Which Factors Predict Placebo Response in Anxiety Disorders and Major Depression? An Analysis of Placebo-Controlled Studies of Escitalopram

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Background: The placebo response rate has increased in several psychiatric disorders and is a major issue in the design and interpretation of clinical trials. The current investigation attempted to identify potential predictors of placebo response through examination of the placebo-controlled clinical trial database for escitalopram in 3 anxiety disorders and in major depressive disorder (MDD).

Method: Raw data from placebo-controlled studies (conducted from 2002 through the end of 2004) of escitalopram in patients meeting DSM-IV criteria for MDD and anxiety disorders (generalized anxiety disorder [GAD], social anxiety disorder [SAD], panic disorder) were used. Potential predictors examined were type of disorder, location of study, dosing regimen, number of treatment arms, gender of patients, and duration and severity of disorder.

Results: Placebo response (defined as the percent decrease from baseline in the reference scale) was higher in GAD and MDD studies conducted in Europe ($p < .0001$ and $p = .0006$, respectively) and was not associated with gender or duration of episode. In GAD, the placebo response rate was higher in a European fixed-dose study, which also had more treatment arms. In SAD and in U.S. specialist–treated MDD, a higher placebo response rate was predicted by decreased baseline disorder severity.

Conclusion: Additional work is needed before definitive recommendations can be made about whether standard exclusion criteria in clinical trials of antidepressants, such as mild severity of illness, maximize medication-to-placebo differences. This analysis in a range of anxiety disorders and MDD suggests that there may be instances in which the predictors of placebo response rate themselves vary across different conditions.

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The purpose of a randomized, double-blind, placebo-controlled trial is to compare the efficacy of a specific treatment or treatments with that of placebo for a certain condition. As the term is commonly used, *placebo response* represents an apparent improvement in the clinical condition of patients randomly assigned to the placebo arm of treatment. When medication and placebo result in similarly high response rates, it is difficult to conclude that the medication is truly inefficacious. Indeed, addressing the placebo response issue may be one of the most important challenges facing the future of psychotropic drug development.[1]

Despite the fact that placebo-controlled trials are a regulatory requirement in current investigations of pharmacologic agents, relatively little attention has been paid to the phenomenology or psychobiology of the placebo response. It has been noted that placebo response rates may be increasing faster than medication response rates in trials of certain anxiety disorders[2] and major depressive

disorder (MDD),[3,4] but the predictors of placebo response in these conditions remain unclear.[5–11] There is some preliminary literature on the neurochemistry[12,13] and neuroimaging[14,15] of the placebo response, but relatively little of this work has been undertaken on anxiety disorders and MDD.[16]

Escitalopram is a serotonin dual-action antidepressant that binds to both the primary site on the serotonin transporter and the allosteric site, which has been shown to greatly augment the efficiency of serotonin reuptake. Escitalopram has proven efficacious and well tolerated in randomized controlled trials in generalized anxiety disorder (GAD),[17–19] panic disorder (PD),[20] social anxiety disorder (SAD),[21,22] and MDD.[23–27] Although the symptom severity scale used as the primary efficacy measure differed according to the specific condition being researched in these investigations, study designs have been fairly consistent across the different disorders. This large database therefore provides an opportunity to investigate predictors of placebo response and to compare data across these 3 anxiety disorders and MDD.

The literature suggests that a range of factors may contribute to the placebo response, including physician's personality traits (e.g., empathy, compassion), patient's personal features (e.g., suggestibility, gender), the design of the study (e.g., setting of trial, dosing regimen, number of treatment arms, frequency of visits), and illness variables (e.g., type of disorder, symptom severity, duration of illness).[28–35] In this set of short-term randomized controlled trials of escitalopram for 3 anxiety disorders (SAD, GAD, PD) and MDD, a number of these variables were explored, including type of disorder (diagnosis), location of trial (region), dosing regimen (flexible, fixed), number of treatment arms, patient gender, and severity and duration of each disorder.

METHOD

Table 1 lists the placebo-controlled studies of escitalopram included in the current analyses—there were 5 studies in MDD, 4 GAD studies, 2 SAD studies, and 1 study in PD. The studies, all of which used DSM-IV criteria, were conducted from 2002 through 2004. All analyses were based on a modified intent-to-treat (ITT) population (i.e., patients with at least 1 dose of study drug and 1 postbaseline efficacy assessment). All analyses were performed using the last-observation-carried-forward (LOCF) method. Only studies for which the raw data were available were included in this analysis.

Response to treatment was defined as the percent decrease from baseline in the reference scale. This definition differs from a categorical analysis of the response rate, which is based on the percentage of patients that show at least a 50% improvement from baseline to last assessment. The reference scales were Montgomery-Asberg Depression Rating Scale (MADRS) for MDD, the Hamilton Rating Scale for Anxiety (HAM-A) for GAD, the Liebowitz Social Anxiety Scale (LSAS) for SAD, and the Panic and Agoraphobia Scale (P&A) for PD.

Analysis of covariance (ANCOVA) was undertaken, with the model including a predictor (type of disorder, location of trial, dosing regimen, gender, duration of disorder, and severity of disorder) and study as factors, and an interaction of the specific predictor with study. Although each disorder is primarily assessed with a different symptom severity scale, the secondary use of the Clinical Global Impressions–Severity of Illness scale (CGI–S) allowed a uniform measure of disorder severity across the different studies. For some predictors (type of disorder, location of trial, and dosing regimen), only GAD and MDD studies were included. Interactions were tested at the $p < .1$ level.

RESULTS

Table 1 shows the rate of the placebo response (mean percent decrease from baseline) on the primary outcome measure for each study (MADRS in MDD, HAM-A in GAD, LSAS in SAD, and the P&A in PD). Of the various predictors examined, type of disorder did not have any effect on the placebo response, with a placebo response rate of approximately 37% to 38% in both GAD and MDD. There were too few of these trials in SAD and PD to be included in this specific comparison, although placebo response rates in these 2 disorders were somewhat lower than in GAD and MDD.

There was also an effect of where the trials were carried out, since GAD and MDD trials performed in Europe had a significantly larger placebo response rate, compared with those trials performed in the U.S. in these same indications (Table 2). In GAD, the study in Europe was undertaken in both general practitioner and specialist settings, had a fixed-dose design, and had more treatment arms. It was not possible to ascertain which of these factors was the determining one.

There was no significant effect of gender on placebo response, which was a mean of 31.3% for men and 35.4% for women, across all indications (Table 3).

When baseline severity was determined using the CGI–S, decreased baseline severity of SAD predicted a higher placebo response (Table 4). In PD, the impact of baseline severity on placebo response rates was restricted to a minority of patients, who had minor symptoms and high placebo response rates. In MDD, the relationship of baseline severity of symptoms to placebo response was dependent on setting; in the general practitioner setting and Europe, increased baseline severity predicted a higher placebo response, but in the specialist setting and U.S., lower baseline severity predicted a higher placebo response, and since these factors are inseparable, it is not possible to say which of these factors is at the basis of this effect—where

Table 1. Description of Placebo-Controlled Studies of Escitalopram Analyzed for Placebo-Response Predictors[a]

Study	Diagnosis	Treatment Duration, wk	Baseline Score, Mean	Treatment and Dosage, mg	No. of Patients	Dosing	Setting	Placebo Response, %
Stahl et al[20]	PD	10	24.9[b]	Placebo	114	Flexible	US, specialist	12.1
				Escitalopram 5–20	125			
				Citalopram 10–40	112			
Kasper et al[22]	SAD	12	95.4[c]	Placebo	176	Flexible	Europe, GP	28.0
				Escitalopram 10–20	177			
Lader et al[21]	SAD	24	94.2[c]	Placebo	165	Fixed	Europe, GP	39.0
				Escitalopram 5	166			
				Escitalopram 10	164			
				Escitalopram 20	163			
				Paroxetine 20	167			
Goodman et al[19]	GAD	8	22.4[d]	Placebo	128	Flexible	US, specialist	33.7
				Escitalopram 10–20	124			
Goodman et al[19]	GAD	8	22.6[d]	Placebo	138	Flexible	US, specialist	32.7
				Escitalopram 10–20	143			
Davidson et al[18]	GAD	8	23.4[d]	Placebo	153	Flexible	US, specialist	30.2
				Escitalopram 10–20	154			
Baldwin et al[17]	GAD	12	27.0[d]	Placebo	138	Fixed	Europe, GP and specialist	54.8
				Escitalopram 5	134			
				Escitalopram10	134			
				Escitalopram 20	132			
				Paroxetine 20	136			
Wade et al[25]	MDD	8	29.0[e]	Placebo	189	Fixed	Europe, GP	45.9
				Escitalopram 10	188			
Lepola et al[24]	MDD	8	29.0[e]	Placebo	154	Flexible	Europe, GP	43.6
				Escitalopram 10–20	155			
				Citalopram 20–40	159			
Burke et al[23]	MDD	8	28.9[e]	Placebo	119	Fixed	US, specialist	31.6
				Escitalopram 10	118			
				Escitalopram 20	123			
				Citalopram 40	125			
Rapaport et al[26]	MDD	8	28.6[e]	Placebo	125	Flexible	US, specialist	40.0
				Escitalopram 10–20	124			
				Citalopram 20–40	119			
Ninan et al[27]	MDD	8	30.5[e]	Placebo	151	Flexible[f]	US, specialist	34.1
				Escitalopram 10–20	143			

[a]Placebo response expressed as percent decrease in symptom scores from baseline, least squares means.
[b]Panic and Anxiety Scale.
[c]Liebowitz Social Anxiety Scale.
[d]Hamilton Rating Scale for Anxiety.
[e]Montgomery-Asberg Depression Rating Scale.
[f]Although the Ninan et al. study was a flexible-dose trial, 70% of patients took 20 mg/day of escitalopram from week 2 onward.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder, PD = panic disorder, SAD = social anxiety disorder.

the study was performed (U.S. vs. Europe) or setting (specialist vs. general practitioner).

Neither decreased duration of the disorder (SAD and GAD) nor of the episode (MDD) predicted the response to placebo (Table 5). The same was true for the age at onset of the disorder.

DISCUSSION

The first finding from this analysis is not surprising but bears repetition; placebo response rates in clinical trials of both MDD and anxiety disorders are high, consistent with reports in the literature. For the escitalopram database, placebo response was not significantly different in GAD versus MDD nor in men versus women, findings that are also consistent with several,[36–39] but not all[40] previous analyses. There were too few SAD studies to allow a formal comparison with other indications, but the placebo response rate was slightly lower than in MDD, again in line with previous work.[7]

From a clinical perspective, if placebo responses in trials are due to the effects of frequent patient evaluation and increased attention, then high placebo response rates underscore the power of expectancy effects created by the therapeutic context and the meaningfulness of the doctor-patient relationship.[28–35,41] From a research perspective, the present analysis reinforces the view that placebo-controlled trials remain crucially important for assessing the benefit of medications and cannot be replaced by non-inferiority designs using 2 active drugs.[36,42,43]

Additional findings of this analysis were as follows:

1. Studies undertaken in Europe had a higher placebo response rate compared with those in the U.S.

Table 2. Effect of Location (Europe or U.S.) and Dosing Regimen (fixed or flexible) on the Placebo Response[a]

Diagnosis	Location	Duration, wk	Baseline Score[b]	Placebo Response, %	p Value
GAD	Europe (fixed)	8[c]	27.1[d]	48.6	< .0001*
		12	27.1[d]	54.8	
	U.S. (flexible)	8	22.7[d]	32.2	< .0001**
MDD	Europe	8	28.7[e]	44.6	.0006*
	U.S.	8	29.7[e]	34.7	
	Fixed	8	29.5[e]	38.1	.1**
	Flexible	8	28.7[e]	42.7	

[a]Placebo response expressed as percent decrease in symptom scores from baseline, least squares means (adjusted values).
[b]Mean baseline score for placebo arm only.
[c]Data based on 8th week of Baldwin's 12-week trial.[17]
[d]Hamilton Rating Scale for Anxiety.
[e]Montgomery-Asberg Depression Rating Scale.
*Europe vs. U.S.
**Fixed vs. flexible.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder.

Table 3. Effect of Gender on the Placebo Response[a]

Diagnosis	Sex	Duration, wk	Placebo Response, %
SAD	Male	8	28.3
		Endpoint 12	33.1
		Endpoint 24	39.8
	Female	8	26.3
		Endpoint 12	31.6
		Endpoint 24	38.2
PD	Male	8	16.2
		Endpoint 10	15.2
	Female	8	10.5
		Endpoint 10	9.5
GAD	Male	8	39.9
		Endpoint 12	53.1
	Female	8	38.9
		Endpoint 12	55.8
MDD	Male	8	39.2
	Female	8	40.7

[a]Placebo response expressed as percent decrease in symptom scores from baseline, least squares means.
Abbreviations: GAD = generalized anxiety disorder, MDD = major depressive disorder, PD = panic disorder, SAD = social anxiety disorder.

2. In GAD, the placebo response rate was higher in the European fixed-dose study, which also had more treatment arms.
3. In SAD and in U.S. specialist-treated MDD, a higher placebo response rate was predicted by decreased baseline disorder severity.

In comparing studies in Europe to those in the U.S., it is notable that the former relied primarily on general practitioners, whereas specialists in psychiatry were primarily involved in the latter. General practitioners may be more likely to engage with research participants in such a way that responses to intervention are encouraged, or may be more likely to magnify any positive change during their

Table 4. Effect of Baseline Clinical Global Impressions–Severity of Illness (CGI-S) on the Placebo Response[a]

Diagnosis	Duration, wk	Effect[b]	p Value
PD	8	0.67	.94
	10	–4.77	.60
SAD	8	–10.2	< .0001
	12	–10.3	< .0001
	24	–9.33	.0031
GAD	8	–1.35	.57
	12	–1.95	.65
MDD	8	1.73	.83

[a]ANCOVA with study as factor and baseline CGI-S as covariate.
[b]Percent of placebo response per additional points on baseline severity scale.
Abbreviations: ANCOVA = analysis of covariance, GAD = generalized anxiety disorder, MDD = major depressive disorder, PD = panic disorder, SAD = social anxiety disorder.

Table 5. Effect of Duration of Disorder or Episode on the Placebo Response[a]

Diagnosis	Duration, wk	Effect	p Value
PD	8	–0.03	.96
	10	–0.24	.71
SAD	8	–0.18	.10
	12	–0.11	.36
	24	0.22	.26
GAD	8	0.13	.31
	12	–0.25	.63
MDD	8	–0.33	.14

[a]ANCOVA with study as factor and chronicity as covariate.
Abbreviations: ANCOVA = analysis of covariance, GAD = generalized anxiety disorder, MDD = major depressive disorder, PD = panic disorder, SAD = social anxiety disorder.

clinical ratings of symptom severity. However, as previous work has reported increased responses in private psychiatric practices as compared with primary care settings,[9] other factors may also be involved. Placebo response rates may be lower in studies that employ fewer sites, each with more experience in research, as well as at sites that have received extensive education about expectation effects.[7,44]

The fixed-dose GAD study[17] with 5 treatment arms had a higher placebo response rate. This finding is difficult to interpret because it was undertaken in Europe and in a general practitioner setting, and under these conditions, placebo response rates were generally higher. However, these findings are consistent with the view that increased physician confidence and patient expectation in multiple treatment-arm trials may result in an increase in response rates. The findings that higher placebo response rates are associated with decreased symptom severity at baseline in SAD and in U.S. specialist-treated MDD are also to some extent consistent with previous literature. Thus, there is work suggesting that an increased placebo response rate is associated with decreased symptom severity[8,45,46] and shorter illness duration[6,37,47] in anxiety disorders and MDD.

Although some have argued that greater medication-to-placebo differences are discernible in more severely or

chronically ill patients,[48–53] not all data are in fact consistent with this view.[6,46–48] The data presented in this analysis do not lead to definitive recommendations about the value of exclusion criteria, such as mild severity of illness, in maximizing medication-placebo differences in clinical trials of antidepressants. It is notable, however, that Bech et al.[53] showed a clear dose-response relationship for escitalopram 10 mg and 20 mg among patients with more severe depression (baseline MADRS total score ≥ 30).

Some authors argue that the placebo effect, as measured by comparing placebo with no treatment, is small in most clinical conditions,[54,55] including MDD,[56,57] and therefore primarily reflects regression to the mean.[58] Although placebo and antidepressant responses appear to have a different neurobiology,[16] the response to placebo in such work may represent spontaneous remission. Certainly, placebo response may not be maintained over time.[59–61] Regression effects may be more likely in cases where symptoms are prone to increased fluctuation. In such cases, it is especially important to establish an accurate baseline level of symptoms, for example, by using a flexible prerandomization baseline period.

On the other hand, some hold that placebo responses can be clinically relevant, that they are consistent with psychological effects such as expectancy, and that they may be mediated by specific biological mechanisms.[15] The finding here that predictors of placebo response differ across anxiety disorders and MDD, together with previous work on differences in placebo response in anxiety,[5,62] may reflect differences in underlying psychobiological factors in these conditions. A meta-analysis found that placebo had larger effects than no treatment in pain and in phobia,[55] although bias could not be ruled out. Similarly, there is evidence for a specific or maintained response to placebo in PD,[63–65] with the pattern of symptom improvement differing between placebo and medication responders.[66,67] Clinically relevant placebo effects would help explain large placebo response rates in trials of anxiety disorders and MDD, despite their chronic course and poor response to waiting list interventions.[68]

Several limitations of the current analysis should be acknowledged. First, the full range of factors previously found to predict placebo response rate was not investigated, and a number of these unreported variables may possibly have better accounted for some of the present findings. Second, subjects who qualified for the trials described here may not be representative of patients seen in other clinical settings; for example, participants with significant comorbidity were excluded, and such patients may have lower placebo response rates. Nevertheless, the database studied here is an extensive one, and is unusual in that it allowed investigation of placebo and medication responses across a range of anxiety disorders and MDD.

Much remains to be understood about the nature of the placebo response. Additional work is necessary to determine the time course of placebo responses in anxiety disorders and MDD[59,64,69] as well as putative psychobiological underpinnings. The phenomenology and psychobiology of nocebo responses in these conditions also deserve further attention.[70–72] Understanding placebo response more fully may ultimately contribute to improving the design and analysis of trials for anxiety disorders and MDD.[5,6,73,74] If the placebo response in anxiety disorders and MDD is based on expectancy effects and the meaningfulness of the therapeutic context, rather than simply regression to the mean, then such effects can potentially be countered in clinical trials,[44] or can perhaps be further enhanced in order to help contribute to the effective treatment of these conditions.[30,35]

Drug names: citalopram (Celexa and others), escitalopram (Lexapro and others), paroxetine (Paxil and others).

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