Is the Problem of a High Placebo Response Unique to Antidepressant Trials?

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Recent studies questioning the effectiveness of antidepressants[1,2] have received considerable attention in the mass media. These articles report the difficulty in demonstrating superiority of antidepressants over placebo among antidepressant trials. Interestingly, placebo response also plays a significant role in trials of other nonpharmacologic somatic treatments for depression as well as treatments for many other chronic psychiatric and nonpsychiatric illnesses; however, this does not seem to have received similar attention.

The aim of this article is to compare the magnitude of placebo response in antidepressant trials to that in trials of nonpharmacologic somatic treatments of depression such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and repetitive transcranial magnetic stimulation. Further, we compare the magnitude of placebo response in antidepressant trials to the magnitude of placebo response in chronic illnesses such as bronchial asthma, hypertension, irritable bowel syndrome, ulcerative colitis, osteoarthritis, and Parkinson's disease that may have a psychological component in symptom manifestations as well as a component of distress. In this respect, we considered these disorders to be analogous to major depressive disorder.

Where available, we used data from meta-analyses; if these data were not available, we reported findings from individual trials. It is important to note here that we did not conduct a systematic review and meta-analysis to examine the placebo effect in all medical disorders, but have used examples from published literature to illustrate the role of placebo in the treatment of selected chronic medical illnesses.

Lastly, we do not consider that all medical disorders are similarly placebo responsive. As a rule, disorders such as diabetes, congestive heart failure, chronic hepatic or renal failure, or malignancies are thought to be relatively placebo "insensitive." Hence, our focus is only on disorders that are somewhat susceptible to placebo effects.

Hrobjartsson and Gotzsche[3,4] have reported that the placebo has no significant effects on outcomes in clinical trials of several illnesses. Their meta-analysis has been criticized for several reasons, including the heterogeneity of the conditions studied and the fact that the healing context created by the provider of therapy was ignored.[5] However, this commentary is designed neither to confirm nor to refute the findings of Hrobjartsson and Gotzsche.

Placebo Response in Antidepressant Clinical Trials

In a review of 11 antidepressant development programs, based on published and unpublished data obtained from the U.S. Food and Drug Administration (FDA), it is remarkable that among the depressed patients participating in these pivotal trials, placebo response could account for approximately 75% of response seen with antidepressants.[6–8] Specifically, the symptom reduction among depressed patients assigned to placebo was about 30%, whereas the symptom reduction among depressed patients assigned to FDA-approved antidepressants was approximately 40%.[6–8]

Further, among these clinical trials of approved antidepressants, only 48% (45/93) of active treatment arms showed superiority over placebo.[9] If, in any double-blind, placebo-controlled antidepressant trial, the symptom reduction with placebo is more than 30%, the chances of the trial showing superiority over placebo decrease to approximately 1 in 5! The problem of "failed" trials (failure to show superiority over placebo) is a major scientific and ethical concern and could possibly act as a deterrent to the development and testing of new drugs.

Placebo Response in Nonpharmacologic Somatic Treatments of Depression

The problem of placebo is not restricted to antidepressant trials alone. As summarized in Table 1, trials of other somatic treatments for depression have suffered due to high placebo response rates. The mean response rate with ECT was 68% compared to 29.4% for sham ECT.[15] Notwithstanding the fact that ECT is significantly more effective than sham ECT, a response rate of nearly 30% is substantial and highlights the important role that nonspecific treatment factors play in depression. Similarly, trials of VNS[16] and transcranial magnetic stimulation[10] failed, perhaps in part due to respectable placebo responses of 10% and 14%, respectively.

Placebo Response in Chronic Medical Disorders

In this context, it is useful to evaluate the placebo response among other chronic medical disorders. Data from Table 1 demonstrate that depression is not the only chronic disorder with a high placebo response. In fact, disorders such as Parkinson's disease,[11] osteoarthritis,[12] bronchial asthma,[13] hypertension,[17] irritable bowel syndrome,[18] and ulcerative colitis[19] all show appreciable placebo responses. Also, in a meta-analysis of NSAIDs in osteoarthritic knee pain, NSAIDs were only 15.6% better than placebo after 2 to 13 weeks.[20] Unfortunately, specific data for each treatment were not available for tabulation in this report.

Unlike the reviews of the placebo-controlled trials in depression that are based on trials reported to the FDA, it is unclear if the reviews of other chronic medical illnesses reviewed in Table 1 are free from publication bias because they are limited to published data. It is possible that the effect size for treatments of some of these disorders might be lower if unpublished data were included.

Conclusions

These data suggest that placebo response plays a significant role not only in antidepressant trials, but also in clinical trials of treatments for other chronic diseases that have characteristics similar to major depressive disorder, such as a psychological component and distress. Interestingly, this fact has not received much attention. In this context, it is critical to highlight that placebo response is not a "no treatment" control, because of the design and constraints of placebo-controlled trials.

As described by Frank and Frank,[21] a placebo pill, though pharmacologically inert, has great symbolic value and power as a conditioned stimulus. Placebo treated patients receive all the components of the treatment situation common to any treatment including a thorough evaluation, an explanation for distress, an expert healer, a plausible treatment, an expectation of improvement, an opportunity to verbalize their distress, as well as a healer's commitment, enthusiasm, and positive regard.

Participating in a clinical trial is an intense experience for most patients and quite unlike visiting an HMO or primary care

Table 1. Symptom Reduction and Treatment Response (%) During Clinical Trials of Depression and Other Chronic Disorders

Disorder and Treatment	Active Treatment	Placebo/Sham
Depression	Symptom Reduction	
SSRIs[6–8,a,b]	41	29
SNRIs[6,8,a,c]	46	33
Transcranial magnetic stimulation[10]	24	14
Parkinson's disease—selegiline[11]	12	10
Osteoarthritis—surgery[12]		
Arthroscopic lavage	36	45
Arthroscopic debridement	43	45
Bronchial asthma—bronchodilators/steroids[13,d]	7	4
Depression	Response Rate	
Tricyclic antidepressants[14,a]	46	31
Electroconvulsive therapy[15]	68	30
Vagus nerve stimulation[16]	15	10
Hypertension—6 antihypertensive agents[17,e]	58	30
Irritable bowel syndrome—clonidine, pirenzepine, and alternative therapies[18]	59	46
Ulcerative colitis—5-aminosalicylic acid[19]	36	20

[a]Treatments consist of both published and unpublished data, minimizing publication bias favoring more positive studies likely to be published.
[b]Fluoxetine, paroxetine, sertraline, citalopram, escitalopram.
[c]Venlafaxine, venlafaxine extended release, duloxetine.
[d]Percentage change in FEV1 (forced expiratory volume in 1 second).
[e]Hydrochlorothiazide, atenolol, clonidine, captopril, prazosin, and diltiazem.
Abbreviations: SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

physician for 5 to 10 minutes once every 3 months for the management of a chronic illness. Thus, these findings have 2 significant implications. First, the concern over placebo exposure in the evaluation of treatments for chronic illnesses is overstated. In fact, placebo plus clinical management of the patient plays a significant role in response. Having said this, it is self-evident that evaluations of new treatments for chronic disorders need to include a placebo control group.

Second, although placebo effects can be expected in clinical practice for all chronic medical or psychiatric disorders, they may be more pronounced in clinical trials due to the more frequent and longer visits that are typical of most trial designs.

Given the modern design and conduct of antidepressant trials, there is no easy way to assess what would have happened to these depressed patients if they either did not receive any treatment or were put on a waiting list (common in clinical practice). Research into novel trial designs should probably focus more on the effects of including a comparison arm with relative lack of intervention/treatment.

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