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WHY ANTIDEPRESSANTS ARE NO BETTER THAN PLACEBOS

BY SHARON BEGLEY ON 1/28/10 AT 7:00 PM

Although the year is young, it has already brought my first moral dilemma. In early January a friend mentioned that his New Year's resolution was to beat his chronic depression once and for all. Over the years he had tried a medicine chest's worth of antidepressants, but none had really helped in any enduring way, and when the side effects became so unpleasant that he stopped taking them, the withdrawal symptoms (cramps, dizziness, headaches) were torture. Did I know of any research that might help him decide whether a new antidepressant his doctor recommended might finally lift his chronic darkness at noon?

The moral dilemma was this: oh, yes, I knew of 20-plus years of research on antidepressants, from the old tricyclics to the newer selective serotonin reuptake inhibitors (SSRIs) that target serotonin (Zoloft, Paxil, and the granddaddy of them all, Prozac, as well as their generic descendants) to even newer ones that also target norepinephrine (Effexor, Wellbutrin). The research had shown that antidepressants help about three quarters of people with depression who take them, a consistent finding that serves as the basis for the oft-repeated mantra "There is no question that the safety and efficacy of antidepressants rest on solid scientific evidence," as psychiatry professor Richard Friedman of Weill Cornell Medical College recently wrote in *The New York Times*. But ever since a seminal study in 1998, whose findings were reinforced by landmark research in *The Journal of the American Medical Association* last month, that evidence has come with a big asterisk. Yes, the drugs are effective, in that they lift depression in most patients. But that benefit is hardly more than what patients get when they, unknowingly and as part of a study, take a dummy pill—a placebo. As more and more scientists who study depression and the drugs that treat it are concluding, that suggests that antidepressants are basically expensive Tic Tacs.

Hence the moral dilemma. The placebo effect—that is, a medical benefit you get from an inert pill or other sham treatment—rests on the holy trinity of belief, expectation, and hope. But telling someone with depression who is being helped by antidepressants, or who (like my friend) hopes to be helped, threatens to topple the whole house of cards. Explain that it's all in their heads, that the reason they're benefiting is the same reason why Disney's Dumbo could initially fly only with a feather clutched in his trunk—believing makes it so—and the magic dissipates like fairy dust in a windstorm. So rather than tell my friend all this, I chickened out. Sure, I said, there's lots of research showing that a new kind of antidepressant might help you. Come, let me show you the studies on PubMed.

It seems I am not alone in having moral qualms about blowing the whistle on antidepressants. That first analysis, in 1998, examined 38 manufacturer-sponsored studies involving just over 3,000 depressed patients. The authors, psychology researchers Irving Kirsch and Guy Sapirstein of the University of Connecticut, saw—as everyone else had—that patients did improve, often substantially, on SSRIs, tricyclics, and even MAO inhibitors, a class of antidepressants that dates from the 1950s. This improvement, demonstrated in scores of clinical trials, is the basis for the ubiquitous claim that antidepressants work. But when Kirsch compared the improvement in patients taking the drugs with the improvement in those taking dummy pills—clinical trials typically compare an experimental drug with a placebo—he saw that the difference was minuscule. Patients on a placebo improved about 75 percent as much as those on drugs. Put another way, three quarters of the benefit from antidepressants seems to be a placebo effect. "We wondered, what's going on?" recalls Kirsch, who is now at the University of Hull in England. "These are supposed to be wonder drugs and have huge effects."

The study's impact? The number of Americans taking antidepressants doubled in a decade, from 13.3 million in 1996 to 27 million in 2005.

To be sure, the drugs have helped tens of millions of people, and Kirsch certainly does not advocate that patients suffering from depression stop

taking the drugs. On the contrary. But they are not necessarily the best first choice. Psychotherapy, for instance, works for moderate, severe, and even very severe depression. And although for some patients, psychotherapy in combination with an initial course of prescription antidepressants works even better, the question is, *how* do the drugs work? Kirsch's study and, now, others conclude that the lion's share of the drugs' effect comes from the fact that patients expect to be helped by them, and not from any direct chemical action on the brain, especially for anything short of very severe depression.

As the inexorable rise in the use of antidepressants suggests, that conclusion can't hold a candle to the simplistic "antidepressants work!" (unstated corollary: "but don't ask how") message. Part of the resistance to Kirsch's findings has been due to his less-than-retiring nature. He didn't win many friends with the cheeky title of the paper, "Listening to Prozac but Hearing Placebo." Nor did it inspire confidence that the editors of the journal *Prevention & Treatment* ran a warning with his paper, saying it used meta-analysis "controversially." Al-though some of the six invited commentaries agreed with Kirsch, others were scathing, accusing him of bias and saying the studies he analyzed were flawed (an odd charge for defenders of antidepressants, since the studies were the basis for the Food and Drug Administration's approval of the drugs). One criticism, however, could not be refuted: Kirsch had analyzed only some studies of antidepressants. Maybe if he included them all, the drugs would emerge head and shoulders superior to placebos.

Kirsch agreed. Out of the blue, he received a letter from Thomas Moore, who was then a health-policy analyst at George Washington University. You could expand your data set, Moore wrote, by including everything drug companies sent to the FDA—published studies, like those analyzed in "Hearing Placebo," but also unpublished studies. In 1998 Moore used the Freedom of Information Act to pry such data from the FDA. The total came to 47 company-sponsored studies—on Prozac, Paxil, Zoloft, Effexor, Serzone, and Celexa—that Kirsch and colleagues then pored over. (As an aside, it turned out that about 40 percent of the clinical trials had never been published. That is significantly higher than for other classes of drugs, says Lisa Bero of the University of California, San Francisco; overall, 22 percent of clinical trials of drugs are not published. "By and large," says

Kirsch, "the unpublished studies were those that had failed to show a significant benefit from taking the actual drug.") In just over half of the published and unpublished studies, he and colleagues reported in 2002, the drug alleviated depression no better than a placebo. "And the extra benefit of antidepressants was even less than we saw when we analyzed only published studies," Kirsch recalls. About 82 percent of the response to antidepressants—not the 75 percent he had calculated from examining only published studies—had also been achieved by a dummy pill.

The extra effect of real drugs wasn't much to celebrate, either. It amounted to 1.8 points on the 54-point scale doctors use to gauge the severity of depression, through questions about mood, sleep habits, and the like. Sleeping better counts as six points. Being less fidgety during the assessment is worth two points. In other words, the clinical significance of the 1.8 extra points from real drugs was underwhelming. Now Kirsch was certain. "The belief that antidepressants can cure depression chemically is simply wrong," he told me in January on the eve of the publication of his book *The Emperor's New Drugs: Exploding the Anti-depressant Myth*.

The 2002 study ignited a furious debate, but more and more scientists were becoming convinced that Kirsch—who had won respect for research on the placebo response and who had published scores of scientific papers—was on to something. One team of researchers wondered if antidepressants were "a triumph of marketing over science." Even defenders of antidepressants agreed that the drugs have "relatively small" effects. "Many have long been unimpressed by the magnitude of the differences observed between treatments and controls," psychology researcher Steven Hollon of Vanderbilt University and colleagues wrote—"what some of our colleagues refer to as 'the dirty little secret.' " In Britain, the agency that assesses which treatments are effective enough for the government to pay for stopped recommending antidepressants as a first-line treatment, especially for mild or moderate depression.

But if experts know that antidepressants are hardly better than placebos, few patients or doctors do. Some doctors have changed their prescribing habits, says Kirsch, but more "reacted with anger and incredulity." Understandably. For one thing, depression is a devastating, underdiagnosed, and undertreated disease. Of course doctors recoiled at

the idea that such drugs might be mirages. If that were true, how were physicians supposed to help their patients?

Two other factors are at work in the widespread rejection of Kirsch's (and, now, other scientists') findings about antidepressants. First, defenders of the drugs scoff at the idea that the FDA would have approved ineffective drugs. (Simple explanation: the FDA requires two well-designed clinical trials showing a drug is more effective than a placebo. That's two, period—even if many more studies show no such effectiveness. And the size of the "more effective" doesn't much matter, as long as it is statistically significant.) Second, doctors see with their own eyes, and feel with their hearts, that the drugs lift the black cloud from many of their depressed patients. But since doctors are not exactly in the habit of prescribing dummy pills, they have no experience comparing how their patients do on them, and therefore never see that a placebo would be almost as effective as a $4 pill. "When they prescribe a treatment and it works," says Kirsch, "their natural tendency is to attribute the cure to the treatment." Hence the widespread "antidepressants work" refrain that persists to this day.

Drug companies do not dispute Kirsch's aggregate statistics. But they point out that the average is made up of some patients in whom there is a true drug effect of antidepressants and some in whom there is not. As a spokesperson for Lilly (maker of Prozac) said, "Depression is a highly individualized illness," and "not all patients respond the same way to a particular treatment." In addition, notes a spokesperson for Glaxo-Smith-Kline (maker of Paxil), the studies analyzed in the *JAMA* paper differ from studies GSK submitted to the FDA when it won approval for Paxil, "so it is difficult to make direct comparisons between the results. This study contributes to the extensive research that has helped to characterize the role of antidepressants," which "are an important option, in addition to counseling and lifestyle changes, for treatment of depression." A spokesperson for Pfizer, which makes Zoloft, also cited the "wealth of scientific evidence documenting [antidepressants'] effects," adding that the fact that antidepressants "commonly fail to separate from placebo" is "a fact well known by the FDA, academia, and industry." Other manufacturers pointed out that Kirsch and the *JAMA* authors had not studied their particular brands.

Even Kirsch's analysis, however, found that antidepressants are a little more effective than dummy pills—those 1.8 points on the depression scale. Maybe Prozac, Zoloft, Paxil, Celexa, and their cousins do have some non-placebo, chemical benefit. But the small edge of real drugs compared with placebos might not mean what it seems, Kirsch explained to me one evening from his home in Hull. Consider how research on drugs works. Patient volunteers are told they will receive either the drug or a placebo, and that neither they nor the scientists will know who is getting what. Most volunteers hope they get the drug, not the dummy pill. After taking the unknown meds for a while, some volunteers experience side effects. Bingo: a clue they're on the real drug. About 80 percent guess right, and studies show that the worse side effects a patient experiences, the more effective the drug. Patients apparently think, this drug is so strong it's making me vomit and hate sex, so it must be strong enough to lift my depression. In clinical-trial patients who figure out they're receiving the drug and not the inert pill, expectations soar.

That matters because belief in the power of a medical treatment can be self-fulfilling (that's the basis of the placebo effect). The patients who correctly guess that they're getting the real drug therefore experience a stronger placebo effect than those who get the dummy pill, experience no side effects, and are therefore disappointed. That might account for antidepressants' slight edge in effectiveness compared with a placebo, an edge that derives not from the drugs' molecules but from the hopes and expectations that patients in studies feel when they figure out they're receiving the real drug.

The boy who said the emperor had no clothes didn't endear himself to his fellow subjects, and Kirsch has fared little better. A nascent collaboration with a scientist at a medical school ended in 2002 when the scientist was warned not to submit a grant proposal with Kirsch if he ever wanted to be funded again. Four years later, another scientist wrote a paper questioning the effectiveness of antidepressants, citing Kirsch's work. It was published in a prestigious journal. That ordinarily brings accolades. Instead, his department chair dressed him down and warned him not to become too involved with Kirsch.

But the question of whether antidepressants—which in 2008 had sales of $9.6 billion in the U.S., reported the consulting firm IMS Health—have any effect other than through patients' belief in them was too important to scare researchers off. Proponents of the drugs have found themselves making weaker and weaker claims. Their last stand is that antidepressants are more effective than a placebo in patients suffering the most severe depression.

So concluded the *JAMA* study in January. In an analysis of six large experiments in which, as usual, depressed patients received either a placebo or an active drug, the true drug effect—that is, in addition to the placebo effect—was "nonexistent to negligible" in patients with mild, moderate, and even severe depression. Only in patients with very severe symptoms (scoring 23 or above on the standard scale) was there a statistically significant drug benefit. Such patients account for about 13 percent of people with depression. "Most people don't need an active drug," says Vanderbilt's Hollon, a coauthor of the study. "For a lot of folks, you're going to do as well on a sugar pill or on conversations with your physicians as you will on medication. It doesn't matter what you do; it's just the fact that you're doing something." But people with very severe depression are different, he believes. "My personal view is the placebo effect gets you pretty far, but for those with very severe, more chronic conditions, it's harder to knock down and placebos are less adequate," says Hollon. Why that should be remains a mystery, admits coauthor Robert DeRubeis of the University of Pennsylvania.

Like every scientist who has stepped into the treacherous waters of antidepressant research, Hollon, DeRubeis, and their colleagues are keenly aware of the disconnect between evidence and public impression. "Prescribers, policy-makers, and consumers may not be aware that the efficacy of [antidepressants] largely has been established on the basis of studies that have included only those individuals with more severe forms of depression," something drug ads don't mention, they write. People with anything less than very severe depression "derive little specific pharmacological benefit from taking medications. Pending findings contrary to those reported here ... efforts should be made to clarify to clinicians and prospective patients that ... there is little evidence to suggest that [antidepressants] produce specific pharmacological benefit for the majority of patients."

Right about here, people scowl and ask how anti-depressants—especially those that raise the brain's levels of serotonin—can possibly have no direct chemical effect on the brain. Surely raising serotonin levels should right the synapses' "chemical imbalance" and lift depression. Unfortunately, the serotonin-deficit theory of depression is built on a foundation of tissue paper. How that came to be is a story in itself, but the basics are that in the 1950s scientists discovered, serendipitously, that a drug called iproniazid seemed to help some people with depression. Iproniazid increases brain levels of serotonin and norepinephrine. Ergo, low levels of those neurotransmitters must cause depression. More than 50 years on, the presumed effectiveness of antidepressants that act this way remains the chief support for the chemical-imbalance theory of depression. Absent that effectiveness, the theory hasn't a leg to stand on. Direct evidence doesn't exist. Lowering people's serotonin levels does not change their mood. And a new drug, tianeptine, which is sold in France and some other countries (but not the U.S.), turns out to be as effective as Prozac-like antidepressants that keep the synapses well supplied with serotonin. The mechanism of the new drug? It *lowers* brain levels of serotonin. "If depression can be equally affected by drugs that increase serotonin and by drugs that decrease it," says Kirsch, "it's hard to imagine how the benefits can be due to their chemical activity."

Perhaps antidepressants would be more effective at higher doses? Unfortunately, in 2002 Kirsch and colleagues found that high doses are hardly more effective than low ones, improving patients' depression-scale rating an average of 9.97 points vs. 9.57 points—a difference that is not statistically significant. Yet many doctors increase doses for patients who do not respond to a lower one, and many patients report improving as a result. There's a study of that, too. When researchers gave such nonresponders a higher dose, 72 percent got much better, their symptoms dropping by 50 percent or more. The catch? Only half the patients really got a higher dose. The rest, unknowingly, got the original, "ineffective" dose. It is hard to see the 72 percent who got much better on ersatz higher doses as the result of anything but the power of expectation: the doctor upped my dose, so I believe I'll get better.

Something similar may explain why some patients who aren't helped by one antidepressant do better on a second, or a third. This is often explained as

"matching" patient to drug, and seemed to be confirmed by a 2006 federal study called STAR*D. Patients still suffering from depression after taking one drug were switched to a second; those who were still not better were switched to a third drug, and even a fourth. No placebos were used. At first blush, the results offered a ray of hope: 37 percent of the patients got better on the first drug, 19 percent more on their second, 6 percent more improved on their third try, and 5 percent more on their fourth. (Half of those who recovered relapsed within a year, however.)

So does STAR*D validate the idea that the key to effective treatment of depression is matching the patient to the drug? Maybe. Or maybe people improved in rounds two, three, and four because depression sometimes lifts due to changes in people's lives, or because levels of depression tend to rise and fall over time. With no one in STAR*D receiving a placebo, it is not possible to conclude with certainty that the improvements in rounds two, three, and four were because patients switched to a drug that was more effective for them. Comparable numbers might have improved if they had switched to a placebo. But STAR*D did not test for that, and so cannot rule it out.

It's tempting to look at the power of the placebo effect to alleviate depression and stick an "only" in front of it—as in, the drugs work *only* through the placebo effect. But there is nothing "only" about the placebo response. It can be surprisingly enduring, as a 2008 study found: "The widely held belief that the placebo response in depression is short-lived appears to be based largely on intuition and perhaps wishful thinking," scientists wrote in the *Journal of Psychiatric Research*. The strength of the placebo response drives drug companies nuts, since it makes showing the superiority of a new drug much harder. There is a strong placebo component in the response to drugs for pain, asthma, irritable-bowel syndrome, skin conditions such as contact dermatitis, and even Parkinson's disease. But compared with the placebo component of antidepressants, the placebo response accounts for a smaller fraction of the benefit from drugs for those disorders—on the order of 50 percent for analgesics, for instance.

Which returns us to the moral dilemma. In any year, an estimated 13.1 million to 14.2 million American adults suffer from clinical depression. At

least 32 million will have the disease at some point in their life. Many of the 57 percent who receive treatment (the rest do not) are helped by medication. For that benefit to continue, they need to believe in their pills. Even Kirsch warns—in boldface type in his book, which is in stores this week—that patients on antidepressants not suddenly stop taking them. That can cause serious withdrawal symptoms, including twitches, tremors, blurred vision, and nausea—as well as depression and anxiety. Yet Kirsch is well aware that his book may have the same effect on patients as dropping the magic feather did for Dumbo: without it, the little elephant began crashing to earth. Friends and colleagues who believe Kirsch is right ask why he doesn't just shut up, since publicizing the finding that the effectiveness of antidepressants is almost entirely due to people's hopes and expectations will undermine that effectiveness.

It's all well and good to point out that psychotherapy is more effective than either pills or placebos, with dramatically lower relapse rates. But there's the little matter of reality. In the U.S., most patients with depression are treated by primary-care doctors, not psychiatrists. The latter are in short supply, especially outside cities and especially for children and adolescents. Some insurance plans discourage such care, and some psychiatrists do not accept insurance. Maybe keeping patients in the dark about the ineffectiveness of antidepressants, which for many are their only hope, is a kindness.

Or maybe not. As shown by the explicit criticism of drug companies by the authors of the recent *JAMA* paper, more and more scientists believe it is time to abandon the "don't ask, don't tell" policy of not digging too deeply into the reasons for the effectiveness of antidepressants. Maybe it is time to pull back the curtain and see the wizard for what he is. As for Kirsch, he insists that it is important to know that much of the benefit of antidepressants is a placebo effect. If placebos can make people better, then depression can be treated without drugs that come with serious side effects, not to mention costs. Wider recognition that antidepressants are a pharmaceutical version of the emperor's new clothes, he says, might spur patients to try other treatments. "Isn't it more important to know the truth?" he asks. Based on the impact of his work so far, it's hard to avoid answering, "Not to many people."