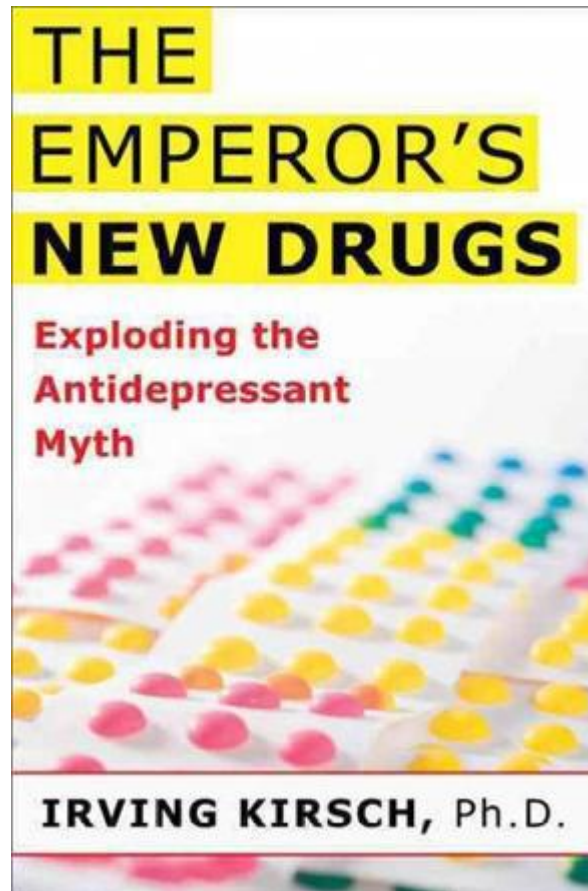


Placebo Versus Antidepressant
Review: *The Emperor's New Drugs: Exploding the Antidepressant Myth*
By Floyd E. Bloom, M.D.



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Review available online at <http://dana.org/news/cerebrum/detail.aspx?id=28024>

The first-century Roman statesman Seneca asserted that “The wish for healing has always been half of health.” In this short book—20 percent of the small pages are notes and references—the American psychologist Irving Kirsch tells us how he went from being a believer in the effectiveness of antidepressants to an extreme skeptic of the view that these drugs were anything more than expensive placebos replacing the snake-oil salesman’s wares. To quote his

statement on The Huffington Post, “Depression is not a brain disease, and chemicals don’t cure it.”¹

The author’s early scientific publications had two focuses: the role of “expectancy” (the mental state of expecting an event) in research subjects participating in attempts to induce hypnotic trances, and the ability to predict who was most susceptible to such inductions. Before becoming a critic of psychopharmacology, Kirsch dealt with clinical hypnosis in his two previous books. Kirsch, who now resides in Hull, U.K., began to question the consensus acceptance of antidepressant utility when he and a colleague performed a meta-analysis of 38 published, placebo-controlled clinical trials of antidepressants. They concluded that the proportion of patients responding to the placebo were 75 percent of those showing a drug response, that there was a very high correlation between drug response and placebo response, and that “virtually all variation in drug-effect size was due to the placebo characteristics of the studies.” In other words, they concluded that the outcomes stemmed not from the therapeutic effect of the drugs but from the placebo effect that such patients express.

This analysis was published in the American Psychological Association journal *Prevention and Treatment*, which existed only from 1998 to 2003. The Kirsch paper was published with a note from the editor stating that the article was controversial in its claim that the therapeutic benefit of antidepressants derives from the placebo effect. The editor warned that the studies selected were heterogeneous in subject-selection criteria and the treatments employed and used “clearly arguable” statistical methods. Undaunted by such criticism, Kirsch has published, republished, and expanded his claims with even larger meta-analyses of unpublished new-drug filings to the Food and Drug Administration. At least 35 of his articles listed in PubMed refer to these data, which strengthened his convictions that antidepressants work only as placebos and led to his conclusion in this book that the only effective therapy available for patients who are depressed is cognitive behavioral therapy.

I point this out because despite public criticisms of his views, Kirsch retains a highly selective attitude toward the pertinent biomedical literature. By obsessing over clinical data only from short-term trials submitted to the FDA to support the approval of new commercial drugs, he misses an extremely rich collection of highly replicated findings. This overlooked research demonstrates repeatedly that antidepressants work effectively for a large, but certainly not

universal, group of patients, and that they produce remissions and greatly lengthen the time between recurrences of depression.

As John Rush, University of Texas Southwestern Medical Center, has pointed out, patients who volunteer for randomized clinical trials designed to demonstrate that new drugs are as effective as older drugs are not typical patients with unipolar major depressive disease whom doctors encounter in clinical practice.² Participants in the trials are often merely symptomatic volunteers, not necessarily previously diagnosed as depressed and not previously treated unsuccessfully with at least one other antidepressant.

In 1965, Gerald Klerman and Jonathan Cole, then at the National Institute of Mental Health, completed the first comprehensive review of the clinical pharmacology of the two original antidepressant medications, tricyclic antidepressants (named for their chemical structure; how they worked was unknown at the time) and monoamine oxidase inhibitors (named for the enzyme such drugs were discovered to inhibit during anti-tuberculosis trials). They reported that in the first four placebo-controlled trials of imipramine (a tricyclic antidepressant) lasting four or more weeks, 54 to 78 percent of treated patients significantly improved, versus 16 to 41 percent of patients who received a placebo. They also observed that “patients under 40 and those with predominantly neurotic depressions have a very high placebo response rate.” Last, they reported that in inpatient studies of newly hospitalized patients, 62 percent of 269 depressed patients who received antidepressants improved while only 46 percent of 199 placebo-treated patients improved. In chronically hospitalized depressed patients, 60 percent of 58 imipramine-treated patients improved, compared with 16 percent of 64 placebo-treated patients.³

It’s not that the high placebo responses Kirsch has repeatedly reported were new or unrecognized. Klerman and Cole noted in their review that “there is some evidence that depressed patients are affected by the attitudes of their doctors towards these drugs, and some evidence that the patient’s expectations influence his response to placebo.”⁴ In the classic textbook of medical therapeutics, Ross Baldessarini has noted that “a major problem with antidepressants is that ... placebo response rates tend to be as high as 30 percent to 40 percent among research subjects diagnosed with major depression” and that “separation of response rates to active antidepressants from placebo improves when patients are selected for moderate but not extreme severity, presence and persistence of classic melancholic ... symptoms, and absence of bipolar states.”⁵

Furthermore, Kirsch does not cite the important observations of B. Timothy Walsh and colleagues at Columbia University, who noted a progressive increase in the proportion of placebo responders in efficacy trials of antidepressants in the past 25 years, perhaps due to the pressures on researchers to recruit patients via advertisements and enroll them quickly.⁶ Similarly, Kirsch neglects the report of FDA-submitted data by Arif Khan, Northwest Medical Research Center, and colleagues (although he cites later data from them), who have observed that when researchers are allowed to use flexible doses rather than fixed doses of antidepressants in FDA efficacy trials, 60 percent of studies showed significantly better results in patients who received antidepressant treatment than in patients who received a placebo.⁷

Kirsch also ignores the data of Martin Keller and colleagues at Brown University, who found that a selective serotonin reuptake inhibitor, sertraline, afforded “significantly greater prophylaxis against recurrence (of depression) than did placebo.” That report concluded that “maintenance therapy with sertraline is well tolerated and has significant efficacy in preventing recurrence or re-emergence of depression in chronically depressed patients.”⁸ In fact, Kirsch seems unaware of the conclusion of colleagues he does cite, Andrea Cipriani and Corrado Barbui, University of Verona, (chapter 4, citation 30, a paper never published), whose research review suggested “that sertraline might be a strong candidate as the initial choice of antidepressant in people with acute major depression.”⁹

In short, despite media attention¹⁰ and potential appeal to people who lack medical training, the book misses the mark. New antidepressants are effective, and depression is a real and serious disabling illness with high global prevalence and high rates of recurrence and chronicity. The search for new drugs will continue, but not because of Kirsch’s short-sighted analyses.

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