Prozac vs. Placebos

A new study concludes that America’s favorite antidepressants are little better than sugar pills. Have the drugs been overhyped? It’s not that simple

By David Noonan and Geoffrey Cowley

July 15 issue — Over the past 14 years, millions of Americans have escaped the debilitating and sometimes lethal grip of depression with the help of a handful of popular drugs, including Prozac, Zoloft and Paxil. This new generation of antidepressants, decidedly safer and easier to use than the medications they replaced, offered welcome relief to a wide variety of patients and racked up billions in sales.
AS THE PILLS changed lives and even saved them, they became part of the cultural landscape, inspiring countless articles, books and talk-show segments. Today more than 7 million Americans take these drugs for depression, and the number is still climbing. All of which leaves Irving Kirsch unimpressed. Indeed, according to Kirsch, the author of a forthcoming study of antidepressants titled “The Emperor’s New Drugs,” America’s favorite pills “may have no meaningful pharmacological effect at all.”

Anti-drug zealots have said that for years, but Kirsch is a scientist, and he has data to back his assertion. Prozac and its cousins—the so-called SSRIs—are all thought to work by boosting the effects of the neurotransmitter serotonin (and in some cases norepinephrine). Is it possible that all this chemical manipulation is unnecessary—that people feel better on these drugs simply because they think they will? In hopes of finding out, Kirsch, a psychologist at the University of Connecticut, pooled data from 38 studies on six drugs approved by the Food and Drug Administration between 1987 and 1999 (the three above, and Serzone, Celexa and Effexor). The studies were placebo-controlled clinical trials in which some depressed patients were given actual drugs while others got pills with no active ingredients. The studies didn’t show any lack of effect. In fact, the patients improved markedly. The problem is that people who got placebos fared almost as well as those getting real drugs. On average, people on placebos enjoyed an eight-point improvement on the 50-point Hamilton Depression Scale, while those on medication managed a 10-point improvement.
It’s no secret that placebos can ease depression in short-term studies, but Kirsch and his colleagues raise an unsettling possibility. In a paper appearing next week in Prevention & Treatment, an online journal published by the American Psychological Association (apa.org), they argue that the SSRIs’ active ingredients may account only for the two-point difference between drug and placebo, not the whole 10-point benefit that users enjoy. If so, says Kirsch, the benefits are “clinically negligible.”

**TESTS AND EXPECTATIONS**

There are a couple of problems, though. First, drug effects and placebo effects may not be “additive.” In other words, even if it’s possible to reproduce 80 percent of a drug’s effect with a placebo, that doesn’t mean the people taking the drug derive 80 percent of their benefit from the placebo response. If people received the drug without their knowledge, would they get only 20 percent of the effect? The question is worth asking, but it’s difficult to answer, because researchers can’t study drugs by slipping them into people’s coffee. Drug trials require informed consent—and once participants know what’s going on in a study, expectations rise. But suppose 80 percent of the antidepressant effect is just placebo. Is there a practical way to tap that benefit in the absence of an actual drug? If clinicians stopped prescribing antidepressants, patients wouldn’t lose only the two-point advantage that treatment offers over placebo, they would lose the whole 10-point improvement. And no one is suggesting that drugmakers start bottling sugar pills.

The new study might well prompt some depressed people to skip the drugs altogether. If the benefits are negligible, why endure side effects that can include nausea, nervousness, sweating, tremors and decreased libido? But while Kirsch thinks psychotherapy—the good old talking cure—is an effective alternative, he does not advise anyone to stop using antidepressants. Neither does Dr. Rodrigo Munoz, past president of the American Psychiatric Association. Like many clinicians, he believes the drugs have a much greater effect than Kirsch’s analysis suggests. “Even if 20 percent is the best we have,” he says, “I’ll live with it until we have something better.” Munoz notes that 15 percent of people with depression end up killing themselves. “When I see a patient who is suicidal, I use all the artillery. I am not going to say, ‘Well, 20 percent is not enough for me’.”
A large part of the problem in assessing the effectiveness of the antidepressants is the maddening complexity of depression itself, with its wide range of symptoms and many levels of disability. Dr. Walter Brown of Brown University Medical School says the antidepressants “are probably not as effective as the hype around them would suggest.” But Brown, who wrote a commentary on Kirsch’s study that will also be published in Prevention & Treatment, believes the drugs are more powerful than Kirsch concludes. He says the mild and moderately afflicted patients who typically participate in clinical trials can exaggerate the placebo response. In Brown’s experience, severely depressed patients do not respond nearly as well when treated with placebos. He believes the drugs are more effective in the real world, where they are used to treat a range of sick people over long periods.

Some who question the efficacy of antidepressants say the massive promotional efforts by the drugmakers may actually boost the placebo response. “One day we may look back and marvel at the stroke of marketing genius that led to calling these medications antidepressants in the first place,” says clinical psychologist David Antonuccio of the University of Nevada School of Medicine. But Dr. Michael Miller of Harvard Medical School says that in his clinical experience, the placebo response is limited. Most of his patients enjoy a brief improvement no matter what treatment they receive. Those getting only a placebo response soon return to their misery, he says. But those responding to medication enjoy longer-term benefits.

Even Kirsch admits that the real problem may be figuring
out the best way to measure the power of the drugs. For the millions who owe their peace of mind to the antidepressants they take, the point may be irrelevant. In the end, anything that lightens the days of those who suffer depression is a good thing.

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