

Role of the placebo effect in evaluating antidepressant efficacy

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The word “placebo” is derived from the Latin for “I shall please.” The Merriam-Webster Online Dictionary defines placebo as “a medication prescribed more for the mental relief of the patient than for its actual effect on a disorder” and “an inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance.” It defines the placebo effect as “improvement in the condition of a sick person that occurs in response to treatment but cannot be considered due to the specific treatment used.” The placebo effect may confound drug efficacy research and evaluation of therapeutic responses in clinical practice, especially in the treatment of depression, for which the rate of response to placebo has been reported to be as high as 50%.¹ Recent meta-analyses have attempted to identify the degree of therapeutic response in depression treatment that may be attributed to the placebo effect. Such studies may also, however, have underestimated the efficacy of antidepressant drug therapy.

The placebo effect

No medical treatment—not even surgery—is immune to the placebo effect. In the late 1950s, a common treatment for angina involved ligation of the bilateral internal mammary arteries to stimulate collateral circulation. This procedure was abandoned soon after two controlled

studies found that 10 (71%) of 14 patients who received sham skin incisions improved, compared with 14 (67%) of 21 patients who were actually treated with the procedure.¹ More recently, arthroscopic surgery for osteoarthritis of the knee has come under scrutiny.² One hundred eighty patients were randomly assigned to receive arthroscopic debridement, arthroscopic lavage, or placebo incisions with simulated debridement. During this 24-month study, while there appeared to be some improvement from baseline in all groups, there was no point at which either intervention group reported significantly greater improvements in pain or function compared with the placebo group. At one year, the mean \pm S.D. Knee-Specific Pain Scale (KSPS) scores were 48.9 ± 21.9 , 54.8 ± 19.8 , and 51.7 ± 22.4 for the placebo, lavage, and debridement groups, respectively; at two years, the scores were 51.6 ± 23.7 , 53.7 ± 23.7 , and 51.4 ± 23.2 .

In addition to medical conditions, drug dosage, color, schedule, route, and brand name have been found to affect the placebo response. Blackwell

et al.³ demonstrated a dose-response relationship and confirmed an influence of product color. Medical students were randomly given packets containing one or several red or blue placebo tablets. Students reported sedative effects after taking the blue tablets and stimulant effects after taking the red ones. In addition, students who received more than one tablet reported larger effects. A meta-analysis found that the healing rate for duodenal ulcer was higher in patients who received placebo four times a day rather than twice a day.⁴ Placebo injections elicited better response rates than placebo tablets in a study of migraine.⁵ Brantthwaite and Cooper⁶ reported that placebo representing brand-name aspirin products was more effective against headache than placebo representing generic aspirin products.

Some may claim that the placebo effect is merely psychological; however, physiological changes have also been associated with placebo. Two recent studies found differences in brain function between subjects responding to antidepressants and subjects responding to placebo.^{7,8} Leuchter et al.⁷ enrolled 51 patients with major depressive disorder in one of two nine-week double-blind studies. Patients were randomized to receive either fluoxetine 20 mg/day or placebo in one study and venlafaxine 150 mg/day or placebo in the other. Quantitative electroencepha-

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lography (QEEG) was performed at baseline and at weeks 1, 2, 4, and 8 to detect any changes in cerebral perfusion. Thirteen of 25 patients receiving antidepressants had a response to treatment, defined as a score on the Hamilton Depression Rating Scale (HAM-D) of less than 10, as did 10 of 26 patients receiving placebo. A significant decrease in prefrontal cordance measures (a mathematical calculation derived from QEEG power that has a moderately strong association with cerebral perfusion) were seen in patients in the medication group who responded at week 2, but the difference partially resolved by weeks 4 and 8. Patients in the placebo group who responded had a significant increase in prefrontal cordance measures at weeks 4 and 8. The QEEG findings indicated that responders in the placebo group had higher levels of cerebral perfusion with treatment than responders in the antidepressant group.

A double-blind study by Mayberg et al.⁸ measured metabolic changes during treatment for a major depressive episode. Seventeen men were randomized to receive fluoxetine 20 mg/day or placebo. Positron emission tomography (PET) was performed at baseline and weeks 1 and 6. Regional cerebral glucose metabolism was measured in patients by injecting a 5-mCi dose of ¹⁸F-labeled fluorodeoxyglucose intravenously 40 minutes before each PET scan. Of the 15 patients who completed the study, 4 in the fluoxetine group and 4 in the placebo group had a therapeutic response (defined as a 50% decrease in HAM-D scores from baseline). Both the fluoxetine-group responders and the placebo-group responders had significant metabolic changes. The placebo-group responders had an increase in metabolism in the posterior cingulate cortex at weeks 1–6, and the fluoxetine-group responders had a decrease in metabolism at week 1 and an increase by week 6. The pattern of metabolic changes in the re-

sponders in the fluoxetine group, visualized by PET, closely matched that seen in the placebo-group responders; however, the fluoxetine-group responders had additional metabolic changes in the brainstem, striatum, and hippocampus. While these two studies show distinct physiological changes in patients who responded to antidepressants or placebo compared with those who did not respond, the physiological changes appeared to vary among responders who received placebo and drug.

In general, the placebo effect, the drug or treatment effect, and the effect of the natural history of the disease (i.e., regression to the mean) are three elements of the therapeutic effect.⁹ The placebo effect and the natural history of the disease make it difficult to discern the actual drug or treatment effect. For example, in hypertension with a fairly static disease course, placebo may cause less distortion of drug efficacy than in a progressively worsening disease, such as terminal cancer, or in an unpredictably fluctuating disease, such as irritable-bowel syndrome. What elicits or influences the placebo response can be difficult to determine. Multiple elements may contribute to the placebo response, and quite often patients begin to feel better as soon as a visit with their physician is scheduled.¹⁰ The physical examination, the laboratory tests, the white coat, the institution name and reputation—all could potentially elicit a placebo response. One could classify the main contributing factors as the physician's expectations, the patient's expectations, and the entire therapeutic milieu.¹¹ Not only does a patient's trust in the physician and the treatment influence the therapeutic response, but the physician's manner may as well (an illustration, perhaps, of the "art" of medicine).

No one has been able to identify any specific features that make a patient more likely to respond to placebo, including personality, cognitive

style, and education.^{9,12} It has been suggested that patients afflicted with chronic conditions with fluctuating courses and highly subjective symptoms (e.g., back and other chronic pain, chronic fatigue, arthritis, insomnia, asthma, and anxiety) may be more vulnerable to the placebo effect, as may patients with less severe forms of depression.¹¹ Patients with psychotic features, psychomotor retardation, or chronic depression are thought to be less responsive to placebo.¹² However, when comparing drug responses and placebo responses, it is thought that patients who show a placebo response have a faster onset of therapeutic response while response to an active drug is usually delayed. Similarly, patients responding to placebo may have a more fluctuating disease course when reacting to environmental stressors, and medication responders may have a more stable course.

The placebo effect and antidepressants

Clinical trials routinely use control groups to estimate the effect of placebo and the natural history of the disease so that the therapeutic efficacy of a drug or treatment can be evaluated. Recent meta-analyses of placebo-controlled trials in patients with depression have attempted to identify the proportion of therapeutic responses elicited by placebo and, in so doing, have suggested that antidepressants are no more effective than placebo.^{13–17} Furthermore, these meta-analyses indicate that, if active placebo (i.e., placebo that mimics the adverse effects of the study drug) is used, there is no significant difference in efficacy between placebo and antidepressants.

Kirsch and Sapirstein¹³ evaluated 19 double-blind, placebo-controlled studies. The studies included 2318 patients treated with amitriptyline, amylobarbitone, fluoxetine, imipramine, paroxetine, isocarboxazid, lithium, liothyronine, adinazolam,

amoxapine, phenelzine, venlafaxine, maprotiline, tranylcypromine, and bupropion. Significant differences in mean effect sizes (mean posttreatment score minus mean pretreatment score, divided by pooled standard deviation) were found between the medication and placebo groups (1.55 and 1.16, respectively) ($p < 0.001$), suggesting that 75% of the benefit of the active drug was obtained from inactive placebo. However, the authors proposed that if active placebo had been used the differences between the groups would have been smaller. The reasoning was that subjects receiving the study drugs would have recognized adverse drug effects and realized that they were receiving active medications, thus inadvertently unblinding the study and magnifying the placebo effect. To extract the impact of the natural history of the disease on the therapeutic effect, the authors evaluated 19 psychotherapy studies with a no-treatment or waiting-list control group. Mean effect sizes were 1.60 for subjects receiving psychotherapy and 0.37 for subjects receiving no therapy. The impact of natural disease history was estimated to account for 23.8% of the therapeutic response; thus, the placebo effect may be calculated to have accounted for 50.97% of the therapeutic response and the drug effect for only 25.16%.

This study design was used further by Kirsch et al.¹⁴ to analyze efficacy data from 47 placebo-controlled, short-term efficacy trials of fluoxetine, paroxetine, sertraline, venlafaxine, nefazodone, and citalopram that were submitted to FDA (9 of the 47 trials were excluded from the analysis because of exclusion of mean improvement scores; fluoxetine, venlafaxine, and nefazodone were analyzed). The results suggested that 85% of the drug response was duplicated by placebo. The authors speculated that the high placebo response in this analysis occurred because all clinical trial results submitted to

FDA, including data not published, were evaluated. Publication bias may have led to the lower placebo response rate estimated in the authors' previous meta-analysis,¹³ since trials with less significant response rates were less likely to be submitted for publication.

Given the idea that the apparent therapeutic effect of antidepressants may in fact be mostly the placebo effect magnified by study unblinding due to adverse effects of the active drug, some may wonder whether the use of antidepressants is justified. However, there are flaws in meta-analyses. Generally speaking, meta-analyses are inferior to direct experimental studies because of the probable heterogeneity of study subjects, treatments, dosages, rating scales, investigators, and statistical methods among the studies included. In addition, assumptions are often made in data analysis because of inconsistent reporting.

Additional factors could potentially skew the conclusions of the two meta-analyses concerning antidepressant efficacy. Most studies included in the meta-analyses were short-term trials. In the meta-analysis by Kirsch and Sapirstein,¹³ study treatment periods ranged from 1 to 20 weeks (mean, 4.82 weeks). The meta-analysis by Kirsch et al.¹⁴ included trials lasting 4 to 8 weeks. The placebo effect is generally not thought to be maintained for long periods.¹² Also, for ethical reasons, enrollment of severely depressed or high-risk study subjects, such as people who are suicidal or in need of immediate medical treatment, in placebo-controlled studies is not recommended.¹⁸ Kirsch et al.¹⁴ reported that the mean baseline HAM-D scores of study subjects ranged from 21.0 to 29.7; in one study, the average baseline score was 17.21. Typically, inclusion of a subject in an antidepressant clinical trial requires a baseline HAM-D score of greater than 18. On a 17-item HAM-D scale, scores below 7 indicate normal mood, while

scores above 20 indicate significant depression in need of treatment. Total scores may range from 0 to 50.¹⁹ Milder and more acute forms of depression are thought to have high placebo response rates.¹¹ Finally, while these meta-analyses did indicate that placebo elicits responses similar to those of active drug therapy, the recent studies by Leuchter et al.⁷ and Mayberg et al.⁸ strongly suggest that the physiological responses differ.

Kirsch et al.¹⁴ questioned the criteria used by FDA to evaluate antidepressant medications. However, according to Temple and Ellenberg,²⁰ up to half of modern trials of antidepressants do not distinguish a drug with known efficacy from placebo, and antidepressants are not the only class of drugs with test-sensitivity problems:

Analgesics, anxiolytics, antihypertensives, hypnotics, antianginal agents, angiotensin-converting-enzyme inhibitors for heart failure, postinfarction beta-blockers, antihistamines, nonsteroidal asthma prophylaxis, motility-modifying drugs for gastroesophageal reflux disease . . . are often indistinguishable from placebo in well-designed and -conducted trials. . . . Even if a drug is statistically significantly superior to placebo in only 50% of well-designed and well-conducted studies, that proportion is still vastly greater than the small fraction that would be expected to occur by chance if the drugs were ineffective.

Variations in study populations, compliance with therapy, concomitant medications, the natural history of the disease, and treatment-refractory illnesses all have the potential to reduce drug-placebo differences.²⁰

Despite the potential problems with placebo-controlled trials, the Declaration of Helsinki recommends testing "the benefits, risks, burdens

and effectiveness of a new method . . . against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo or no treatment in studies where no proven prophylactic, diagnostic, or therapeutic method exists."²¹

The National Depressive and Manic-Depressive Association states the following about the use of placebo in clinical trials of mood disorders:

- Patients with mood disorders have inherently high placebo response rates. Without placebo . . . most study findings are difficult to interpret, and the risks associated with research cannot be justified.
- Placebo is justified when testing a new antidepressant with a novel mechanism of action . . . and when . . . newer members in a class may offer important advantages over the original drug.
- If mood disorder research ever reaches a point at which effect sizes for standard drugs are large and can consistently be shown to be superior to placebo, it may be appropriate to consider noninferiority trials for new drugs. However, the state of research is not at the point at which noninferiority trials can be considered scientifically valid.
- Placebo-controlled trials in unipolar depression are ethical given sufficient informed consent, monitoring, and safety procedures, except in patients who are suicidal, have acute psychosis, or need immediate treatment.¹⁸

Discussion

Placebo-controlled trials continue to be invaluable, since they allow for smaller samples without decreasing statistical power. Noninferiority trials, in which a new agent is compared with a standard therapy, require larger samples to minimize the potential for false-positive results.²² The added cost may dissuade researchers from evaluating possible

new therapies and may increase the number of people who are treated with potentially inferior agents. Therefore, we can expect to see placebo continue to be used in clinical studies of antidepressants.

The recent meta-analyses discredit the efficacy of antidepressants and perhaps seek to reinforce the role of psychotherapy in the treatment of depression. Such conclusions have the potential to misinform the public by implying that antidepressants are useless, even though a small effect of antidepressants was found in the meta-analyses. The studies observed a 15–25% benefit of antidepressants above the placebo effect, which is relatively consistent with the results of antidepressant clinical trials.^{13,14} It is also important to keep in mind that “change on dimensional measure may be difficult to extrapolate to a clinical setting.”¹²

Because the placebo effect is an important element of the therapeutic response, further study is needed to enhance our understanding of what patient characteristics or clinical factors promote placebo responses in order to control for the interference of these responses in clinical trials of therapeutic efficacy. While knowledge of these factors may eliminate future controversies regarding therapeutic response rates—and perhaps further investigation of the use of active placebo is warranted—their manipulation also has the potential to amplify clinical responses in practice to improve therapeutic outcomes. Clinicians should keep in mind several factors about the placebo effect: (1) the placebo effect can occur with any treatment, and anyone is susceptible, (2) there are not only psychological responses to placebo, but also physiological ones, (3) the placebo effect has the potential to increase therapeutic effects and should be used to advantage, (4) the placebo effect tends to be rapid and fluctuating; drug effects tend to be more stable, and (5) placebo responses appear

to differ physiologically from responses to drug therapy.

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