Exploring the Small Specific Effects of Antidepressants: Myth Busting or Misguiding the Public?

A review of

The Emperor’s New Drugs: Exploding the Antidepressant Myth
by Irving Kirsch
$23.95

Reviewed by
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In *The Emperor’s New Drugs: Exploding the Antidepressant Myth*, Irving Kirsch draws upon his research, including both laboratory-based studies of placebo expectancy effects and meta-analyses of randomized controlled trials (RCTs), to write an exposé about antidepressant medications. Aimed at the general public, this book makes a compelling case for the power of placebo expectancy effects and provides a concise, constructive summary of the major alternatives to taking antidepressants for people suffering from depression. Indeed, readers will gain new insights into the magnitude of the placebo response in illnesses as diverse as migraine, osteoarthritis, and coronary artery disease and, hopefully, will
appreciate that many people with “real” illnesses can obtain profound benefit from a placebo.

The findings of several relatively recent meta-analyses conducted by Kirsch and his colleagues, which demonstrated that the specific effects of antidepressants (i.e., the drug vs. placebo difference) are smaller than previously appreciated, provide a sound empirical basis for this book. In the most recent article, for example, which was based on 35 RCTs of newer generation antidepressants (Kirsch et al., 2008), the average effect favoring antidepressant drugs over placebo was only about 2 points on the Hamilton Depression Rating Scale (HAM–D), with the placebo accounting for almost 80 percent of the antidepressant’s efficacy.

However, Kirsch goes far beyond these data to reach the polemical conclusion that antidepressants actually have no specific efficacy, even discounting his own finding of larger effects in studies of more severe depression. To make this case, Kirsch posits that side effects can unblind studies and, as antidepressants almost always cause more side effects than placebo, the participants who receive the active drug will have higher expectancy for benefit (i.e., they can “see through” the blind).

To buttress this point, Kirsch cites the work of Moncrieff, Wessely, and Hardy (2004), who found that only two of nine studies comparing a tricyclic antidepressant with an “active” placebo, that is, one that causes side effects, found significant differences. However, he ignores the earlier review of Quitkin, Rabkin, Gerald, Davis, and Klein (2000), which concluded that “active” placebos do not have stronger effects than inert placebos. Rather, Quitkin et al. concluded that methodological issues—not amplification of the placebo response—explained the dearth of significant differences in this relatively small set of older studies.

Kirsch also places great weight on a secondary finding from an early meta-analysis of fluoxetine RCTs (Greenberg, Bornstein, Zborowski, Fisher, & Greenberg, 1994), noting a “Faustian” correlation ($r = 0.96$) between “side effects and improvement when taking Prozac” (p. 18). The source article revealed that this correlation is based on only four studies (i.e., four pairs of data points) and actually describes the relationship between the effect size (i.e., the standardized drug vs. placebo difference) on a patient-rated symptom measure and the percentage of patients in the fluoxetine group reporting any side effects.

Correlations based on such a small number of observations are inherently unstable, and there is a high risk of Type I error, particularly when one does not know how many different correlations were computed. It is important to note that the correlation coefficient doesn’t tell us that patients who experience side effects are more likely to respond to an antidepressant. Rather, this relationship is more likely to be curvilinear, with patients who experience the most severe side effects likely to drop out, with relatively little symptom improvement.

Consistent with this view, one recent meta-analysis reported that several of the modern antidepressants with heavier side effect burdens were less efficacious than were
antidepressants with better tolerability profiles (Cipriani et al., 2009). Sadly, it is likely that the most Faustian thing about that correlation is that, like the immortal fictional character of Marlowe’s and Goethe’s classics, it is an artifact.

Kirsch is on even thinner empirical ice when he tries to explain away the well-replicated finding that symptom severity moderates drug versus placebo differences. Specifically, he speculates that the more severely depressed also tend to be more chronically ill, and together these factors lead clinicians to prescribe higher doses, which in turn results in more side effects and further unblinding. The reader is not told that it is nonresponse, not initial severity, that drives upward dosing in RCTs that permit flexible titration; nor is it mentioned that approximately 40 percent of RCTs use fixed-dose protocols (i.e., upward titration is not permitted).

Kirsch either casually dismisses or simply ignores the areas of the treatment literature in which larger drug–placebo differences are consistently reported, such as the RCTs of the first-generation antidepressants conducted prior to 1980 or those of longer term antidepressant therapy (see, e.g., Geddes et al., 2003). Meta-analyses that document clinically important differences between different types of antidepressants in particular subgroups of patients are similarly ignored (Anderson, 1998; Quitkin et al., 1993; Thase, Trivedi, & Rush, 1995).

As announced by the book’s subtitle, one important aim of The Emperor’s New Drugs is myth busting, which may be incompatible with fairly evaluating alternate hypotheses. In this regard, the book does not seriously consider the most credible alternate explanation, namely that a small mean difference in studies of a disorder as heterogeneous as depression can result from a large effect in a clinically meaningful subset of that population.

For example, a 2-point mean difference in HAM–D scores observed in a meta-analysis actually can be explained by a large advantage (i.e., a 15 or 20 point HAM–D difference) among 10 to 20 percent of the participants (see, for example, Thase, Entsuah, & Rudolph, 2001; Thase et al., 2005, 2007). Although such differences in response or remission rates are still modest, they correspond to Numbers Needed to Treat ranging from 5 to 10, which are of sufficient magnitude to be considered clinically relevant by the National Institute of Clinical Excellence guidelines and the independent review groups such as the Cochrane Collaboration.

Likewise, The Emperor’s New Drugs pays little attention to the thorny methodologic issues that can undermine the assay sensitivity of RCTs and inflate placebo response rates. Not addressing these issues in detail is understandable: Topics such as interrater reliability and statistical power are of little interest to the general public and can even put researchers to sleep during conference presentations.

Nevertheless, it is a shame that the seminal work of Walsh, Seidman, Sysko, and Gould (2002), who found that the placebo response rate grew dramatically between 1980 and 2000, is not cited. As the chemical formulation of placebo has not changed, one must
conclude that temporal changes in study implementation and/or subject characteristics have eroded the precision of modern studies.

It is a good thing for people seeking treatment for depression, as well as for the professionals deciding how to best help them, to know that the specific effects of antidepressants are modest and that nonspecific factors—including the placebo effect—account for a large amount of the benefit of treatment. However, prescribing a placebo is not an ethical option for physicians, and, when treatment is indicated, the options for the vast majority are antidepressant medication, counseling or psychotherapy, or the combination of the two.

_The Emperor’s New Drugs_ makes a compelling case that the specific benefits of antidepressants have been overestimated and that other options may be better for some people. I wholeheartedly agree. However, as illustrated by a graph in the first chapter, the efficacy of psychotherapy in depression RCTs is almost identical to that of antidepressants, which likely means that the specific effects of psychotherapy are comparable to those of drugs.

In fairness, Kirsch does refer to psychotherapy as the “quintessential placebo” (p. 157) toward the end of the book. But, whereas this book tells us a lot about the unblinding of pharmacotherapy studies, the inherent “unblinding” of psychotherapy in comparative RCTs is only obliquely mentioned, and the impact of allegiance effects in psychotherapy studies (Gaffan, Tsaousis, & Kemp-Wheeler, 1995; Luborsky et al., 1999) is not discussed. Kirsch argues that psychotherapy is a preferable option because the active ingredient is learning new ways of coping and handling problems, yet he fails to acknowledge that the aggregate effects of placebo expectancy factors, unblinding, and therapeutic allegiance on psychotherapy outcome may be much more important to outcome than might be the actual strategies that are being learned.

In summary, _The Emperor’s New Drugs_ is thought provoking and offers the general public much useful information about the limitations of antidepressants, the power of the placebo effect, and the alternatives that are available for people who do not wish to take antidepressants. But this book would have been more valuable to the general public if Kirsch had not strayed in his myth-busting quest from the conclusion that is best supported by the data, namely that antidepressants have relatively small specific effects in contemporary RCTs.

For a condition as common as depression, even a modest average benefit can improve the lives and lessen the suffering of millions of depressed people. Antidepressants have large, life-saving effects for some people, and, as Kirsch and others have found, the more severe the depression, the greater the specific advantage of the active medication over that of a placebo.
References


depressives with better response to MAOI than to tricyclic antidepressants or placebo.

*The British Journal of Psychiatry*, (Suppl. 21), 30–34.


*Disclosure:* Michael E. Thase reports that he has had income-earning relationships with the manufacturers of almost every new medication introduced for the treatment of depression or bipolar affective disorder since the introduction of fluoxetine (Prozac), which was approved by the U.S. Food and Drug Administration for the treatment of depression in late 1987. These relationships have included honoraria for giving talks, consulting, and attending advisory boards, as well as research grants.