

Antidepressants: Do They "Work" or Don't They?



Question: Are antidepressants effective or ineffective?

Answer: Yes!

In my view, both these statements are true: Antidepressants do work. And antidepressants don't work. Not to put too fine a Clintonian point on it, but determining whether antidepressants work depends on the definition of the word "work."

A [controversial article](#) just published in the prestigious Journal of the American Medical Association concluded that [antidepressants](#) are no more effective than placebos for most depressed patients. Jay Fournier and his colleagues at the University of Pennsylvania aggregated individual patient data from six high-quality clinical trials and found that the superiority of antidepressants over [placebo](#) is clinically significant only for patients who are very severely depressed. For patients with mild, moderate, and even severe depression, placebos work nearly as well as antidepressants.

There have been at least four other [review articles](#) published in the last eight years that have come to similar conclusions about the limited clinical efficacy of antidepressants, and one of the study authors, psychologist [Irving Kirsch](#), has recently published a book on the topic, provocatively entitled *The Emperor's New Drugs: Exploding the Antidepressant Myth*.

The recent review articles questioning the clinical efficacy of antidepressants run counter to the received wisdom in the psychiatric community that antidepressants are highly effective. Indeed, it wasn't so long ago that psychiatrist Peter Kramer wrote in his best-selling book *Listening to Prozac* that this miracle drug made patients "better than well." Prozac was a Rock Star. Its extraordinary success even led to a photograph of the green and white capsule on the cover of *Newsweek Magazine* in 1990.

The essential facts about antidepressant efficacy are not in dispute. In double-blind, randomized controlled trials – meaning that patients are randomly assigned to receive either drug or placebo, and neither patient nor clinician knows who gets what – antidepressants show a small but statistically significant advantage over placebos. The debate is over the interpretation of these findings, and it revolves around the distinction between clinical significance and statistical significance.

Statistical significance means that an effect is probably not due to chance and is therefore likely to be reliable. But statistical significance says nothing about the magnitude of the effect or its practical implications. Clinical significance indicates the degree to which an effect translates to a meaningful improvement in symptoms for patients. Although the superiority of antidepressants over placebos has been shown to be statistically significant, the observed differences are not clinically significant. In fact, the average difference between drug and placebo is approximately two points on a depression scale that ranges from 0 to 52. This difference does not exceed the [commonly accepted standard](#) for a minimally significant clinical improvement of a 3 point improvement on the depression scale.

But what of the testimonials from patients and their doctors reporting dramatic relief of symptoms in response to antidepressants? Such reports really aren't in conflict with the data from randomized controlled trials. In clinical trials, patients treated with antidepressants do show substantial improvement from baseline. However, the clinical trial data also show that patients treated with placebos improve about 75% as much as patients treated with antidepressants, suggesting that only a quarter of the improvement shown by patients treated with antidepressants is actually attributable to the specific effect of the drugs. The rest of the improvement is a placebo response. In clinical practice, of course, there is no placebo group, and therefore patients and their doctors are likely to attribute all symptom improvement to the medication.

What seems clear from double-blind, randomized controlled trials is that antidepressants are, on average, only marginally superior to placebos. One might reasonably ask, however, whether there might be a sub-set of patients for whom antidepressants are

highly effective. This is certainly possible, but to date no one has been able to reliably predict which subset of patients will respond best.

Moreover, because average antidepressant efficacy is small and not clinically significant, if there is a sub-set of patients for whom antidepressants are highly effective, there must also be a sub-set of patients for whom antidepressants have no effect, or are even [harmful](#). In addition, since pharmaceutical companies are now the major sponsors of [drug trials](#), and they have an interest in maximizing the number of people for whom their medications can be prescribed, they have little interest in performing any trials whose aim would be to identify such sub-sets of patients. To do so would risk reducing their profits.

Some have suggested that critics of antidepressant efficacy should keep quiet and not publicize their work. The reasoning is that if the effectiveness of antidepressants depends in large part on the faith of patients and their doctors, then publicizing the fact that antidepressants appear to have only minimal efficacy as compared to placebos will have the practical effect of harming patients. But this is putting our heads in the sand. The history of medicine is littered with treatments initially thought effective that we now know to be ineffective at best and actually harmful at worst (For example, bloodletting contributed to the death of George Washington). To ignore the evidence, is to return to a pre-scientific form of medicine. In the long run, this will not be beneficial to patients.

So what's the bottom line? In clinical practice, many people suffering from depression improve after taking antidepressants. But the evidence indicates that much of that improvement is a placebo response. Antidepressants do work in the sense that many patients in clinical practice show substantial improvement. However, if the standard is efficacy in comparison to placebo, the best available scientific evidence suggests that antidepressants do not work very well. Given their cost and side effects, the psychiatric community and the general public should not be satisfied with antidepressant medications that provide only a marginal benefit over placebo.

Indeed, as early as 1994, Brown University School of Medicine psychiatrist Walter Brown suggested treating mild to moderately depressed patients with placebos for an initial 4-6 week period, and then switching to active medications if patients did not improve. To surmount ethical concerns, Brown proposed prescribing placebos openly by informing patients that clinical trials showed that many depressed patients improved after being treated with placebos, and asking whether they would like to try a placebo initially. It's been sixteen years since Brown offered up his radical prescription for harnessing the placebo effect in the treatment of depression. Is it time to fill the prescription?

