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Introduction to the target article

## Yes, There *Is* a Placebo Effect, but Is There a Powerful Antidepressant Drug Effect?

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Imagine reading, in a prestigious medical journal, an article bearing the provocative title, "Is Medicine Powerless? An Analysis of Clinical Trials Comparing Medical Treatment With No Treatment." Suppose that the authors of this meta-analysis had "conducted a systematic review of clinical trials in which patients were randomly assigned to either medical treatment or no treatment" and had identified 130 trials that met their inclusion criteria. These included clinical trials of medical treatments for the common cold, alcohol abuse, smoking, poor oral hygiene, herpes simplex infection, infertility, mental retardation, marital discord, fecal soiling, Alzheimer's disease, carpal tunnel syndrome, and "undiagnosed ailments." Noting that medical treatment "is difficult to define satisfactorily," the authors "defined medical treatment practically as an intervention labeled as such in the report of a clinical trial." Besides drugs and surgery, the medical treatments in the clinical trials they identified include psychotherapy, homeopathy, acupuncture, meditation, chiropractic, and faith healing. Finding a small but significant treatment effect, along with significant heterogeneity of outcomes, the authors concluded that they had "found little evidence in general that medicine had powerful clinical effects."

At the risk of stating the obvious, let me note two of the flaws in the design of this fictitious meta-analysis and the conclusions drawn from it. First, the definition of *medical treatment* is too broad because most of the treatments the authors identified are not representative of what is typically meant by the term. Second, there are very effective medical treatments for some disorders, less effective treatments for others, and some conditions (including some of those evaluated in the meta-analysis) for which there currently are no known effective medical treatments. Given a set of clinical trials of diverse treatments for an arbitrary subset

of disorders with little in common, it does not make much sense to evaluate the effects of medical treatments in general. Instead, one needs to evaluate the effects of particular treatments on particular disorders (see [Kirsch & Scoboria, 2001](#)).

The meta-analysis described above is fictional, and had it been done, I doubt that it would have been accepted for publication in a reputable journal. However, a meta-analysis similar to this one and sharing its defects was recently published in the *New England Journal of Medicine* ([Hróbjartsson & Gøtzsche, 2001](#)). The article was titled, "Is the Placebo Powerless? An Analysis of Clinical Trials Comparing Placebo With No Treatment." The authors of this meta-analysis "conducted a systematic review of clinical trials in which patients were randomly assigned to either placebo or no treatment" ([Hróbjartsson & Gøtzsche, 2001](#), p. 1594) and identified 130 trials that met their inclusion criteria. These included clinical trials of treatments for the common cold, alcohol abuse, smoking, poor oral hygiene, herpes simplex infection, infertility, mental retardation, marital discord, fecal soiling, Alzheimer's disease, carpal tunnel syndrome, and "undiagnosed ailments" ([Hróbjartsson & Gøtzsche, 2001](#), p. 1596). Noting that the term *placebo* "is difficult to define satisfactorily" (p. 1594), the authors "defined placebo practically as an intervention labeled as such in the report of a clinical trial" (p. 1595). Besides placebo pills, the placebos in the clinical trials they identified included relaxation (classified as a treatment in some of the studies and as a placebo in others); leisure reading; answering questions about hobbies, newspapers, magazines, favorite foods, and favorite sports teams; and talking about daily events, family activities, football, vacation activities, pets, hobbies, books, movies, and television shows. Finding a small but significant "placebo effect," along with significant heterogeneity outcomes, the authors concluded that they had "found little evidence in general that placebo had powerful clinical effects" ([Hróbjartsson & Gøtzsche, 2001](#), pp. 1594-1595).

The flaws in the design of this real meta-analysis and the conclusions drawn from it are similar to the shortcomings of the fictional meta-analysis of medical treatments. First, the definition of *placebo* is too broad; most of the supposed placebos the authors identified are not representative of what is typically meant by the term. Second, there are very strong placebo effects in the treatment of some disorders, weaker placebo effects in others, and some conditions for which placebos may not be effective at all. Given a set of clinical trials of diverse treatments for an arbitrary subset of disorders with little in common, it does not make much sense to evaluate the placebo effect in general. Instead, one needs to evaluate the effects of particular treatments on particular disorders (see [Kirsch & Scoboria, 2001](#)).

## Defining Placebo and the Placebo Effect

Typically, placebos are physically inert substances and medical procedures that are identical in appearance to an active pharmacological or (less commonly) other medical treatment being investigated. Occasionally, active substances are used as placebos. These active placebos have side effects that mimic those of the drug being investigated but do not possess the physical properties hypothesized to produce the beneficial treatment effect. Placebos are used to control for the psychological effects of administering a particular physical treatment for a particular disorder. Active placebos are used to prevent patients from using the sensory cues provided by side effects to deduce the condition to which they have been randomized. Placebo effects are the effects produced by placebos.

When the terms *placebo* and *placebo effect* are confined to controls for pharmacological

substances and other physical interventions, they are not at all difficult to define. It is only when attempts are made to extend the concept to psychotherapeutic procedures that great difficulties are encountered (see [Kirsch, 1978](#)). One problem is that all of the effects of psychotherapy are due to the psychological properties of the treatment; thus, there is nothing to control for. A second problem is that it is not possible to construct a "placebo" psychotherapy that is identical in appearance to the "active" treatment; a treatment that looks, sounds, tastes, and smells like a particular psychological therapy *is* that therapy. For these reasons, evaluations of placebo effects might best be confined to conventional medical placebos (i.e., placebo pills, injections, and surgery).

## Evaluating the Placebo Effect

One difficulty in evaluating placebo effects is the paucity of clinical trials with no-treatment control conditions. This is important because the placebo effect is not the same as the response to placebo treatment. Observed changes following placebo administration (the placebo response) might have occurred even if a placebo had not been administered. They could have been due to spontaneous remission, the natural history of a particular disorder, or statistical regression to the mean. Presuming that the blind is not broken (i.e., that participants are not able to determine whether they have been assigned to drug or placebo condition prior to the production of any treatment-induced therapeutic effect), the difference between the drug response (changes following drug administration) and the placebo response provide a conservative (possibly too conservative, in some cases; [Kirsch, 2000](#)) assessment of the drug effect. Similarly, differences between the placebo response and naturally occurring changes can provide a conservative estimate of the placebo effect.

To compensate for the paucity of clinical trials that include both placebos and no-treatment control groups, [Hróbjartsson and Gøtzsche \(2001\)](#) used a broad definition of placebo that includes psychotherapy control procedures. Whereas there are few clinical trials of medications with both placebo and no-treatment control groups, there are a great many psychotherapy outcome studies that include no-treatment controls as well as so-called psychological placebos. In fact, it is easy to identify many such studies that were not included in the [Hróbjartsson and Gøtzsche \(2001\)](#) meta-analysis, including the seminal study using this design ([Paul, 1966](#)). The problem is that one cannot evaluate the effects produced by medical placebos by examining studies in which the so-called placebo consists of such irrelevant procedures as answering questions about one's favorite foods, talking about pets, or reading short stories.

## Evidence of Placebo Effects

Although there are relatively few clinical trials of medications that include no-treatment control conditions, a number of experimental studies have been designed to investigate the effects of placebos. Numerous studies not included in [Hróbjartsson and Gøtzsche's \(2001\)](#) meta-analysis have shown that placebo analgesics, tranquilizers, stimulants, and alcohol produce effects beyond those observed in untreated control conditions ([Abrams & Wilson, 1979](#); [Baker & Kirsch, 1993](#); [Bridgell, Rimm, Caddy, Krawitz, Sholis, & Wunderlin, 1978](#); [Brodeur, 1965](#); [Buckalew, 1972](#); [Camatte, Gerolami, & Searles, 1969](#); [Fillmore, Mulvihill, & Vogel-Sprott, 1994](#); [Fillmore & Vogel-Sprott, 1992](#); [Frankenhaeuser, Jarpe, Svan, & Wrangsjö, 1963](#); [Frankenhaeuser, Post, Hagdahl, & Wrangsjö, 1964](#); [Gelfand, Ullmann, & Krasner, 1963](#); [Kirsch & Weixel, 1988](#); [Lang, Goeckner, Adesso, & Marlatt, 1975](#); [Lang, Searles, Lauerman, & Adesso, 1980](#); [Lansky & Wilson, 1981](#); [Lieberman, 1964](#); [Lyerly,](#)

[Ross, Krugman, & Clyde, 1964](#); [Montgomery & Kirsch, 1997](#); [Morris & O'Neal, 1974](#); [Ross, Krugman, Lyerly, & Clyde, 1962](#); [Wilson & Abrams, 1977](#); [Wilson & Lawson, 1976](#)). In addition, a controversial meta-analysis published in *Prevention & Treatment* indicates a change of 1.16 standard deviations on measures of depression following administration of placebo antidepressants, compared with a change of 0.37 standard deviations among untreated controls ([Kirsch & Sapirstein, 1998](#)). These data indicate a placebo effect size of 0.79 standard deviations. This is a powerful effect by any standard.

These are not the only data indicating the reality of placebo effects. Just as inclusion of a placebo control is only one method of evaluating the effects of medical treatments, the inclusion of a no-treatment control group is only one method of evaluating the placebo effect. Medical treatment effects can be inferred when different doses of the same drug produce different effects or when a particular treatment is found to be significantly more effective than an alternative treatment. Similarly, placebo effects can be inferred when different placebos or apparent doses of the same placebo produce significantly different effects or when the effects of a placebo vary as a function of the information provided to the person to whom it is administered. Effects of this sort have been reported in a number of studies. For example:

- Asthmatic patients have been shown to exhibit bronchoconstriction after inhaling a placebo described as a bronchoconstrictor and bronchodilation after inhaling a placebo described as a bronchodilator ([Luparello, Lyons, Bleeker, & McFadden, 1968](#); [McFadden, Luparello, Lons, & Bleeker, 1969](#); [Neild & Cameron, 1985](#); [Spector, Luparello, Kopetzky, Souhrada, & Kinsman, 1976](#)).
- Placebo morphine is considerably more effective than placebo Darvon, which in turn is more effective than placebo aspirin ([Evans, 1974](#)). In each case, the placebo is about half as effective as the pharmacologically active drug. Similarly, placebos produce more pain relief when given after a more potent drug than they do when given after a less potent drug ([Kantor, Sunshine, Laska, Meisner, & Hopper, 1966](#)). Thus, the effectiveness of a placebo pain reliever varies as a function of its believed effectiveness.
- Placebo and active analgesics are more effective when presented with a well-known brand name ([Branthwaite & Cooper, 1981](#)).
- Placebo injections are more effective than placebo pills ([de Craen, Tijssen, de Gans, Kleijnen, 2000](#)).
- The color of a placebo can influence its effects (reviewed in [de Craen, Roos, de Vries, & Kleijnen, 1996](#)). When administered without information about whether they are stimulants or depressives, blue placebo pills produce depressant effects, whereas red placebos induce stimulant effects ([Blackwell, Bloomfield, & Buncher, 1972](#)). Patients report falling asleep significantly more quickly after taking a blue capsule than after taking an orange capsule ([Luchelli, Cattaneo, & Zattoni, 1978](#)). Red placebos seem to be more effective pain relievers than white, blue, or green placebos ([Huskisson, 1974](#); [Nagao, Komia, Kuroanagi, Minaba, & Susa, 1968](#)).
- Finally, the magnitude of the placebo response has been shown to vary as a function of the dose that the person is asked to consume ([de Craen, Moerman, Heisterkamp, Tytgat, Tijssen, & Kleijnen 1999](#); [Kirsch & Weixel, 1988](#)).

Taken together, these data provide ample documentation of the presence of a placebo effect.

## Is There a Powerful Antidepressant Drug Effect?

The response to antidepressant placebos is particularly interesting because it leaves relatively little room for a substantial active drug response. In the [Kirsch and Sapirstein \(1998\)](#) meta-analysis, 75% of the response to active medications was duplicated in placebo control conditions, and the placebo effect (i.e., the placebo response minus changes observed in no-treatment control conditions) was about double the active drug effect (i.e., the drug response minus the placebo response).

Not surprisingly, these data provoked considerable controversy (e.g., [Dawes, 1998](#); [Kirsch, 1998](#); [Klein, 1998](#)). Because of this controversy, and also because of the importance of the issue, I responded positively when Thomas Moore sent me a note suggesting that I replicate the meta-analysis of antidepressant medication using data submitted to the U.S. Food and Drug Administration (FDA) by pharmaceutical companies in the process of seeking approval for that medication. The result of this collaboration is the focus of this issue of *Prevention & Treatment*.

When Guy Sapirstein and I undertook our meta-analysis ([Kirsch & Sapirstein, 1998](#)), we did not doubt that antidepressants are pharmacologically effective. Our intent was to evaluate the placebo effect. The results of that analysis surprised us. We expected a substantial placebo effect, but we did not expect such a small medication effect. In the meta-analysis reported by [Kirsch, Moore, Scoboria, and Nicholls \(2002\)](#), the focus is somewhat different. Our concern was not to assess the placebo effect but rather to examine the magnitude of the drug effect. Our analysis of the FDA data is likely to prove as controversial as the [Kirsch and Sapirstein \(1998\)](#) meta-analysis. Although the difference in response between antidepressant medication and inert placebo was statistically significant, in clinical terms it was very small, leading us to ask whether these medications are "the emperor's new drugs."

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