

Prevention & Treatment

Prevention & Treatment, Volume 5, Article 24, posted July 15, 2002
[Copyright 2002 by the American Psychological Association](#)

Commentary on [The Emperor's New Drugs: An Analysis of Antidepressant Medication Data Submitted to the U.S. Food and Drug Administration](#)

Antidepressants and Placebos: Conceptual Problems and Research Strategies

John D. Salamone
University of Connecticut

ABSTRACT

The work of [I. Kirsch, T.J. Moore, A. Scoboria, & S.S. Nicholls \(2002\)](#) has focused attention on the relatively small effect size of antidepressant drug treatment and has stimulated additional debate about the therapeutic utility and scientific importance of these drugs. Nevertheless, it is important not to exaggerate the claims of minimal effect size, and it is vital not to ignore that some people may be helped substantially by antidepressants. Moreover, it is extremely weak to claim that psychotherapy cannot be studied relative to control conditions that are comparable to placebos. In the present commentary, depression is discussed in terms of neurochemical systems that promote interaction with the environment, and this view allows for recognition of the importance of environmental stimulation, placebo effects, and drug actions.

Correspondence concerning this article should be addressed to John D. Salamone, University of Connecticut, Storrs, Connecticut 06269-1020.
E-mail: salamone@psych.psy.uconn.edu

The work of [Kirsch, Moore, Scoboria, & Nicholls \(2002\)](#) has focused attention on the relatively small effect size of antidepressant drug treatment and has stimulated additional debate about the therapeutic utility and scientific importance of these drugs. Nevertheless, it is important not to exaggerate the claims of minimal effect size, and it is vital not to ignore that some people may be helped substantially by antidepressants. Moreover, it is extremely weak to claim that psychotherapy cannot be studied relative to control conditions that are comparable to placebos. In the present commentary, depression is discussed in terms of

neurochemical systems that promote interaction with the environment, and this view allows for recognition of the importance of environmental stimulation, placebo effects, and drug actions.

In reading [Kirsch, Moore, Scoboria, & Nicholls's \(2002\)](#) article and the accompanying introductory comments, I feel very conflicted. On the one hand, I feel as though Kirsch and his colleagues are emphasizing a very important point about antidepressant drugs, one that is often overlooked. The effect size of these compounds is quite small. This is something that is noted and sometimes remarked on by clinicians familiar with this area. Yet, this is not something that is generally emphasized in the literature, and this point has not been central to most of the scientific debates about antidepressant drugs, which have instead tended to focus on issues such as which neurotransmitters were involved and which mechanisms mediated the long therapeutic latency. If Kirsch and his colleagues have made any contribution, it has been to hammer away at the central point of minimal effect size. This has, to a certain extent, put many people on the defensive and has stirred debate both in the scientific literature and in the popular press. In this sense, Kirsch et al.'s work has made an enormous contribution.

On the other hand, I cannot escape the feeling that some of [Kirsch et al.'s \(2002\)](#) claims and implications are exaggerated and that some of his points are overly simplistic or misleading. Moreover, it appears to me as though this pattern of polemical exaggeration is taking place in the context of the evolution of the "placebo" issue from a scientific debate into a sort of political campaign. Currently, there are several political forces at play within psychology and psychiatry, including debates about prescription rights for psychologists, insurance reimbursements, and the utility of various models, including the "medical model," for therapeutic interventions. In the wake of the psychopharmacology revolution of the last five decades, we appear now to be in the midst of a backlash. Amidst all of these swirling political forces, coupled with the popular press attention to this issue, I fear that some of the essential scientific points are being underemphasized or lost. My fears are not at all lessened by the title of the article, which begins "The Emperor's New Drugs." This title appears to be directed more at the popular press than at the scientific community, and I hope that such things will be avoided in the future.

At any rate, there are several scientific points identified by [Kirsch et al. \(2002\)](#) that need to be discussed. Kirsch and his colleagues note that, in the clinical trials studied, improvement at the highest doses of antidepressant medication was not different from improvement at the lowest doses. My response to this observation is that clinical trials are actually constructed to identify effective treatments and doses but not to determine dose relatedness in a scientific manner consistent with the principles of pharmacology. If they were, we would consistently see clinical trials with six or seven doses, varying over several log units. One rarely sees true dose-response curves and ED50s generated in clinical studies. Most dose-response curves are sigmoidal or hyperbolic, or even quadratic, in shape. Thus, clinical trials would only yield dose-related data if several doses were selected to be in the ascending, linear portion of the dose-response curve. If the doses are instead spanning a few points in the portion of the curve near the maximal effect, then these studies will yield more information about the therapeutic window of action than they will about dose relatedness. Although this may be a scientific limitation of clinical trials, I do not understand this criticism in the context of Kirsch et al.'s overall argument. Surely, even if one believes that antidepressant drugs are merely "active placebos" that elicit only such mundane actions as dry mouth, one would still expect that this dry mouth effect would be dose related.

[Kirsch et al. \(2002\)](#) emphasize the low effect size of antidepressant drugs, they report the average effect size of placebo to be about 80% of the effect size for antidepressant drugs (a figure equivalent to saying that the drug effect is 25% larger than placebo; $10 / 8 * 100 = 125$). Overall, they judge the effect of antidepressants to be statistically significant but "clinically meaningless" (§ 26). As I stated above, it is important to emphasize the minimal effect size of antidepressants. Yet, I also feel it is important not to overinterpret these findings. For example, it seems too easy to slide from identifying the small effect size to implying that there is no effect at all. It seems an exaggeration to state, even hypothetically, that the therapeutic effects of antidepressants "are duplicated or masked by placebo" (§ 23). That is not what Kirsch et al.'s own data show in detail. What happened to qualified statements such as "mostly duplicated" or "largely masked"? It may be careless to leave out such qualifiers, or it may reflect the gentle slide from scientific hypothesis to expectancy to belief to subtle propaganda. In addition, amidst all the statements about these drug effects being clinically meaningless, I notice that there are no references for these statements and no validation or serious discussion of this point. What is the basis of this judgment? Is it Kirsch et al.'s opinion as experienced clinicians? What about the opinions of clinicians who feel otherwise? It can be argued that the small effect sizes at which Kirsch and his colleagues scoff may make a difference for some individual people with depression. Another point is that, whereas the average effect sizes may indeed be small, there may be individual variability, meaning that some people will receive little or no benefit while others will have a more substantial therapeutic effect. Magnified across the whole population, this of course would mean that, despite their shortcomings, antidepressant drugs do help many thousands of people. In view of reports indicating that antidepressant effects are somewhat persistent, as compared with the more transient effects of placebos ([Quitkin, 1992](#)), this suggests that the overall benefit of antidepressant drugs, if prescribed properly, is not as meaningless as Kirsch et al. would suggest. Given the difficulty of treating depression, it is reasonable to suggest that antidepressant drugs should continue to be used as a therapeutic tool, while at the same time, the limits of this tool should be recognized.

I have a substantial problem with the notion, raised in [Kirsch's \(2002\)](#) introductory article ("Yes, There *Is* a Placebo Effect, but Is There a Powerful Antidepressant Drug Effect?"), that the concepts of "placebo" or "placebo effect" are clear only when defined in terms of pharmacological substances. [Kirsch \(2002\)](#) states that "it is only when attempts are made to extend the concept to psychotherapeutic procedures that great difficulties are encountered" (§ 6). To me, this is a thinly veiled and rather weak attempt to mount a smoke screen designed to protect psychotherapy from the scientific scrutiny that drug therapies must face. This smoke screen is rather convenient in view of the publications suggesting that psychotherapies rarely demonstrate themselves to be more successful than the control treatments that Kirsch wants us to ignore. As reported by [Prioleau, Murdock, and Brody \(1983\)](#), studies of psychotherapy that have used placebo controls have reported that several types of behavioral activities (e.g., organized reading or discussion sessions, viewing films, playing with puzzles) can generate placebo effects comparable in size to various psychotherapeutic interventions. These data need to be considered in parallel with the examination of the placebo effect in pharmacology.

As I have stated several times, it is reasonable for Kirsch to be so persistent in his emphasis of the small effect size of antidepressant drugs. Another positive aspect of the [Kirsch et al. \(2002\)](#) article is the discussion of the possible additivity or nonadditivity of drug and placebo effects. Kirsch and his colleagues suggest several possible strategies for future research. Indeed, one of the positive things about the present debate is that it will probably stimulate a new generation of research in this important area. I would add a few more

suggestions to the things Kirsch et al. have already said. In the past, there has been some confusion about which drugs would be useful as "active placebos." Such drugs are designed to be therapeutically inactive compounds that induce side effects, such as dry mouth or constipation, that can be identified by patients. The inclusion of such compounds is useful because it prevents the patient from easily breaking the blind in their experiment by simply discriminating between two choices (i.e., either placebo, with no effects, or drug, which has some effect). Some of the past confusion has occurred because many of the drugs that have been labeled as "active placebos" may in fact have therapeutic effects as antidepressants ([Salamone, 2001](#)). This confusion might be avoided in the future by specifically including drugs that do not penetrate the brain readily but do produce peripheral side effects, as active placebos. These possible drug tools would include peripherally acting antihistamines or peripheral anticholinergics such as methylscopolamine.

Another important research tool would be the limited use of drugs that are thought to induce or exacerbate symptoms of depression. This would include the monoamine storage blocker reserpine or inhibitors of monoamine synthesis. Although there are ethical problems with the use of these drugs on depressed patients, the research could be of substantial benefit, and some research on depression has already been done with these compounds. Such drugs would be useful to include as control compounds in some clinical studies or trials. The value of these drugs is that they would demonstrate the nonarbitrary nature of the direction of the effect of antidepressant drugs. In other words, the inclusion of such drugs could demonstrate, in the context of a clinical trial or study, that simply being on some drug that produces side effects does not produce an antidepressant effect, because some drugs would actually produce an effect on depression in the opposite direction (i.e., worsening of symptoms).

Although the neuropharmacology of depression is quite complicated, progress is being made in identifying potential mechanisms for the therapeutic action of antidepressants. An excellent example is the work of [Miller et al. \(1996\)](#), who studied the effects of catecholamine synthesis inhibition on the therapeutic actions of antidepressants that act on norepinephrine and serotonin. They observed that inhibition of catecholamine synthesis reduced the antidepressant effect of a norepinephrine uptake blocker but did not affect the antidepressant action of a serotonin uptake blocker. Moreover, they used an active placebo to control for the side effects produced by inhibition of catecholamine synthesis. These results need to be extended by examining the effects of serotonin synthesis inhibition to determine whether there is a double dissociation effect. This line of work is important because it provides evidence for the relative independence and dissociability of the diverse mechanisms through which various antidepressants exert their effects. We may eventually come to an understanding of how various neurotransmitters, including norepinephrine, serotonin, dopamine, and acetylcholine, are involved in distinct aspects of emotion, motivation, and cognition that are related to depression.

Ultimately, all this research points to the difficulties in treating depression as well as to our fundamental lack of understanding, despite years of research, of the basic neurochemical correlates of this disorder. In addition, the debate about antidepressant drugs and placebo effects challenges us to revise how we think about the neurochemical effects of drugs, the responsiveness of neurochemical systems to environmental challenges, and the relation between the two. Fundamentally, all conditions that have an effect on depression, whether they are drug treatments, psychotherapies, inert pills, or placebo behavioral treatments, must have some action on the brain. Recent scanning evidence indicates that placebo treatments can affect neurotransmitter release within the brain ([de la Fuente-Fernandez et al., 2001](#)).

Considerable research with animals indicates that environmental conditions such as stressors, or various behavioral treatments, can have profound effects on neurotransmitter release (see review by [Salamone, 1996](#)). My view of depression is that it is fundamentally a problem with the process of interaction with the environment, including dysfunctions in the responsiveness to stressors and alterations in the activating effects of stimuli. For example, with the psychomotor slowing that is seen in some people with depression, there is probably a complex behavioral/ neurochemical feedback loop between the activational effects of stimuli and release of neurotransmitters such as dopamine, which facilitates activational aspects of motivation ([Salamone, 1996](#)). The depressed person with psychomotor slowing may be caught in a cycle in which dopaminergic function may be altered; thus, there is reduced behavioral activation, and less interaction with the environment, and in turn, less opportunity to encounter invigorating stimuli or conditions with positive valence. Is such a feedback system "behavioral," or is it "neurochemical"? Is such a distinction, in an absolute sense, even valid? It is possible that many depressed people are helped by environmental stimulation of various sorts because it breaks the pattern of this cycle. Indeed, the fact that conditions as diverse as placebos, psychotherapy, and organized reading or discussion sessions can have some effect in depressed patients seems to suggest that various forms of restructuring of the environment, or environmental stimulation, can have a positive effect. Perhaps, just being in a clinical trial, even in a control group, is essentially a form of environmental stimulation that itself could have some minimal therapeutic effect. It is possible that antidepressant drugs do all this plus, in some people, a bit more by affecting the regulation of the neurotransmitter systems that normally are involved with various forms of behavioral, emotional, or cognitive response to environmental stimuli. In this view, antidepressant drugs are neither the panacea for depression nor the quackery suggested by the phrase "the emperor's new drugs."

References

de la Fuente-Fernandez, R., Ruth, T. J., Sossi, V., Shulzer, M., Calne, D. B., & Stoessl, A. J. (2001). Expectation and dopamine release: Mechanism of the placebo effect in Parkinson's disease. *Science* 293, 1164-1166.

Kirsch, I. (2002). Yes, There *Is* a Placebo Effect, but Is There a Powerful Antidepressant Drug Effect? *Prevention & Treatment*, 5, Article 22. Available on the World Wide Web: <http://www.journals.apa.org/prevention/volume5/pre0050022i.html>

Kirsch, I., Moore, T. J., Scoboria, A., & Nicholls, S. S. (2002). The emperor's new drugs: An analysis of antidepressant medication data submitted to the U.S. Food and Drug Administration. *Prevention & Treatment*, 5, Article 23. Available on the World Wide Web: <http://www.journals.apa.org/prevention/volume5/pre0050023a.html>.

Miller, H. L., Delgado, P. L., Salomon, R. M., Berman, R., Krystal, J. H., Heninger, G. R., & Charney, D. S. (1996). Clinical and biochemical effects of catecholamine depletion on antidepressant-induced remission of depression. *Archives of General Psychiatry* 53, 117-128.

Prioleau L., Murdock, M., & Brody, N. (1983). An analysis of psychotherapy versus placebo studies. *Behavioral and Brain Sciences* 6, 275-310.

Quitkin, F. M. (1992). Methodology of measuring the efficacy of antidepressants.

Psychopharmacology 106, S87-S89.

Salamone, J. (1996). The behavioral neurochemistry of motivation: methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine. *Journal of Neuroscience Methods* 64, 137-149.

Salamone, J. (2001). A critique of recent studies on placebo effects of antidepressants: Importance of research on active placebos. *Psychopharmacology* 152, 1-6.