Antidepressant-Placebo Debate in the Media
Balanced Coverage or Placebo Hype?

A spate of articles has recently appeared in the popular media with such intriguing titles as "Maybe It's All in Your Head," "Make-Believe Medicine," "New Study of Brain Illustrates the Power of Placebo," "Antidepressants: Hype or Help?" and "Misguided Medicine: A Stunning Finding about Antidepressants Is Being Ignored," to name but a few. Journalists have found a new public-interest story about mental health that readers seem to be hungry for—the antidepressant versus placebo controversy.

For over 50 years, the inclusion of a placebo-control condition, typically involving the use of a sugar pill, has been the standard practice of researchers attempting to determine the efficacy of a new drug (Leber, 2000). The aim of these trials is to provide controlled conditions under which treatment effects can be separated. Without adequate comparison conditions, it is impossible to differentiate any specific effects of the drug from other "nonspecific" factors, which include such things as chance variation, regression to the mean (i.e., the statistical tendency for extreme scores on a measure to move closer to the group mean when the measure is readministered), healthcare provider attention, treatment credibility and rationale, persuasion, patient expectancy effects, researcher allegiance effects, effort justification, spontaneous remission, demand characteristics, and so on (e.g., Lohr, Lilienfeld, Tolin, & Herbert, 1999). Placebo controls are especially critical to the investigation of pharmacotherapy for psychiatric disorders, which by their very nature pose challenges in diagnosis and assessment relative to medical conditions with more objective and pathognomonic biological markers.

For a drug to gain U.S. Federal Drug Administration (FDA) approval, data from double-blind controlled studies must show safety and efficacy for the disorder being treated. Drug companies routinely invest billions of dollars in drug research and development. It typically takes a number of years to produce an effective and marketable psychiatric medication such as a new antidepressant. Although much of this time and effort is understandable given the inherent complexities of clinical drug trials, several concerns have begun to attract increased attention. The FDA requires at least two placebo-controlled trials with positive results to authorize a drug indication, regardless of how many trials fail to demonstrate the drug's superiority to placebo. This appears to have led to situations in which many studies are conducted to obtain the requisite two positive results, which are then highlighted to suggest the drug's superiority to placebo. For example, the efficacy of Prozac could not be distinguished from placebo in 6 out of 10 clinical trials (Moore, 1999). Critics further point out that many antidepressant trials have serious methodological weaknesses, including the unblinding of raters due to the common side effects of these drugs compared with the inert sugar pill (Gaudiano & Herbert, 2003). In addition, the "file-drawer problem" (i.e., the fact that negative results are less likely to be published than those with positive results; Rosenthal, 1979) renders it difficult to ascertain the meaningfulness of those studies actually showing differences. These and other problems have led
some to question the specific efficacy of antidepressants relative to pill placebos.

In a controversial meta-analysis published in 1998, Irving Kirsch and Guy Sapirstein compared the mean effect size changes in symptoms of depression across 19 double-blind studies assessing the efficacy of antidepressant medications. Results demonstrated that placebos reproduced approximately 75% of the improvement found in the active drug. Furthermore, the authors assert that the remaining 25% of improvement accounted for by the active drug is debatable, and could be the result of an enhanced placebo response due to the side effects that patients experience when taking the active drugs, or other nonspecific factors.

Recently, Kirsch and colleagues (2002) replicated and extended the results of the Kirsch and Sapirstein (1998) meta-analysis using studies from the FDA database. The advantage of using the FDA dataset is that it reduces the problem of publication bias in conventional meta-analyses that rely only on published reports. They found a small but statistically significant superiority of active drug over inert pill placebo. Kirsch et al. reported an 18% difference between drug and placebo, representing an average 2-point difference on a semi-structured clinical interview commonly used to assess treatment outcome. Because of the small effect size for active drug over placebo, Kirsch et al. question the clinical significance of antidepressants.

Because antidepressants are among the most prescribed medications, and because major depression is estimated to have a lifetime prevalence rate of approximately 13% for men and 21% for women (Kessler et al., 1994), it is no wonder that the media would pick up on this debate with considerable interest. Many consumers are personally invested in finding out the truth about this issue. But how adequately are those in the media fulfilling this need? In a provocative piece in the Washington Post entitled "Against Depression, a Sugar Pill Is Hard to Beat," Shankar Vedantam (2002) asserts: "After thousands of studies, hundreds of millions of prescriptions and tens of billions of dollars in sales, two things are certain about pills that treat depression: Antidepressants like Prozac, Paxil and Zoloft work. And so do sugar pills" (p. A01).

Although numerous other articles review many of the same studies and viewpoints, Vedantam's piece provides the most comprehensive coverage of this area in a single article. Vedantam does a good job of surveying the recent research relevant to the antidepressant-placebo debate, and quotes several of the major researchers in this area. Although he does not interview Kirsch, he does speak with Arif Khan, who investigated the placebo effect in FDA antidepressant trials. Khan is quoted by Vedantam as indicating that in 52% of FDA trials, the effects of antidepressants could not be distinguished from those of placebo. However, Vedantam neglects to mention that Kahn's research also indicated that increased severity of depression was associated with greater change in depressive symptoms in those treated with antidepressants, with the reverse effect observed in those in the pill placebo condition (Kahn, Leventhal, Kahn, & Brown, 2002). In other words, the incremental effects of antidepressants relative to placebos appear to increase as the severity of depression increases.

Furthermore, Vedantam (2002) interviews the lead authors of two recent brain imaging studies, shedding new light on the placebo effect's biological markers. Andrew Leuchter and colleagues (2002) examined the brain functioning of responders to selective serotonin reuptake inhibitors (SSRIs; a class of antidepressants including Prozac, Zoloft, and Paxil) or inert placebo after 9 weeks of treatment for major depression using quantitative electroencephalography. They found that placebo responders showed a significant increase in prefrontal concordance (i.e., a measure of
cerebral perfusion), whereas medication responders showed a decrease in this area. In contrast, Helen Mayberg and colleagues (2002) examined changes in brain glucose metabolism in clinically depressed patients receiving an SSRI or placebo using positron emission tomography. After 6 weeks of treatment, there was significant overlap in the change of certain brain areas for responders in both groups. However, those receiving the antidepressant showed additional changes in subcortical regions compared with those in the placebo condition.

In general, Vedantam (2002) provides a thorough review of recent research showing the substantial placebo response found in antidepressant trials. However, readers of the article may be left with the false impression that these results indicate that the efficacy of antidepressants and sugar pills are equal. The only "critic" interviewed in the piece representing the antidepressant position is a psychiatrist in private practice, who speaks more about clinical anecdotes regarding the efficacy of antidepressants than about the research literature. Although Vedantam's article does not clearly discuss this point, there remains healthy disagreement among researchers concerning the exact benefits of antidepressants relative to placebos. Donald Klein, a noted psychiatrist and researcher, has been a vocal critic of those promoting the idea that placebos are as effective as antidepressants. Klein (1998) criticized Kirsch and Sapirstein's (1998) meta-analysis, suggesting that they included an unrepresentative and flawed set of studies and conducted improper statistical analyses. Furthermore, Klein criticized the results from studies using FDA data, arguing that the methodological flaws in these studies are responsible for the poor differentiation between antidepressants and placebos. He points out that when methodologically sound antidepressant trials are analyzed, the benefit of antidepressants over placebos is often clear and substantial (Quitkin, Rabkin, Gerald, Davis, & Klein, 2000).

Although Vedantam (2002) provides considerable evidence from recent research showing the substantial placebo effect in antidepressant clinical trials, he neglects to cover adequately alternative explanations for these findings. Therefore, the article may leave some readers with the erroneous impression that the antidepressants that they are being prescribed are no more worthwhile than sugar pills. Even critics of antidepressants acknowledge that a genuine difference exists between antidepressants and placebos, with the debate focusing on how large this difference is and the mechanisms responsible for it. It is true that some speculate that the remaining difference is attributable to such factors as the unblinding of raters resulting from the side effects of active drugs. They argue that active placebos, or pills that mimic common side effects but contain no clinical benefit, should be used more often in these trials. However, Quitkin et al. (2000) assert that, in their analyses, the placebo response rate in studies using active placebos is similar to that using inert sugar pills (viz., about 30%). In contrast, Moncrieff and colleagues (2002) conducted a meta-analysis of available antidepressant trials using active placebos and found that the difference between antidepressants and active placebo was negligible, and was much smaller than in trials using inert placebos. Furthermore, unblinding still could not be ruled out entirely in the active placebo trials because of methodological limitations. Only more research will be able to provide definitive answers to these questions.

Therefore, contra some of the media "hype" on this topic, antidepressant research confirms an empirically demonstrated drug-placebo difference, although careful examination of this literature reveals that this difference is not nearly as large as most individuals believe, or as many of the pharmaceutical companies would have the public believe. Currently, the methodological problems with antidepressant trials preclude us from concluding definitively that the difference actually indicates specific biological effects of the drugs, as various nonspecific factors have not been adequately ruled out. Until these questions are answered, the media should
understand that placebos can be double-edged swords, and that "expectancy" effects can result in harm as well as benefit. In a piece on this topic for the Guardian, a UK newspaper, Jerome Burne (2002) reports that many subjects in Leuchter's trial (2002) relapsed and requested to be placed on the active medication after learning they were in the placebo arm. Vedantam's Washington Post piece is similar to other articles on this topic that have appeared in the popular press recently, in that it occasionally betrays an imbalanced presentation of the evidence. The media should continue to follow this complicated debate and report on it responsibly, making certain not to overhype the "power" of placebo and, as a consequence, the "powerlessness" of antidepressants.

References


