

Antidepressants: Can't Live With Them, Can't Live Without Them

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A new wave of meta-analyses suggests that antidepressants are no better than placebo for major depressive disorder (MDD), and therefore, antidepressants not only don't work, but even worse, they harm patients because of the risk of adverse effects. The authors¹⁻³ analyzed data from all antidepressant studies submitted to the Food and Drug Administration for registration (including failed studies with inordinately high placebo responses), or used a metanalysis filter and selected those few studies that meet those criteria. In aggregate, the data, at best, show a clinically trivial advantage of the antidepressants over placebo in acute randomized trials. However, their conclusions range from antidepressants don't work at all to the antidepressants should be reserved only for the most seriously depressed patients. Kirsch is capitalizing on this trend with his recently published book. I view this debate through my perspective of over 25 years of clinical experience, serving as a rater for clinical trials, planning and conducting National Institute of Mental Health and industry efficacy and effectiveness clinical trials, and consulting to the pharmaceutical industry. The real story, I believe, is a bit more complicated.

Give everyone with fever penicillin and many will improve. Compare penicillin to placebo and on average, you would find no difference. Why? Most people with fever have viral infections or non-penicillin sensitive bacterial infections that are time limited (eg, common upper respiratory infections). One could reasonably conclude that penicillin doesn't work and we should all take chicken soup instead.

Give everyone with MDD an antidepressant and many will improve. Compare any given antidepressant to placebo and on average, you should find no difference. Yet, a difference does exist and even if the trials have an overall small effect size in favor of antidepressants, it is not quite accurate to state that antidepressants are equal to placebo. Why? If that were true, then in a third of the trials placebo would beat antidepressants, in a third of the trials antidepressants would beat placebo, and the remaining third of the trials it would be a tie. MDD is analogous to fever. It is a heterogeneous, nonspecific syndrome that is the final common pathway of multiple dysregulated psychological and brain processes. Genetic epidemiological studies strongly suggest that stress is a causal factor and that the persistence or recur-

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rence of the syndrome is a hallmark of the disorder for those who are vulnerable to develop depression. MDD is associated with persistent dysfunction or recurrent episodes, and is distinct from a time-limited, stress-induced adjustment reaction with the same symptoms.⁴ For an adjustment reaction, take away the stress and the depression lifts. For MDD, take away the stress and the depression persists. Furthermore, MDD is usually accompanied by other psychiatric disorders, especially anxiety and other medical disorders,^{5,6} with an increased risk of death from all causes,⁷ especially cardiovascular diseases. In fact, MDD is associated with decreased heart rate variability and for those who are post-myocardial infarction, MDD is as potent a predictor of poor outcomes.⁸⁻¹⁰

Why am I stating the obvious that MDD is a real disorder with serious burdens on patients and their families? Because the meta-analysis, while provoking a useful debate, risks trivializing the disorder, and mistakes the inherent inefficiencies and difficulties of conducting clinical research for proof of absence of efficacy of treatments.

So what are the challenges of finding an effect of antidepressants if an effect actually exists?

Challenge #1: Participants. Why do people participate in clinical trials and who are they? Everything we know from clinical trials depends on the good will and courage of participants. People have many motivations to participate including to get a systematic evaluation, to obtain treatment, to provide a larger altruistic meaning to their disorder by helping others, or to gain financially if they are paid. Furthermore, the group that is willing to take placebo and meet inclusion and exclusion criteria is different than the group that presents for treatment.¹¹ Many participants are eager to please and some report their symptoms enthusiastically, especially at the beginning of a trial.

Challenge #2: Raters. The data analyzed originates from raters who meet with participants and generate scores on depression rating scales. With the pressure to meet recruitment goals, raters routinely err on the side of inflating baseline ratings to meet minimal rating scale entry criteria scores. As the study progresses, the raters have less pressure to inflate the scores and all scores have a tendency

to drop, showing a false placebo response.¹² Some raters are also pressured for time and rush their ratings so that the scores lack precision. Studies have found that these rushed raters are unable to distinguish active drugs from placebo while those raters who take more care can. These phenomena have become so widespread that an industry has arisen to provide remote or computerized ratings to solve these problems (see MedAvante and Concordant Rater Systems). Given these challenges, it is surprising that an effect of antidepressants can be found at all.

In the same month that Fournier and colleagues published their meta-analysis, another paper showed that most people with MDD don't get adequate treatment with antidepressants.¹³ It's like the old joke of two people at a hotel: one complains that the food is bad and the other complains that the portions are too small. **CNS**

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