A promising new drug for depression failed to clear efficacy tests this year, illuminating a decades-old problem in psychopharmacology that deserves more study, researchers say

Can the Placebo Be the Cure?

Last winter, psychiatrists and drug company executives were eagerly anticipating the arrival of a new product to fight depression. A novel compound—a Merck invention known as MK-869—then in several clinical trials, seemed set to become a new millennium drug for millions of people who take antidepressant medication every day. Results published in *Science* (11 September 1998, pp. 1624, 1640) had shown that it worked well and caused almost no sexual dysfunction, a side effect of many other pills on the market. Merck assured financial analysts in December that MK-869 was likely to be a big moneymaker. But on 22 January, those hopes were dashed when Merck, in an abrupt reversal, disclosed that MK-869 would be shelved as an antidepressant, although it may find a limited market as a treatment for nausea during chemotherapy. What went wrong?

Merck was struck by "the curse of the placebo effect," some researchers concluded. A Merck press release explained that when the company analyzed data from a new clinical trial in January, it found that patients who had received a dummy pill had done unexpectedly well. They did almost as well, in fact, as those on MK-869, wiping out the rationale for the new drug. The news was a downer for Merck and Wall Street: The price of the company's stock dropped 5% on the day Merck broke the news. It rebounded within the week, however, in part because Merck is already testing a new antidepressant that could be more potent and "much better than MK-869," according to Reynold Spector, executive vice president of Merck Research Laboratories in Rahway, New Jersey (see sidebar).

The MK-869 reversal may have been a temporary setback for Merck, but it highlights a chronic problem for psychopharmacology—the placebo effect. It's a phenomenon that bedevils many trials of antidepressant drugs, spoiling some and driving up the cost of others, as clinicians are forced to recruit more patients to obtain statistically significant data. Drug developers regard it as an occupational hazard that masks the effects of potentially useful compounds. But there's more to it than that. Some psychiatrists and clinical psychologists are fascinated by the power of the placebo effect, viewing it not as a problem but as a source of insight into mental health. And a few—such as University of Connecticut, Storrs, psychologist Irving Kirsch—go further, challenging the scientific basis of much of the multibillion-dollar market for antidepressant drugs: They argue that many compounds, even those with good scientific pedigrees, may be little more than sophisticated placebos themselves.

This is a minority view, but one that's getting new attention as researchers try to understand how promising drugs like MK-869 can fail. Even mainstream scientists agree that the subject has been neglected. William Carpenter, director of the Psychiatric Research Center at the University of Maryland, Baltimore, says the placebo effect has been "kind of a soft underbelly" that both academic and industry researchers "have been more comfortable leaving out of sight."

Mood management. The demand for psychoactive medications is booming.

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Miracle cures

The placebo effect has complicated medical research ever since its miraculous powers were discovered in the 1950s. Administering a simple sugar pill or injecting water, for instance, can alleviate symptoms or even cure a disease—as long as patients believe they could be getting a real drug.

To ensure that new drugs have "real" value, companies test them in a trial where the patients are randomly assigned to a group that gets the placebo or the drug. Because hopeful patients and doctors can unknowingly skew the results, most trials are double-blind: Neither party knows what the patient gets. Only afterward, when the blind is broken, does a comparison between the results in both groups show whether a new drug is a hit or a miss.

For afflictions that have a strong psychological component, like pain, anxiety, and depression, the placebo response rates are often high, making it more difficult to prove a drug's efficacy. In trials of antidepressants, says Dennis Charney, director of the Yale Mental Health Clinical Research Center, it's not uncommon for 65% of the patients on the new drug to get better. But 35% of the patients in the placebo group also typically improve. Frequently, the differences between the two groups are so small as to be statistically insignificant. "That's probably the most common reason for depression studies to fail," says Thomas Laughren, team leader for the psychiatric drug products group at the U.S. Food and Drug Administration (FDA).

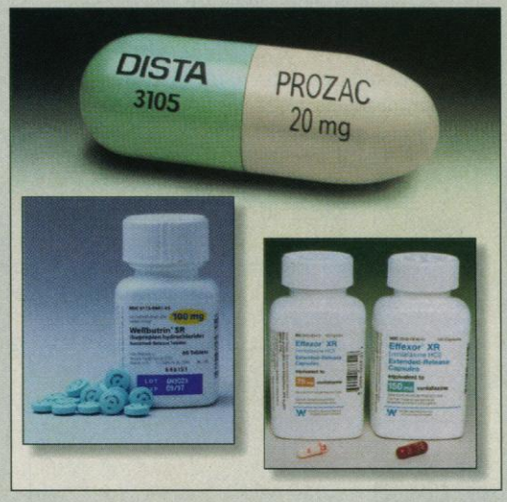
Researchers think several different factors play a role in helping some people get better on a dummy pill. Depressions often wax and wane, so improvements observed during a trial may be part of the disease's natural cycle. Simply enrolling in a trial helps some patients, says Charney, no matter what's in the capsules they take home: "You come in, you haven't gotten any help, and [now] you're seeing somebody who cares about you, who is asking about your life. That will improve symptoms."

Trial results may also be blurred because it's difficult to measure depression. When testing the value of, say, a cholesterol-lowering drug, says Spector, scientists can count the deaths in each group at the end: "You don't have to be a rocket scientist to do those trials." But depression is usually measured using the Hamilton scale, which gives patients one to four points on items like mood, guilty feelings, suicidal thoughts, and insomnia. Generally, patients are recorded as "responders" to a drug if the "Ham" score drops by at least 50%. But many patients in the placebo group also fit that criterion.

Poor patient selection may play a role, too. When many participants in an experi-

Drug Therapies for Depression: From MAO Inhibitors to Substance P

Antidepressants have evolved through several generations since the 1950s, each a huge improvement over its predecessor—or so advocates have claimed. But a government-sponsored study published last month confirmed what other analyses had shown before: The fashionable antidepressants of the 1990s are no more effective than those of previous generations. Even the heavy-duty drugs of the Eisenhower era appear to be on a par with those used today. The newer drugs do have a plus, however: fewer side effects.



The study, a meta-analysis commissioned by the Agency for Health Care Policy and Research (a part of the Department of Health and Human Services) and carried out by the Evidence Based Practice Center in San Antonio, Texas, looked at 315 studies carried out since 1980. It focused primarily on the hottest pills that have hit the market since 1987, the "selective serotonin reuptake inhibitors" (SSRIs), a group that includes such brands as Prozac, Paxil, and Zoloft. The study found that on average, about 50% of patients in SSRI treatment groups improved, compared to 32% in placebo groups. But in the more than 200 trials that compared new drugs with older ones, the two classes proved equally efficacious. Because the newer drugs appear to have less severe side effects, however, patients may be able to stay on them longer.

The failure to find evidence of progress is disappointing, scientists admit. And one of the biggest disappointments is that researchers still don't understand what causes—or relieves—depression. Most antidepressant drugs are based on the assumption that depression results from a shortage of serotonin or norepinephrine in the brain. Both are neurotransmitters, chemical messengers that cross the synapse, the cleft between two nerve cells. The first generation of antidepressants, discovered during the early 1950s, the MAO inhibitors, block monoamine oxidase, an enzyme that breaks down serotonin and norepinephrine. This allows the neurotransmitters to linger in the synapse, increasing their effect. Another type of drug discovered in the late 1950s, the tricyclics, prevents the nerve cells that excrete the neurotransmitters from mopping up these compounds shortly after they are released. Blocking "reuptake" also prolongs their effect. Because studies pointed to serotonin shortage as the main culprit in depression, industry developed the selective reuptake inhibitors, which now dominate the market. But even the SSRIs have side effects.

Psychiatrists are "desperately waiting for effective antidepressants that use other mechanisms," says Steven Hyman, director of the National Institute of Mental Health. In the past few years they have zeroed in on a mechanism that drives the "fight-or-flight" reaction—the hypothalamic-pituitary-adrenal (HPA) pathway. Studies have suggested that in depressed people, this system churns out cortisol, increasing alertness but depressing sexual drive and appetite. Some researchers think this may lead to depression, and several companies are studying drugs that block activation of the HPA pathway.

Another hot target is substance P, a short neuropeptide found abundantly in brain regions that control emotion which may be involved in depression. Substances like Merck's MK-869 block the natural receptor for substance P and prevent its action. Other companies are testing similar methods of regulating emotions. But this strategy has yet to deliver: After disappointing trial results, Merck sidelined MK-869 this year as an antidepressant (see main text). Hoping for good news soon, Hyman says: "All of us are holding our breath." **–M.E.**

ment aren't really suffering from the affliction under study or have mild symptoms, the results may be ambiguous. Laughren says his experience at the FDA supports that idea. When companies started testing drugs for obsessive-compulsive disorder back in the mid-1980s, he recalls, the placebo response rate was almost zero. "As time went on, you began to get a creep upward—up to a point where you could reasonably conclude that some trials failed because of high placebo response rates," he says. One possible cause is that as more and more studies are done, competition for patients increases, and clinicians loosen criteria, admitting people who are more likely to respond to a placebo.

Because a high placebo response rate can make a drug look less effective, the FDA recommends that drug companies add a third "arm" to every trial—a group of patients that gets a drug whose effectiveness has been demonstrated in previous trials. If the trial doesn't prove the new drug's effectiveness, but also fails to find a difference between the placebo and the old drug, "at least you can chalk it up to a failed trial, rather than concluding that your drug doesn't work," says Laughren. In regulatory review, a failed trial—unlike a negative outcome—isn't scored against a drug. Laughren adds, "It's sort of an insurance policy to protect the company." Many companies heed this advice; in its MK-869 trial, for example, Merck included an established drug from the Prozac generation—the company declines to say which one—and found that it, too, failed to beat the placebo.

What is "real?"

Researchers agree that a clever trial design may reduce, but will never eliminate, the placebo response. And the sheer size of the phenomenon, Kirsch argues, suggests that it is an integral part of the effectiveness of almost all antidepressant drugs. To test this idea, Kirsch and his colleague, psychologist Guy Sapirstein from Westwood Lodge Hospital in Needham, Massachusetts, carried out a meta-analysis of 19 antidepressant drug trials last year. They found the usual placebo response but expressed it in a different way—not as an independent factor but as a percentage of the "real" effect of the test drugs. Their conclusion: Antidepressants in these trials probably relied on the placebo effect for 75% of their effectiveness. If an antidepressant caused a 12-point drop on the Hamilton scale, for example, the placebo effect might be responsible for nine of those 12 points. They published these findings in June in *Prevention and Treatment*, a new, peer-reviewed online journal of the American Psychological Association (journals.apa.org/prevention).

The study triggered a series of angry

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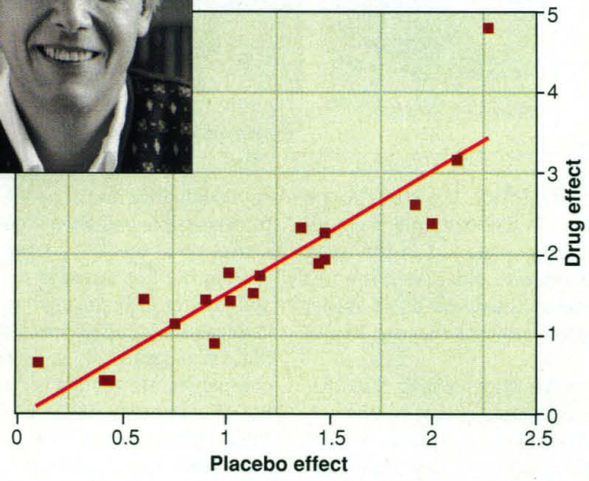
commentaries, all published on the same Web site. Many criticized the way the authors had drawn numbers from a series of different trials—an "unacceptable methodology," fumed Columbia University psychiatrist Donald Klein. Other researchers objected that even if the authors were right, a small difference on the Hamilton score can represent a big difference in a patient's condition.

What really stirred things up, however, was an even more provocative contention: Kirsch and Sapirstein argued that even the 25% "real" drug effect might be little more than a disguised placebo effect. They noted that patients often see through the carefully applied double-blind mask. Because real antidepressants have noticeable side effects—like dry mouth, nausea, dizziness, or sexual dysfunction—trial participants may figure out whether they have swallowed a drug or a placebo. Indeed, some studies have shown that up to 80% of patients could guess correctly to which group they were assigned. Such unblinding may cause a greater improvement in the drug group, not because of the drug's psychoactive effect but because both the patient and the doctor expect the drug to work. The patients in the control group, on the other hand, suspecting they're not getting that potential new cure, may do less well. Even small differences between the drug and placebo group may exaggerate the drug's power, says Kirsch.



Controversial study. Kirsch's meta-analysis of 19 antidepressant trials, each represented by a dot, revealed a pattern: The placebo effect on average accounted for 75% of the effect of real drugs.

Some of Kirsch's and Sapirstein's colleagues have supported their findings. For example, Roger Greenberg, head of the division of Clinical Psychology at the State University of New York Health Science Center in Syracuse, reached similar conclusions in several studies and in a 1997 book that reviewed the evidence, *From Placebo to Panacea*. "If people get physical sensations in the context that they may be on a real drug, they tend to be responsive," says Greenberg. He points to a few studies in which tricyclics (the pre-Prozac generation of antidepressants) were tested against a compound like atropine, which mimics these drugs' side effects but is not psychoactive. In these, Greenberg says, the differences between drug and placebo were small. And in a meta-analysis of Prozac trials published in 1994, Greenberg found that the severity of side effects correlated with the drug's efficacy. "This was ironic, because [Prozac] was marketed as having few side effects," he says. "We found that the more side effects, the better it did."

The idea that antidepressants may be just a tiny bit better than a placebo doesn't sit well with pharmaceutical companies. Eli Lilly of Indianapolis, Indiana, the manufacturer of Prozac, declines to discuss the issue because, a spokesperson says, "Prozac's efficacy has been well established." Spector concedes that the blind in some trials may not be perfect but says the effect on the outcome is "exceedingly speculative." He thinks "the antidepressants on the market actually do work, and it cannot be explained by placebo effect or anything else." He adds, "I would give them to my mother."

Many academic researchers feel the same way. Only a moderate percentage of all candidate drugs make it through FDA's screening process, says Klein, so "if active placebos did the job, they would all get through." To him, Kirsch's idea "doesn't make much sense." Steven Hyman, director of the National Institute of Mental Health (NIMH) in Bethesda, Maryland, calls Kirsch's interpretation "rather radical. ... As a doctor, it would be very miraculous if all the people I've seen getting better were getting better only by virtue of placebo," he says. Kirsch says he isn't surprised by such reactions. "Antidepressant drugs have become the mainstay of the psychiatric profession," he notes.

To bolster his case, Kirsch is now working on a new study together with Thomas Moore of the Center for Health Policy Research at George Washington University Medical Center in Washington, D.C. Using the Freedom of Information Act, the duo obtained data from 30 trials submitted to the FDA for the approval of five modern antidepressant drugs: Prozac, Zoloft, Paxil, Effexor, and Serzone. "I'm just beginning to write this up," says Kirsch, "But again, we get about 78% of the drug effect duplicated by placebo." He hopes the uniform methodology imposed by FDA guidelines will preempt the criticism this time.

But to understand exactly how the placebo response influences results, Kirsch says he would like to try a new design. In this setup, which he has used in a study of caffeine, half the patients are told they'll be on placebo, the other half, that they will get the active drug. In reality, however, each half is subdivided into a placebo and a test group. The design makes it possible to find out what a drug does when people think they're not getting it. Kirsch admits that it involves deceit, but he thinks it is ethically acceptable if the research is important and the patients are debriefed afterward. Kirsch says he wants to approach Merck to see if the company is interested in running such a trial with MK-869. But Spector dismisses the idea out of hand: "That's a no-no," he says. "You can't lie to patients, because then they can't give informed consent."

Greenberg agrees that the standard trial should not be abandoned, but says one or two refinements might be worth it if they help uncover the importance of the placebo effect. For instance, subjects could be asked what group they think they were in, and drugs could more often be compared with "active placebos" that mimic side effects.

Who will support such experiments? "You can be assured that the pharmaceutical industry is not about to finance studies that minimize their claims," says psychologist and neuroscientist Elliot Valenstein of the University of Michigan, Ann Arbor. Nor have many academics been very interested in exploring the issue in depth, says Carpenter. "It would help us have a better appreciation of the limitations of our treatments," he says, but "the truth is, as biomedical scientists, we see all this information, we know it matters, but we don't really grapple with it."

But that may be about to change. Hyman says he would like to see more research into the role of the placebo. "If we got a [grant] application to study placebo in depression and it was good science, I would be really interested," he says. Hyman says he would also like to cooperate on such studies with a new center for alternative and complementary medicine, which the National Institutes of Health is currently setting up at the request of Congress. "The more we understand about the role of placebo ... the better trials we can design without fooling ourselves."

—MARTIN ENSERINK

SOURCE: APA, I. KIRSCH AND G. SAPIRSTEIN