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Before You Quit Antidepressants...

By Richard A. Friedman, M.D.

Last week, The Journal of the American Medical Association published a study questioning the effectiveness of antidepressant drugs. The drugs are useful in cases of severe depression, it said. But for most patients, those with mild to moderate cases, the most commonly used antidepressants are generally no better than a placebo.

For the millions of people who take these drugs, and the doctors who prescribe them, this provocative claim had to be confusing, if not alarming. It contradicted literally hundreds of well-designed trials, not to mention considerable clinical experience, showing antidepressants to be effective for a wide array of depressed patients.

But on close inspection, the new study does not stand up to that mountain of earlier evidence. To understand why, it helps to look at the way it was conducted.

The study is a so-called meta-analysis — not a fresh clinical trial, but a combined analysis of previous studies. A common reason for doing this kind of analysis is to discover potential drug effects that might have been missed in smaller studies. By aggregating the data from many studies, researchers gain the statistical power to detect broad patterns that may not have been evident before.

But meta-analyses can be tricky. First, they are only as good as the smaller studies they analyze. And when there are hundreds of studies out there, how to decide which ones to include?

For the recent analysis in the journal, the authors identified 23 studies (out of several hundred clinical trials) that met their criteria for inclusion. Of those 23, they could get access to data on only 6, with a total of 718 subjects. Three trials tested the antidepressant Paxil (a selective serotonin reuptake inhibitor, in the same class as Prozac and three used an older drug, imipramine, in the class known as tricyclics.

That is not many studies if your goal is to answer a broad question about the efficacy of antidepressants as a class. Indeed, as Robert J. DeRubeis, a professor of psychology at the University of Pennsylvania who is one of the new paper's authors, told me, "Of course, we can't know that these results generalize to other medications."

Admittedly, it is not easy to find studies that include large numbers of people with mild to moderate depression; most trials focus on severely ill patients. But the authors of the new analysis gave themselves an additional handicap: they decided to exclude a whole class of studies, those that tried to correct for the so-called placebo response.

Researchers argue all the time about which patients to include in a study. Antidepressant studies come to such different conclusions partly because patient characteristics vary so widely.

Many patients with depression — as many as 50 percent, in some studies — get better with no drug at all, just a placebo pill and attentive treatment by a therapist. For that reason, researchers often design their studies to exclude such people, to determine whether the drugs are working independent of any placebo response.

An analysis that eliminates such studies is bound to show a comparatively small average

difference between drug treatment and placebo treatment. Not surprisingly, this is just what happened in the recent analysis. But in randomized clinical trials[1] that try to correct, or wash out, the placebo effect, patients with mild to moderate depression respond to antidepressants at rates nearly identical to patients with severe depression (who tend to have a much lower response to placebos).

Another drawback of the study is that its conclusions are based on studies that included only two antidepressants — when there are 25 or so on the market. By contrast, when the Food and Drug Administration wanted to investigate the safety of antidepressants, it analyzed data from some 300 clinical trials, with nearly 80,000 patients, involving about a dozen antidepressants.

Antidepressants are not interchangeable; studies show that a patient who fails to respond to one has about a 30 percent chance[2] of responding to another.

Still, antidepressants are not panaceas, and their advocates have sometimes been overly optimistic about their efficacy. Only about 35 percent of depressed patients will achieve remission with the first antidepressant they receive. But with sequential treatments, most can expect to feel a lot better.

And the real test of an antidepressant is not just whether it can lift someone out of depression; it is whether it can keep depression from returning. For a vast majority of people with depression, the illness is chronic. Relapses and low-level symptoms between episodes are common.

Scores of studies show that antidepressants are highly effective in preventing relapse; on average, the risk of relapse in patients who continue on an antidepressant is one-half to one-third of those who are switched to a placebo.

Every once in a while, a landmark study comes along and overturns everyone's cherished ideas about a particular treatment. But the current study is not one of them. So it would be a shame if it discouraged depressed patients from taking antidepressants.

Experts may disagree about what constitutes the best treatment for depression, and for whom. But there is no question that the safety and efficacy of antidepressants rest on solid scientific evidence.

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