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Against Depression, a Sugar Pill Is Hard to Beat

Placebos Improve Mood, Change Brain Chemistry in Majority of Trials of Antidepressants

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After thousands of studies, hundreds of millions of prescriptions and tens of billions of dollars in sales, two things are certain about pills that treat depression: Antidepressants like Prozac, Paxil and Zoloft work. And so do sugar pills.

A new analysis has found that in the majority of trials conducted by drug companies in recent decades, sugar pills have done as well as -- or better than -- antidepressants. Companies have had to conduct numerous trials to get two that show a positive result, which is the Food and Drug Administration's minimum for approval.

What's more, the sugar pills, or placebos, cause profound changes in the same areas of the brain affected by the medicines, according to research published last week. One researcher has ruefully concluded that a higher percentage of depressed patients get better on placebos today than 20 years ago.

Placebos -- or dud pills -- have long been used to help scientists separate the "real" effectiveness of medicines from the "illusory" feelings of patients. The placebo effect -- the phenomenon of patients feeling better after they've been treated with dud pills -- is seen throughout the field of medicine. But new research suggests that the placebo may play an extraordinary role in the treatment of depression -- where how people feel spells the difference between sickness and health.

The new research may shed light on findings such as those from a trial last month that compared the herbal remedy St. John's wort against Zoloft. St. John's wort fully cured 24 percent of the depressed people who received it, and Zoloft cured 25 percent -- but the placebo fully cured 32 percent.

The confounding and controversial findings do not mean that antidepressants do not work. But clinicians and researchers say the results do suggest that Americans may be overestimating the power of the drugs, and that the medicines' greatest benefits may come from the care and concern shown to patients during a clinical trial -- a context that does not exist for millions of patients using the drugs in the real world.

"The drugs work, and I prescribe them, but they are not what they are cracked up to be," said Wayne Blackmon, a Washington psychiatrist whose practice largely comprises patients who suffer from depression. "I know from clinical experience the drugs alone don't do the job."

Still, drugs may have become the reflexive treatment for the vast majority of Americans receiving medical attention for depression: As the number of doctor visits for depression rose from 14 million in 1987 to almost 25 million last year, medications were prescribed for nine in 10 patients, according to research published last week.

It is not clear how many patients received medicines in a context of therapy, although research has indicated that combining medicines with psychotherapy produces the best results.

But Randall Stafford, the Stanford University physician who conducted the study on doctor visits, found

that less than one-third of them in 2001 were to psychiatrists and two-thirds of them were to primary care physicians. The former are more likely to situate the medicines in a larger context of therapy, while the latter are less knowledgeable about therapy, more pressed for time and less likely to offer patients anything like the attention they would receive in a clinical trial.

The average participant in an eight-week trial spends about 20 hours being examined by top experts and highly trained caregivers, said Seattle psychiatrist Arif Khan, who studied the placebo effect in trials submitted to the FDA. Participants -- including those being given sugar pills -- are asked detailed questions about how they are feeling, and their every psychological change is closely noted.

In comparison, Khan noted, the average patient with depression sees a doctor perhaps 20 minutes a month.

His analysis of 96 antidepressant trials between 1979 and 1996 showed that in 52 percent of them, the effect of the antidepressant could not be distinguished from that of the placebo. Khan said the makers of Prozac had to run five trials to obtain two that were positive, and the makers of Paxil and Zoloft had to run even more. He analyzed trials that were made public in the medical literature, which tend to show positive results, and those that were not.

"It speaks to the difficulty we have in classifying and identifying the disorders we deal with," said Thomas Laughren, who heads the group of scientists at the FDA that evaluates the medicines. "Psychiatric diagnosis is descriptive. We don't really understand psychiatric disorders at a biological level."

Patients with similar symptoms, he explained, may have different problems with their brain chemistry. Scientists don't understand the neural mechanisms of depression -- or why medicines like Prozac and Paxil work.

"We like to think we give people treatments and they get better," said Andrew Leuchter, a professor of psychiatry at UCLA. "We have this fallacy of success, but we don't know in any individual why they get better. Undoubtedly one of those factors is the time we spend with people and the connectedness that gives patients."

In January, Leuchter published a study in the *American Journal of Psychiatry*, in which he tracked some of the brain changes associated with drugs such as Prozac and Effexor, which are called selective serotonin reuptake inhibitors. When Leuchter compared the brain changes in patients on placebos, he was amazed to find that many of them had changes in the same parts of the brain that are thought to control important facets of mood.

Patients who got better on placebos showed heightened activity in the prefrontal lobe, and that activity continued to rise during the eight weeks of the study. Those who responded to medicine initially showed a decline in prefrontal brain activity, then a rise that eventually tapered off. Thirty-eight percent of patients responded to the placebo, and 52 percent to the medicines.

Once the trial was over and the patients who had been given placebos were told as much, they quickly deteriorated. People's belief in the power of antidepressants may explain why they do well on placebos. Patients in trials are not told which they are receiving.

Likewise, see changes in the treatment of depression -- including the reduction in the stigma attached to mental illness, the widespread use of antidepressants and the immense marketing efforts by their

manufacturers -- may explain why Timothy Walsh, a psychiatrist at Columbia University, recently found that the placebo effect has grown in recent years. He found that greater percentages of people tended to get better on placebos during trials of antidepressants in 2000 than in 1981.

Some observers assert that the medicines themselves work because of the placebo effect, but most psychiatrists believe the drugs do have an effect of their own. Drugs are a "placebo-plus" treatment, said Helen Mayberg, head of neuropsychiatry at the Rotman Research Institute at the University of Toronto.

In a study published last week in the *American Journal of Psychiatry*, Mayberg evaluated brain changes during trials using a sophisticated brain imaging technique. She found that medicines, besides working on areas that are activated by placebos, also work on areas deep in the brain stem, the hippocampus and striatum.

Since both depression and the effect of the medicines are still not well understood, it's not clear what these changes mean. While they could be irrelevant effects, Mayberg said a better explanation is that the drugs affect areas deep within the brain and then work upward to affect parts of the brain that control mood. Placebos may work in the reverse direction. In part, this may explain why drug effects tend to be more reliable than placebos in the long run.

Mayberg likened depression to a room with a hole in one window.

"You are trying to set a thermostat -- it's 100 degrees outside and you want it to be 70," she said. "If you set the thermostat to 70, that doesn't work. But if I set my thermostat to 50, that fools the system and gets the temperature back to 70."

Both drugs and placebos -- chemicals and beliefs -- may impose different chemical pressures on the brain that reset the "temperature." The real problem, of course, is that no one knows how to fix the hole in the window, or even where exactly it is. "This is a thousand-piece puzzle with no picture on the box," sighed Mayberg.

Blackmon, the Washington psychiatrist, said it behooved mental health clinicians to better integrate the power of biological treatments with the effects of belief and therapy.

"We would say it's absurd if an internist says, 'I believe in penicillin, so everyone should get penicillin whether they have cancer or a broken bone,'" he said.

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