlated with the efficacy and tolerability of ADHD medications; and 3) whether demographic, clinical and trial design features could predict placebo/nocebo effects.

**METHODS**

The protocol was pre-registered with PROSPERO (CRD42019130292). Changes to the pre-specified protocol, are in Appendix 3. Data sources, searches, and study selection were based on a network meta-analysis (NMA) of RCTs by Cortese et al. 1, that we updated for the present analyses.

***Data Sources and Searches***

First, we selected RCTs meeting our inclusion criteria from Cortese et al. 1, excluding head-to-head RCTs without a placebo arm. We then updated the search by Cortese et al. 1, using the same search strategy/syntax. Additional details on the search are in Appendix 1 of the supplement.

***Study Selection***

As in Cortese et al. 1, we retained double-blind RCTs, lasting at least 1 week, including children (≥5 and <12 years), adolescents (≥12 and <18 years) or adults (≥18 years) with a primary diagnosis of ADHD according to DSM-III, DSM III-R, DSM-IV(TR), DSM-5, ICD-9 or 10. No restrictions were imposed on ADHD subtype/presentation, gender, IQ, socio-economic status, or comorbidity (except for comorbidity requiring concomitant pharmacotherapy; Appendix 2).

**Outcomes**

The primary efficacy outcomewas defined as the mean change in ADHD symptom severity for children, adolescents or adults, as measured by clinicians in placebo and active medication arms. Supplemental Tables S1-S2 list rating scales considered for inclusion. As in Cortese et al. 1, for children/adolescents, teachers’ ratings were considered as co-primary efficacy outcomes. In secondary analyses, we also considered Clinical Global Impression ratings and ratings from parents and self-ratings. Our primary tolerability outcome was dropouts due to adverse events. We also assessed dropouts due to any reason, and changes in weight, heart rate or blood pressure.

***Data Extraction and Quality Assessment***

Data were extracted by at least two independent investigators. The initial data extraction began on 21 March 2019. We updated with an additional extraction on 26 June 2019. Risk of bias of individual RCTs was assessed using the Cochrane risk of bias tool (<http://methods.cochrane.org/bias/assessing-risk-bias-included-studies>; Appendix 2).

***Data Synthesis and Analysis***

We used the random effects model to analyse standardized mean differences (Cohen's dz) and the I² index to assess heterogeneity 14. Egger’s 15 method assessed for publication biases and the “trim and fill” method of Duval and Tweedie 16 adjusted for such biases. To assess whether there was a correlation between placebo and active medication response, we computed Pearson correlations between the baseline to endpoint responses in the placebo and active medication groups. Meta-analysis regression a) assessed the association of study design features with the placebo response and b) determined if significant variables from (a) predicted the drug vs. placebo response. Because some countries had only one or two studies, we stratified countries into the following regions: Australasia, Europe, North America and Other.

Two sensitivity analyses were performed: 1) excluding cross-over studies; and 2) excluding trials rated at overall high risk of bias using the Cochrane risk of bias tool. We used STATA’s suite of meta-analysis programs (STATA, version 16). Our PROSPERO protocol (CRD42019130292) specified three primary outcomes: clinician and teacher ratings of efficacy and dropouts due to adverse events for tolerability. These were used in nine analyses of our primary hypotheses and were tested with a Bonferroni corrected p-value of 0.0056. We also examined seven secondary outcomes involved in 21 tests evaluated with a Bonferroni corrected p-value of 0.0018. We did not adjust tests of significance for heterogeneity and publication bias so as not to reduce the sensitivity of those analyses to detect problems with the data. In exploratory analyses, we assessed the ability of study features to predict placebo response. Because these analyses required many statistical tests, they must be considered hypothesis generating. For them, we used a p-value of 0.01, to improve sensitivity for hypotheses to be followed-up in future work.

**Data sharing**

In the spirit of Open science, the full dataset will be available online (Mendeley Data) following publication of this paper.

**Role of the funding sources**

This was not a funded study. SVF and SC had full access to the data; SVF was responsible for the decision to submit for publication.

**RESULTS**

We retained 123 RCTs from Cortese et al. 1, excluding 10 head-to-head RCTs without placebo (Appendix 4) and including five RCTs published after the search date of the NMA by Cortese et al. 1 (Appendix 5) for a total of 128 RCTs (75 in children/adolescents and 53 in adults). For the study selection process, see the PRISMA diagram Figure S1a, and supporting material in Appendices 6-7. The PRISMA checklist is in Figure S1b. Studies retained included 10,578 children/adolescents and 9,175 adults. For 58% of studies, we used additional data/information not reported in the full-text paper. Tables S3-S8 report the main characteristics of included studies. 27%, 64%, and 9% of studies examining children/adolescents and 32%, 53% and 15% examining adults were rated at overall *low*, *unclear*, and *high* risk of bias, respectively (Table S9). The differences in risk of bias between the age groups was not significant (X2(2) = 1.8, p = 0.4).

Table 1 summarizes the results of the meta-analysis of the baseline to endpoint placebo effects for efficacy and nocebo effects for tolerability. For symptom severity rated by clinicians, the placebo SMD was -0.75 and was statistically significant (Table 1). The SMDs for each study are shown in Figure S2. We found significant placebo effects for all the other raters (Table 1). Figure 1 shows the distribution of the percent of patients in the drug and placebo groups who were improved or very much improved at endpoint on the Clinical Global Impressions (CGI) scale. The mean improvement rate of 25% for the placebo groups indicates that, for many individuals, placebo response can be substantial. The mean CGI improvement rates were 60% for stimulants and 47% for non-stimulants.

The placebo effects for each type of scale were highly heterogenous with no evidence of publication bias. Conclusions about statistical significance did not change after conducting the two sensitivity analyses, which excluded crossover studies and studies at high risk of bias. The placebo SMDs for clinician symptom ratings were significantly greater than the placebo SMDs for parent ratings (N=28; t =-5.12, p<0.001). Other differences among placebo SMDs were not significant (all p's > 0.2), possibly due to the small number of studies providing relevant information.

For our primary tolerability outcome, the pooled percent dropout due to adverse events for placebo was 2.4% and was statistically significant (Table 1). These data were highly heterogenous. The SMDs for each study are in Figure S3. Other tolerability outcomes are reported in Table 1, which shows significant nocebo effects for percent dropouts due to any reason and weight loss, but not for heart rate and blood pressure. All effect sizes were significantly heterogenous. Egger's test of publication bias was significant for percent dropouts due to any reason. After adjusting for this publication bias, the effect size for dropouts increased from 23% to 24%.

Apart from self-ratings of ADHD symptom severity, each of the clinical scales showed a statistically significant positive correlation between the baseline to endpoint placebo effect and the baseline to endpoint active medication effect. For efficacy, these correlations were 0.69 for clinician symptom ratings (p < 0.0001), 0.44 for parent ratings (p = 0.005), 0.85 for teacher ratings (p < 0.0001) and 0.37 for self-ratings (p = 0.24). The corresponding data are plotted in Figure 2. For the tolerability analyses, the correlations were 0.54 for dropouts due to adverse events (p < 0.001), 0.79 for dropouts for any reason (p < 0.001), 0.37 for systolic blood pressure (p = 0.007), 0.35 for diastolic blood pressure (p = 0.002), 0.21 for weight (p = 0.21), and 0.32 for heart rate (p = 0.004).

The correlations between the baseline to endpoint placebo effect and the active medication vs. placebo effect were -0.10 for clinician symptom ratings (p = 0.28), -0.23 for parent ratings (p = 0.71), 0.73 for teacher ratings (p = 0.0001) and -0.56 for self-ratings (p = 0.0006). The correlation for teacher ratings became non-significant (r = 0.36, p = 0.12) after removing an outlier 17. For the nocebo effects, we found statistically significant positive correlations between the baseline to endpoint nocebo effect and the active medication vs. placebo effect for systolic blood pressure (r = -0.33, p = 0.004) and dropouts due to adverse events (r = 0.36, p = 0.002) but not for diastolic blood pressure (r = -0.28, p = 0.05), weight (r = -0.08, p = 0.50), heart rate (r = -0.07, p = 0.89) dropouts for any reason (r = 0.20, p = 0.03).

Table 2 lists variables which significantly predicted baseline to endpoint placebo SMDs in exploratory analyses. All variables listed are significant in univariate analyses. Variables highlighted in brown, blue and purple remained significant in multiple regression analyses. The following predictors were not significant: the ratio of the number of participants assigned to drug vs. placebo, the length of the trial in weeks, the percent of patients with a current comorbid psychiatric disorder, and sequence generation risk of bias. Although one might have expected higher placebo responses among treatment naïve patients in stimulant trial, their placebo response to our primary efficacy outcome was non-significantly weaker than the placebo response of non-naïve patients (-0.46 vs. -0.71, p = 0.08).

In exploratory analyse, we tested if the significant predictors of the baseline to endpoint placebo group SMDs (Table 2) predicted the drug vs. placebo SMDs. This was true only for selective reporting bias as a predictor of differential weight gain between the drug and placebo groups (F(2,15) = 11.2, p = 0.001). All other highlighted effects in Table 2 were not significant (all p's > 0.20). Consistent with these results, the baseline to endpoint placebo/nocebo effects did not significantly predict the drug vs. placebo effects (all p's > 0.01).

Some studies assigned patients to placebo prior to the trial to exclude placebo responders. Use of this "placebo run-in" methodology was only a significant univariate predictor of the placebo and drug responses for clinician symptom ratings but was not significant in multivariate analyses. In exploratory analyses, the interaction between age group and use of run-in methodology was significant (t64 = 3.16, p = 0.002); placebo run-in had a significant effect on the placebo response for youth (t41 = 4.07, p < 0.0001) but not adults (t22 = 1.37, p = 0.19). The run-in also reduced the baseline to endpoint drug response (t64 = 2.91, p = 0.005) and had no significant effect on the drug vs. placebo effect (t64 = 1.67, p = 0.12; Figure S4).

**DISCUSSION**

We identified 128 RCTs of medications for ADHD with information about the placebo response. All measures of ADHD symptoms showed significant improvements for patients on placebo. For each type of rater assessing ADHD symptoms, the magnitude of the placebo response varied considerably across studies and showed no evidence of publication bias. We also found significant nocebo effects for dropouts due to adverse events, dropouts for any reason and weight loss.

The placebo response was modestly predictable from study design and patient characteristics. The highest placebo response was seen for clinician symptom ratings and this significantly exceeded the placebo response for parent ratings. The greater placebo response for clinician ratings may be due to a synergy between placebo effects that act on the parent and those that act on the clinician when interviewing the parent. This finding is especially important given that clinician ratings of ADHD symptoms are frequently used for the primary outcome in clinical trials of medications for ADHD. Teacher ratings showed the lowest placebo response but the small number of studies using teachers makes this difficult to interpret. Consistent with our findings, Ben-Sheetrit et al. 10 found that placebo response rates were higher for clinician-rated compared with self-rated measures of ADHD symptoms. Taken together, these findings suggest that trials using clinician ratings as the primary outcome will be at higher risk for elevated placebo responses. This is noteworthy, because the US Food and Drug Administration (FDA) requires clinician ratings be used as primary outcomes in ADHD registration trials.

Age and sex did not predict the placebo response, although younger age was a significant predictor in a prior study 8. Variables that predicted placebo response were not consistent across outcomes. The most consistent finding was for baseline severity, which increased placebo response for parent ratings, teacher ratings and weight gain. Baseline severity had previously been reported as a predictor of the placebo response in several prior studies 8, 9, 18, though not others 12. This finding may reflect regression toward the mean. The type of medication tested did not influence the placebo response

For each efficacy scale, except self-ratings, symptom reduction on placebo group was positively correlated with symptom reduction on active medication. This extends results from Cohen et al. 18 who reported significant correlations between the response to placebo and the response to methylphenidate. Our results suggest that the baseline to endpoint drug effect in a clinical trial combines the improvement seen with placebo and the improvement specifically attributable to the drug. Thus, decreases in symptoms due to expectation of benefit and other factors related to the psychosocial context of treatment are not limited to study participants receiving placebo. Extrapolating to clinical practice, any intervention that increases placebo response in ADHD could enhance the efficacy of medications. More work is needed to determine if such increased efficacy would last longer than the several weeks typical of the clinical trials we reviewed. Importantly, because we found nocebo effects for weight gain and dropouts due to adverse effects. Although clinicians should discuss the potential for adverse events, they should discuss potential adverse effects in a manner that minimizes nocebo effects when informing patients and parents about risks and benefits of treatment 19.

Given concerns related to possible unblinding in trials of ADHD medications due to recognizable adverse events, some authors 20 have proposed the use of nocebo (i.e., an intervention that leads to adverse events but not efficacy). However, concerns have been expressed around the ethical aspects related to the use of a substance which causes exclusively adverse effects, especially for children. Alternatively, the use of independent raters of adverse events and of clinical improvement has been advocated to overcome the issue of unblinding due to adverse events 21.

Clinicians treating ADHD patients can leverage the placebo effect by following guidelines of an international consensus group of twenty-nine researchers who had studied placebo effects in somatic and psychiatric conditions 3, 22. They recommended that clinicians incorporate factors known to produce placebo effects into standard treatments, i.e., by creating a trusting, warm and empathic patient-clinician relationship, optimizing the patient's expectation of benefit and using open-label placebo prescriptions (though the latter has not yet been validated for ADHD). They concluded that the impact of these procedures would be greatest when outcome is evaluated by patient reports and placebo responses are substantial, which is the case for ADHD. Other factors that can increase placebo response include attention to the patient's condition, providing multisensory cues to promote conditioning, describing placebo effect as a way to promote healing, confidence in the treatment, use of technological devices to enhance improvement and treatment provider's reassurance and enthusiasm regarding expected outcomes 4, 19, 23, 24. Our finding that medication and placebo effects are highly correlated suggests that a variety of contextual and psychological factors not related to medication may augment response to medication. Precisely defining these factors and delineating the magnitude of their impact on clinical practice should be a topic of future research.

Would the administration of open-label placebos be effective for ADHD as has been the case for other conditions 6, 7, 25? This idea gains support from a small crossover study of 26 children with ADHD ages 7 to 15 years old 26. The authors compared a 50% dose reduction with a 50% reduction plus placebo that appeared not to reduce the dose, which was disclosed to parents and children prior to the study. Use of placebo was acceptable to parents and a trend suggested that use of placebo during dose reduction allowed patients to maintain the same degree of symptom reduction at the reduced dose as they had attained on the full dose. Much larger studies are needed before open-label placebos can be recommended for ADHD. For now, data support the recommendation that, when treating ADHD, clinicians introduce factors that enhance placebo effects into care.

Our findings suggest that attempts to reduce the placebo effect to increase the drug vs. placebo signal may not be useful because the magnitude of baseline to endpoint placebo effects did not significantly predict drug vs. placebo effects for all efficacy outcomes except self-ratings. Khan et al. 13 found, as we did, that the placebo response to ADHD medications has risen significantly over the past decades, whereas estimates of drug vs. placebo efficacy have not. Given these findings, clinical trialists should weigh the costs of using design features that putatively reduce the placebo effect against the costs of simply increasing sample size, which is guaranteed to improve power. For example, the placebo run-in design only influenced the placebo response for clinician ratings and lost significance in multivariate analyses. Although exploratory analyses show that the run-in reduced placebo response in studies of youth, it also reduced the drug response. So, its impact on the drug vs. placebo efficacy signal was small and not significant.

We must consider some limitations. Like all meta-analyses, we inherit the problems of the constituent studies and the data available in their publications. We addressed this issue by systematically searching/asking for unpublished data but, inevitably, were not able to access some datasets. Thus, not all studies have information about all the issues we studied. Further, the constituent studies were not designed with the goal of studying placebo/nocebo responses. We analysed aggregate data from included studies, which limits the ability to identify predictors. A more thorough analysis would require data at the participant level 27. For some of our analyses, samples were relatively small; in such cases lack of significant differences should be interpreted cautiously. Readers should also not generalize these findings to disorders other than ADHD or to other measures of efficacy such as cognitive and emotional outcomes. These results may not generalize to longer term outcomes than are typically used in randomized controlled trials.

Despite these limitations, our analyses provide insight and guidance for both researchers and clinicians, by illustrating that the psychosocial milieu that leads to the placebo response also increases response to medications for ADHD. Clinicians should consider the full range of factors that contribute to treatment response and embrace practices that are likely to increase contextual and psychosocial factors that augment response to treatments for ADHD.

**Statement about author contributions**

SVF, JHN, AC and SC designed the study protocol. SVF ran the analyses and wrote the first draft. All authors provided critical comments on multiple drafts of the manuscript. SC designed the search strategy and data extraction protocol and addressed data management issues. SH, AK and AH completed the literature search and extracted data under the supervision of SC.

**DISCLOSURES**

In the past year, Dr. Faraone received income, potential income, travel expenses continuing education support and/or research support from Takeda, OnDosis, Tris, Otsuka, Arbor, Ironshore, Rhodes, Akili Interactive Labs, Enzymotec, Sunovion, Supernus and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child’s Mental Health, Oxford University Press: Schizophrenia: The Facts and Elsevier: ADHD: Non-Pharmacologic Interventions. He is Program Director of [www.adhdinadults.com](http://www.adhdinadults.com). In the past year, Dr. Newcorn is/has been an advisor and/or consultant for Adlon Therapeutics, Arbor, Eisai, NLS, OnDosis, Rhodes, Shire/Takeda, and Supernus. He was a DSMB member for Pfizer and Sunovion, and received research funds from Otsuka, Shire and Supernus. He also has received speaker fees from Shire/Takeda for disease-state presentations and served as a consultant for the US National Football League. Dr Cipriani has received research and consultancy fees from INCiPiT (Italian Network for Paediatric Trials), CARIPLO Foundation and Angelini Pharma. Dr. Brandeis serves as an unpaid scientific consultant for an EU-funded neurofeedback trial. Anna Kaiser reports has no financial disclosures. Sarah Hohmann has no financial disclosures. Dr. Häge received conference support, speaker´s fee and/or served in an advisory role for Shire/Takeda and Lily. He was involved as investigator in clinical trials by Shire, Janssen-Cilag, Otsuka, Sunovion, Servier, Lundbeck, Takeda, Nuvelution, Gedeon Richter, and Emalex. The present work is unrelated to the above relationships. Dr. Cortese declares reimbursement for travel and accommodation expenses from the Association for Child and Adolescent Central Health (ACAMH) in relation to lectures delivered for ACAMH, Canadian ADHD Resource Alliance (CADDRA), British Association of Psychopharmacology (BAP), and from Healthcare Convention for educational activity on ADHD.

**ACKNOWLEDGEMENTS**

We thank the European ADHD Guidelines group (EAGG) for creating the publicly available data used in this manuscript. Dr. Faraone is supported by the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602805, the European Union’s Horizon 2020 research and innovation programme under grant agreements No 667302 & 728018 and NIMH grants 5R01MH101519 and U01 MH109536-01. Dr Cipriani is supported by the National Institute for Health Research (NIHR) Oxford Cognitive Health Clinical Research Facility, by an NIHR Research Professorship (grant RP-2017-08-ST2-006), by the NIHR Oxford and Thames Valley Applied Research Collaboration and by the NIHR Oxford Health Biomedical Research Centre (grant BRC-1215-20005). The views expressed are those of the authors and not necessarily those of the UK National Health Service, the NIHR, or the UK Department of Health.

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| **Table 1: Results of Baseline to Endpoint Placebo Effects Meta-Analyses** |
|  |  | **Pooled Effect Sizes** | **Test of Heterogeneity** | **Egger Test of Publication Bias** |
| **Measure** | **N of Studies** | **Effect****Size\*** | **z-score** | **p-value** | **I2** | **Q** | **p-value** | **Beta1** | **z-score** | **p-value** |
| Clinician Symptom Rating | 78 | -.75 | -20 | < .0004 | 100 | 16507 | < .0001 | .6 | 2.1 | .8 |
| Parent Rating | 27 | -.43 | -11 | < .0004 | 97 | 1399 | < .0001 | -3.0 | -1.9 | .06 |
| Teacher Rating | 16 | -.36 | -4.6 | < .0004 | 99 | 897 | < .0001 | -4.2 | -1.5 | .15 |
| Self-Rating | 22 | -.66 | -14 | < .0004 | 99 | 1389 | < .0001 | 1.3 | 1.2 | .28 |
| Percent Dropouts due to AEs | 173 | 2.4\* | 7.3 | < .0005 | 0 | 8.7 | 1.0 | -0.2 | -0.7 | 0.5 |
| Percent Dropouts due to Any Reason | 173 | 22.6\* | 913.0 | < .0005 | 48.9 | 336 | < .0001 | -1.4 | -3.7 | .0002 |
| Heart Rate  | 38 | .01 | .4 | .7 | 99 | 4216 | < .0001 | -5.2 | -34 | .0006 |
| Weight  | 62 | .49 | 10.6 | < .0005 | 100 | 19113 | < .0001 | 1.7 | 0.6 | .5 |
| Diastolic Blood Pressure  | 65 | .01 | .3 | .7 | 98 | 2832 | < .0001 | -1.7 | -1.6 | .1 |
| Systolic Blood Pressure  | 65 | .01 | .7 | .5 | 98 | 2296 | < .0001 | -.5 | -.6 | .6 |
| The effect sizes are expressed as standardized mean differences (SMDs) or (for dropouts) percentages. They indicate the magnitude of change. Data are reported so that tolerability increases as the effect size decreases. If significant, the test of homogeneity suggests that the studies being pooled are not measuring the same underlying effect size. The test for publication bias, if significant, suggests that the decision to publish is influenced by the effect size. |

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|  | **Table 2: Predictors of Baseline to Endpoint Placebo SMDs that are Significant in Table 1** |
| **Measure** |  |
| Clinician Rating  | **Year of Publication**, Use of Placebo Run-in, Age (youth vs. adults), Comparison Drug, Industry Sponsorship, Author Conflict of Interest, **Selective Reporting Risk of Bias** |
| Parent Rating | Length of Trial in Weeks, Industry Sponsorship, Author Conflict of Interest, Use of Treatment Naïve Patients, **Baseline Severity** |
| Teacher Rating | N in Drug Group, Type of Rating Scale, Number of Visits Before First Dose, **Incomplete Data Outcome Risk of Bias,** Global Risk of Bias, Baseline Severity, **Region** |
| Self-Rating | N of Arms, Type of Rating Scale, Length of Trial in Weeks, % with Current Depression, Region |
| Weight  | N in Placebo Group, Mean Age (youth vs adults), % Males in Study, **% with Current Depression**, % with Current Anxiety, Comparison Drug, Industry Sponsorship, Use of Treatment Naïve Patients, Allocation Concealment Risk of Bias, Blinding Participant Risk of Bias, Blinding Therapist Risk of Bias, **Blinding Assessor Risk of Bias,** Selective Reporting Risk of Bias, **Baseline Severity, Region** |
| NOTE: ROB = All variables listed were significant at p < 0.01 in univariate regression analyses. Variables in **brown, blue** and **purple** remained significant (p<0.01) in the multiple regression analysis. **Brown** indicates that the predictor decreases the placebo effect; **purple** indicates that the predictor increases the placebo effect. **Blue** indicates a categorical variable. |