

Placebo effect in Generalized Anxiety Disorder (GAD) trials: a meta-regression analysis

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ABSTRACT

INTRODUCTION: Several meta-analyses have studied the moderators of placebo response in psychiatry clinical trials for Schizophrenia, Depression, Attention Deficit Hyperactivity Disorder and Obsessive Compulsive Disorder amongst others. These analyses have identified that number of sites, publication date, sample size and baseline severity are moderators of placebo response. To our knowledge, no meta-regression analysis has been conducted for Generalized Anxiety Disorder (GAD).

AIM: The objective of the present study is to characterize the moderators of placebo response in GAD trials.

METHODS: We conducted a systematic literature search in PubMed to identify randomized, placebo-controlled trials of pharmacological treatments for GAD. The search strategy combined terms related to GAD, randomized controlled trials, placebo, and the Hamilton Anxiety Rating Scale (HAM-A). The search was limited to studies published from 1994 onwards given that the diagnostic criteria changed substantially in 1994 with the publication of the DSM-IV. We added studies of drugs approved by the FDA as well. A mixed-effects meta-regression model was conducted using a restricted maximum likelihood (REML) estimator to examine the association between study-level covariates and the observed effect sizes. The model included the following moderators: sample size, number of study arms, baseline scores, treatment duration, number of sites, and publication year. Residual heterogeneity was quantified using I^2 statistics. The significance of moderators was assessed using Wald-type tests, and an omnibus test of moderators (QM) was used to evaluate the joint contribution of covariates. The analysis was performed using R and the package metafor.

CONCLUSIONS: There were no significant moderators of placebo response in GAD trials. Moderators identified in other psychiatric disorder trials were not significant and most of the variance remains unexplained, suggesting that other factors specific to GAD trials moderate the placebo effect in drug trials for this disorder.

Figure 1. Identification of GAD clinical trials.

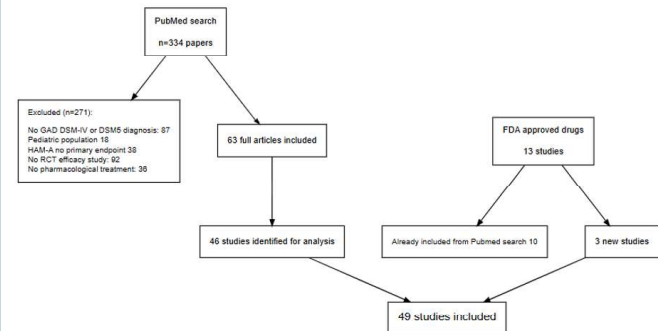


Table 1. Statistical results of the meta-regression multivariate analysis.

Taken together, the five moderators significantly explain variation in the observed effect sizes (p -val = 0.0097). I^2 residual = 82.47% means that a large portion of the variance is unexplained by the model.

Moderator	estimate	SE	Z value	P value	CI low	CI upper	Significance
Intercept	-7.1705	1.1948	-6.0015	<.0001	-9.5122	-4.8288	***
Placebo-arm sample size (n)	-0.0066	0.0056	-1.1759	0.2396	-0.0177	0.0044	
Number of treatment arms	-0.3774	0.2966	-1.2722	0.2033	-0.9588	0.2040	
Baseline severity	-0.2396	0.1455	-1.6464	0.0997	-0.5248	0.0456	
Number of study sites	-0.0196	0.0137	-1.4389	0.1502	-0.0464	0.0071	
Treatment duration	-0.0989	0.1426	-0.6936	0.4879	-0.3783	0.1805	

Table 2. Statistical results of the meta-regression univariate analysis

Moderator	Comparison	k	Estimate (95% CI)	t (df)	p	Omnibus p
Treatment duration	—	48	-0.226 (-0.490, 0.039)	-1.72 (46)	.092	—
Publication year	—	48	-0.013 (-0.120, 0.094)	-0.24 (46)	.814	—
HAM-A entry criterion score	—	47	0.062 (-0.048, 0.172)	1.13 (45)	.264	—
SD of placebo-arm baseline score	—	46	-0.533 (-1.125, 0.058)	-1.82 (44)	.076	—
Visits per week	—	48	1.611 (-1.353, 4.575)	1.09 (46)	.280	—
Number of countries	—	46	-0.084 (-0.312, 0.145)	-0.74 (44)	.464	—
Trial phase	Phase 3 vs. Phase 2	43	-0.381 (-1.936, 1.174)	-0.50 (40)	.624	.648
	Phase 4 vs. Phase 2	—	-2.019 (-6.584, 2.546)	-0.89 (40)	.377	
Diagnostic criteria	DSM-IV vs. DSM-5	48	-0.005 (-2.824, 2.814)	0.00 (45)	.997	.702
	DSM-IV-TR vs. DSM-5	—	-0.696 (-3.807, 2.415)	-0.45 (45)	.654	
Trial result	Positive vs. negative	48	0.394 (-1.077, 1.866)	0.54 (46)	.592	—
Placebo lead-in period	Present vs. absent	40	1.148 (-0.126, 2.423)	1.82 (38)	.076	—
	fixed/flexible vs. fixed	—	0.565 (-3.776, 4.906)	0.26 (44)	.794	
	Flexible vs. fixed	48	0.632 (-0.654, 1.917)	0.99 (44)	.328	
Dosing schedule	Flexible/fixed vs. fixed	—	-1.425 (-5.795, 2.945)	-0.66 (44)	.515	.648
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Figure 2. Studies with full data for the multivariate meta-regression and mean placebo effect.

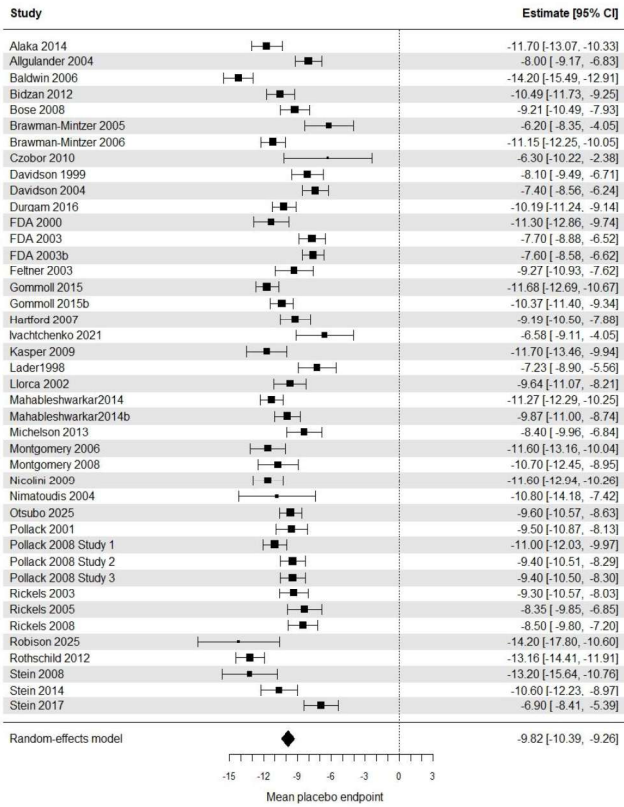


Figure 3. Examples of univariate meta-regressions.

