



ASKED BY THOSE WHO TAKE ANTIDEPRESSANTS AND THOSE WHO PRESCRIBE THEM:
 How do these drugs work? // How are drug trials conducted? // How are trial results
 interpreted? // How can we learn more about **depression itself?**

Somber Questions

■ BY ANITA SLOMSKI // PHOTOGRAPHS BY TINA TYRELL

More than one in 10 Americans takes one or more antidepressant medications, and for that large chunk of the population, recent events surely have been unsettling. Three books published in 2010 were uniformly damning of the No. 1 type of medication taken by people ages 18 to 44, though each author takes aim at antidepressants from a different angle. Clinical psychologist Irving Kirsch lays out evidence that antidepressants simply don't work in *The Emperor's New Drugs: Exploding the Antidepressant Myth*—he argues that they're no more effective than the dummy pills used in clinical trials. Journalist Robert Whitaker, in *Anatomy of an Epidemic: Magic Bullets, Psychiatric Drugs, and the Astonishing Rise of Mental Illness in America*, makes a more harrowing claim—that chronic use of antidepressants and other psychotropic drugs has created legions of mentally disabled people who are far worse off as a result of treatment. And psychiatrist Daniel Carlat, in *Unhinged: The Trouble With Psychiatry—A Doctor's Revelations About a Profession in Crisis*, charges that psychiatrists have engaged in “a binge of drug prescribing” because they can earn half again as much by adjusting medications as they would be paid for talk therapy. “The income differential is a powerful incentive to drop therapy from our repertoire of skills, and psychiatrists have generally followed the money,” Carlat writes.

One hallmark of depression is extreme self-doubt, and the furor the books have caused seems to have led many patients to question their treatment. In the wake of their publication, a number of people under the care of depression researcher Madhukar H. Trivedi abruptly stopped taking antidepressants. Some of those patients then relapsed, again suffering major depression, says Trivedi, professor of psychiatry and director of the Mood Disorders Research Program and Clinic at the University of Texas Southwestern Medical Center at Dallas. But others who quit the drugs have done just fine, Trivedi says.

That's how it is with antidepressants. Physicians who prescribe them have no doubt that the drugs are essential for the treatment of many patients, particularly those who are most seriously ill. Yet uncertainty about how antidepressants work and whom they can help has increasingly fueled the notion that they may be useless or even dangerous. To improve the understanding of who is most likely to respond to the drugs in this rather broad class, Trivedi has launched a study that he hopes will identify a treatment response “signature.” Four hundred volunteers, randomly assigned to take an antidepressant or a placebo, will receive a battery of tests—functional and conventional magnetic resonance imaging, electrophysiology, and behavioral and cognitive assessments—at the start of the study and again after eight weeks. “We hope this trial will begin to give us biological and clinical signatures of people who are

likely to do well versus those who won't respond to antidepressants, as well as help us determine whether there are unique biological characteristics of those who report improvement with placebo alone," says Trivedi, who expects results in mid-2014.

Such work could help explain why no current therapy, including psychotherapy without drugs, is consistently effective. "It's important to ask whether and how well antidepressants work, just as we debate the effectiveness of mammography, prostate cancer screening and surgery for back pain," says Andrew A. Nierenberg, co-director of the Bipolar Clinic and Research Program and associate director of the Depression Clinical and Research Program at Massachusetts General Hospital. But it's crucial, says Nierenberg, for those on both sides of the antidepressant question to remain scientifically objective, for the sake of individuals suffering from depression. "People's lives are at stake when they become needlessly frightened of antidepressants and stop taking them," he says.

The first antidepressant was actually a tuberculosis drug, iproniazid, created in 1951 by Hoffmann-La Roche. But physicians noticed that many TB patients who were also depressed improved when they took iproniazid: It increased levels of serotonin and norepinephrine, chemicals called neurotransmitters that relay messages among the brain's 100 billion neurons. Research in animals at about the same time found that a drug that reduced serotonin, norepinephrine and another neurotransmitter, dopamine, made the animals lethargic and apathetic. Noting how psychotropic drugs changed levels of neurotransmitters, other researchers began to hypothesize that abnormal amounts of neurotransmitters caused schizophrenia and other mental disorders. Even then, the evidence was inconclusive, with some studies finding a direct correlation between depression and low levels of serotonin, norepinephrine and dopamine, while others saw no connection. Nevertheless, the idea that chemical imbalances caused depression had taken hold, and creating drugs to restore neurotransmitter health seemed the most promising treatment.

Many of today's antidepressants indeed increase the levels of neurotransmitters that neurons release into synapses—the spaces between neurons—causing neurons to fire and carry

electrical impulses. After a neurotransmitter attaches to receptors on the receiving neurons, transporter pumps suck up and recycle the used chemicals to terminate the signal. Selective serotonin reuptake inhibitors, or SSRIs, are antidepressants that interrupt the transporter pumps so that serotonin remains in the synapses longer than it normally would. That's supposed to compensate for low levels of the neurotransmitter in people with depression, and the best-known antidepressants—Prozac, Paxil, Zoloft, Celexa and Lexapro—are all SSRIs. Another class of antidepressants—serotonin and norepinephrine reuptake inhibitors, or SNRIs (Effexor and Cymbalta)—work by allowing both serotonin and norepinephrine to flood synapses. And yet another class enhances the release of norepinephrine and dopamine.

The only problem with these popular drugs is that the theory of chemical imbalances they're based on has largely been discredited. Nierenberg says the neurotransmitter theory of depression is about 20 years out of date, and in his book, Robert Whitaker notes that in 1984 investigators at the National Institute of Mental Health concluded serotonin wasn't likely to be associated with depression—four years before Prozac

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came to market, promoted as a new way to restore serotonin levels. Whitaker also quotes researchers writing in 1995, 2000, 2003 and 2005, all of whom say the neurotransmitter theory needs to be put to rest because it's not true. As far back as 1956, a clinical trial of the drug reserpine, which decreases levels of norepinephrine, serotonin and dopamine, showed that the drug not only didn't cause depression but actually alleviated it. And according to Kirsch, there have been at least 90 studies in which artificial depletion of neurotransmitter levels did not trigger depression in people with no history of the disease.

Such findings have fueled the controversy about antidepressants. If the drugs are designed to correct something that in fact has no negative effects, then it seems reasonable to ask why they should be prescribed at all. Nierenberg's answer is



that depression isn't tied to a single neurotransmitter system or to one brain region, but rather is likely to involve multiple neural circuits and neurotransmitters, as some studies suggest. And antidepressants appear to do more than alter neurotransmitters. They also protect neurons and help reverse the negative changes that occur in the brain as a result of depression's stresses, according to a study by an international group of researchers published in *Molecular Psychiatry* in 2011. And they may help impaired brains process information more efficiently so individuals can learn new ways of coping with stress. "We are at the very beginning of understanding the complexity of the brain," says Nierenberg.

Kirsch isn't persuaded by arguments about how antidepressants might work, and in *The Emperor's New Drugs*, he writes that they are "drugs with very little specific therapeutic benefit, but with serious side effects.... The belief that antidepressants can cure depression chemically is simply wrong." To support his position, Kirsch analyzed the results of the randomized controlled clinical trials that pharmaceutical companies must do to obtain Food and Drug Administration approval to market any drug. Typically a drug-maker has to submit results from at least two trials showing that participants who received the active drug showed greater

improvement than subjects who took a placebo. But because many antidepressant trials fail to demonstrate a positive effect, pharmaceutical companies often do lots of studies, and though they don't publish the results of failed trials, they have to reveal them to the FDA. Using the Freedom of Information Act, Kirsch obtained records on every placebo-controlled clinical trial for six widely prescribed antidepressants: Prozac, Paxil, Zoloft, Effexor, Serzone and Celexa. According to his analysis of the published and unpublished studies, both groups of patients—those who took placebos and those who got antidepressants—showed improvement, and the difference between the two groups was not clinically significant except for the most severely depressed patients.

In Kirsch's analysis, the effect attributable to antidepressants translated into less than a two-point improvement on the Hamilton Rating Scale for Depression, a questionnaire that evaluates the severity of depression on a scale of 0 to 52. In comparison, getting a good night's sleep is worth six points, according to Kirsch. Moreover, he argues that the marginal advantage of antidepressants over placebo can be explained by



iPAD EXTRA: VIDEO: Massachusetts General Hospital chief of psychiatry Jerrold F. Rosenbaum on the ups and downs of antidepressants

side effects from the active drugs—when trial participants feel something while on a pill, they assume they’re receiving an active drug and therefore expect to feel better. “The more side effects that depressed patients experience on the active drug, the more they improve,” writes Kirsch.

The placebo effect or placebo response—that tendency of some patients to benefit just because they think they should—indeed has real power in treating depression, says Michael E. Thase, professor of psychiatry at the University of Pennsylvania’s Perelman School of Medicine. “The placebo response represents people’s inherent ability to get better when they’re cared for and engaged in an enterprise devoted to getting better,” Thase says. That’s exactly what happens in a drug trial, in which participants get attention and concern from investiga-

tors, are interviewed about their symptoms and find a receptive audience for talking about their depression.

But that’s not to say antidepressants have no therapeutic effect. “If it were true that antidepressants are no better than placebo, you would expect, in the hundreds of clinical trials comparing drugs and placebo, for placebo to win half the time and the drugs to win half the time,” says Jerrold F. Rosenbaum, chief of psychiatry at MGH and president and executive director of MGH’s Mood and Anxiety Disorders Institute. “The reality is that though sometimes the drug wins and sometimes there’s a tie, placebo essentially never wins. Drugs do work, but the way the drugs are studied is so fraught with methodological problems and distortions that it’s extremely hard to detect a signal of effectiveness.”



Running Away From the Blues //

Is exercise superior to drugs for treating depression?

Could taking a run or going for a swim be an effective alternative to drug therapy in treating depression? In one recent experiment, Madhukar H. Trivedi, professor of psychiatry and director of the Mood Disorders Research Program and Clinic at the University of Texas Southwestern Medical Center at Dallas, found that almost 30% of patients who had improved only marginally while taking a standard antidepressant medication reported that their depression had lifted after four months of adding exercise to their regimen. And researchers at Duke University, in a 2007 study, found that 40% to 45% of people with depression became symptom-free with exercise alone, compared with 47% of those on

antidepressants and 31% of those taking a placebo.

“Exercise has many effects on the brain, including the creation of new neurons,” says Amar Sahay of the Center for Regenerative Medicine and department of psychiatry at Massachusetts General Hospital. Neurogenesis in the hippocampus, a brain region important for mood regulation and cognition, may protect against depression or alleviate it by strengthening connections to other brain areas crucial to decision-making, pleasure and rewards. “Researchers have found atrophies in these brain connections in depressed individuals,” Sahay adds.

In experiments with mice genetically

engineered to make twice as many new neurons without fundamentally changing the rest of the brain, Sahay has found that exercise encouraged mice to explore more and to show less anxiety when put in bright open spaces than did control mice.

If making new neurons in the hippocampus proves effective in people, Sahay imagines that a drug to stimulate neurogenesis rather than a prescription for exercise may become the first line of treatment. “People with severe depression don’t have the motivation to get on a treadmill; they can’t even get out of bed,” he says. “But once someone gets over that threshold, maybe combining therapy with exercise will be the right treatment.”

It's those issues—how drug trials are conducted and how their results are interpreted—that are at the heart of the controversy over the effectiveness of antidepressants. Kirsch looked at the average benefit of drugs vs. placebos, and he found the drugs' impact to be marginal at best. But when Thase examined data from five trials of Lexapro, he noticed that among a particular subset of patients—those with the most severe symptoms—what he terms a “meaningful minority of patients” (almost one in four) showed a “massive amount” of improvement on the drug. A small mean difference between drug and placebo among all subjects may obscure a large benefit for individual participants.

In an effort to find out why so many trials fail, recently John H. Krystal, chair of the department of psychiatry at the Yale

contrast, may have severe depression that may be accompanied by such problems as drug or alcohol abuse, panic disorder, or anxiety or personality disorders. According to a 2005 study, 79% of depressed patients treated in clinical practices had multiple issues that would exclude them from drug trials.

Because volunteers accepted for trials tend to be less sick than many depressed patients are, there's a better chance that all of those in a study will get a little better. And some candidates, eager to be chosen (either for the attention or to try a drug that might make them feel better), may exaggerate their symptoms and not have depression at all, Nierenberg observes. The private research companies paid to fill slots in a study may also overstate the severity of volunteers' conditions. “Then, trial participants want to please the investiga-



School of Medicine, and his team analyzed the data from all the trials Eli Lilly conducted to test Cymbalta, involving more than 2,500 people with major depression. They found that of the participants who received the active drug, about 75% responded favorably and 25% showed little or no improvement. “This tells us the clinical benefits of antidepressant medications are real,” he says. But because individual studies are conducted with much smaller groups of participants, the mix of people who respond to the drug and those who don't can greatly skew the results. (Some people just don't respond to antidepressants, and scientists don't know why.)

In fact, how trial volunteers are chosen is a major reason drugs often show little benefit over placebos. To demonstrate that a medication works, drugmakers tend to select trial participants who have only mild symptoms of depression and no other psychiatric or medical problems. Real-world patients, in

tors, so those on placebo report that they are getting better even when they aren't,” says Nierenberg. Another problem is that as many as a third of trial subjects don't even take the drug, according to research undertaken at Sweden's Uppsala University Hospital and published in 2003 in *International Clinical Psychopharmacology*.

So what would better-designed research reveal about the effectiveness of antidepressants? Unlike trials sponsored by pharmaceutical companies, which advertise for volunteers, the \$35 million STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial—the largest and longest study to evaluate treatment for major depression—recruited patients newly diagnosed with depression through psychiatric and primary care practices. In addition to having moderate to severe depression, which was often chronic (in other words,



constant) or recurrent, many subjects also had other significant problems, such as alcohol and drug abuse or other psychiatric disorders that make treating depression especially challenging. Moreover, STAR*D set a higher bar for results than the standards used in most drug company trials. “This was the first large-scale trial that used complete remission of symptoms—not just feeling better—to define a successful outcome,” says Trivedi, a leader of the study.

Four thousand patients participated, and 10 drugs used to treat depression were tested in four phases, with results published in 2008. After the first round of therapy—12 to 14 weeks on Celexa, an SSRI—about a third of subjects achieved full remission of their depression and an additional 10% to 15% reported some improvement.

Volunteers who were still depressed then entered Phase II, in which they had the option either to switch to a different

antidepressant or to add a second treatment to Celexa. They also could choose to begin psychotherapy, with or without drugs. In the group that switched to a new antidepressant, 25% became symptom-free, and among those who added a second drug, about a third achieved remission. Switching to or adding cognitive therapy ultimately achieved results similar to the drug-only treatments, though the drugs worked faster.

Those who still hadn’t improved moved to Phase III. They either switched to an antidepressant targeting a different neurotransmitter or added such a drug to a previous medication. Participants in the add-on group were also randomly prescribed lithium, a mood stabilizer, or a thyroid drug known to enhance the effectiveness of antidepressants. Depending on which treatment they received, 12% to 20% became symptom-free. And in the final phase of the study, subjects who were still depressed were taken off antidepressants and prescribed other drugs thought to work in people resistant to other treatments. Only 7% to 10% of the Phase IV group achieved remission of their depression.

In all, about half of the people in the STAR*D trial were symptom-free after two treatments, and almost 70% achieved remission after four treatments. But with each subsequent treatment, fewer additional people got well and increasing numbers dropped out of the study because of drug side effects. “Once you haven’t been successful treating depression with two treatments, additional treatments don’t produce as much benefit as we used to think,” says Trivedi, who terms the percentage of people in STAR*D who achieved remission of their depression on antidepressants decent, but not optimal. According to Peter Kramer, clinical professor of psychiatry at Brown University and author of *Listening to Prozac*, “medications for mental illness are as effective as medications doctors use for other indications. Doctors treating hypertension, for example, often need to switch or supplement medications. The use of antidepressants is comparable.”

The results of STAR*D suggest that antidepressants do help many patients. But that still leaves the contentions in the other two books—psychiatrist Carlat’s assertion that there is rampant overuse of the drugs at the expense of such alternatives as psychotherapy, and journalist Whitaker’s argument that a surge in antidepressant use has led to a rise in debilitating mental illness.

A report last year from the Centers for Disease Control and Prevention indeed showed that antidepressant use in the United States had soared 400% between 1988 and 2008, and

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Whitaker contends that the numbers of disabled mentally ill people have skyrocketed during the same period. Tallying how many people receive a monthly Supplemental Security Income or Social Security Disability Insurance payment because mental illness makes it impossible for them to support themselves, he finds that, in 2007, one in 76 Americans received SSI or SSDI payments, more than double the number in 1987. And as antidepressants gained popularity during the 1990s, the number of people disabled by depression and bipolar disease, including children, began to climb, Whitaker asserts. By 2002, one in 40 children was taking an antidepressant compared with one in 250 children in 1988. And in 2007, more than 561,000 children received a federal payment for a serious mental illness, 35% more than two decades earlier.

But according to Nierenberg, epidemiological and other data simply don't support Whitaker's contentions. Citing statistics from the U.S. Census Bureau, Nierenberg shows that the percentage of Americans whose depression or anxiety seriously interfered with their functioning stayed steady at around 2% in 1991, 1997 and 2002. Nor has the prevalence or severity of mental disorders increased in the United States, according to a 2005 epidemiological study by Harvard Medical School, published in the *New England Journal of Medicine*. It found that from 1990 through 1992, 29.4% of the U.S. population had anxiety, mood and substance disorders; from 2001 through 2003, a nearly identical 30.5% of the population had those mental conditions.

At least part of the jump in antidepressant use appears to have resulted from efforts to alleviate rampant undertreatment of depression. During the 1990s, responding to evidence that only 20% of Americans with depression were getting any kind of help, the National Institute of Mental Health launched an initiative to educate people on the dangers of untreated depression. And while more people with severe depression are getting antidepressants today, the disorder is still undertreated, Thase says. However, he agrees with critics of antidepressants that they shouldn't be the default treatment. “The consequence of that 400% increase is that alternative therapies, such as

counseling, psychotherapy and exercise programs, haven't been widely used,” Thase says. “The ease of prescribing antidepressants and the influence of marketing, including on physicians, have caused us to undervalue nonmedication alternatives.”

Indeed, Krystal thinks that people who stay on antidepressants that haven't been effective should consider alternative treatments. If the treatment is in fact blocking their recovery, getting off medication and trying psychotherapy might be the answer. Or perhaps they'd do better on a different type of psychotropic drug, such as a mood stabilizer or a second-generation antipsychotic medication. “Some doctors and patients consider no change an acceptable outcome for depression treatment, and our data suggest such patients may be missing an opportunity to get better,” says Krystal.

“Our challenge is to learn enough about the biology of depression and its genetic propensities to be able to predict and match treatments to those patients so we get it right,” says Rosenbaum at MGH. “We are now quite primitive” in that knowledge, which is a fact everyone can agree on. ■

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1. “What Did STAR*D Teach Us? Results From a Large-Scale, Practical, Clinical Trial for Patients With Depression,” by Bradley N. Gaynes et al., *Psychiatric Services*, Nov. 1, 2009. In summarizing the results of the landmark trial that challenged many psychiatrists' views about the effectiveness of antidepressants, the authors call for recruiting more real-world patients in clinical trials of antidepressants and using remission as a goal of therapy.
2. “Assessing the ‘True’ Effect of Active Antidepressant Therapy v. Placebo in Major Depressive Disorder: Use of a Mixture Model,” by Michael E. Thase et al., *The British Journal of Psychiatry*, December 2011. Using statistical modeling, the authors found that antidepressants that fail to show much effectiveness in clinical trials actually do provide a substantial benefit to a subgroup of trial participants—leading the authors to argue that evaluating data only from the group of subjects as a whole may lead to wrong conclusions.
3. “Effect of Exercise Training on Depressive Symptoms Among Patients With a Chronic Illness: A Systematic Review and Meta-Analysis of Randomized Controlled Trials,” by Matthew P. Herring et al., *Archives of Internal Medicine*, Jan. 23, 2012. In a meta-analysis of 90 studies of the chronically ill, the authors found that exercise training significantly reduced depressive symptoms.