

brain imaging and depression.

The UCLA researchers compared a group given the antidepressant Effexor with a group given a placebo. They also compared a group given Prozac with another placebo group. None of the 51 patients or the scientists knew who was taking what.

2 weeks (change from baseline)
4 weeks (change from baseline)
8 weeks (change from baseline)
Subjects who responded to the placebo
Subjects who responded to medication
Subjects who didn't respond to the placebo
Subjects who didn't respond to medication

Over eight weeks, the team measured electrical activity in the subjects' brains several times, and monitored whether depression symptoms were improving. In the end, 52 percent of the people who had taken antidepressants felt better, along with 38 percent on the placebo.

Then the scientists noted the brain activity trends among the different groups.

"Dogma has been that placebo is no treatment," says Dr. Leuchter. "Placebo is *not* no treatment."

The new research tries to address an important question, says Dr. Eric Nestler, chairman of psychiatry at the University of Texas Southwestern Medical Center at Dallas. "You take two depressed patients and give them medication: One gets better just by placebo response, the other really needs the active medication to get better. The question is why," he says. "The related question is ... are they getting better in the same way?"

Yet the caveats involved in such research are huge – for one thing, "we don't even know if the people have the same disease," Dr. Nestler notes.

"Out of 100 depressed patients, it's quite likely that there are 10 different diseases contained in what we call depression," he says. "We're not at the point yet that we can differentiate depression" the same way doctors can tell whether a cough is caused by pneumonia or a cold.

Depression subtypes

Dr. Pizzagalli says the new study may help address this very question. "The point is that possibly neuroscience will be able one day to identify subtypes of depression with very specific functional impairment in the brain."

The UCLA researchers also found that among those whose symptoms improved, people didn't report feeling much better till about two weeks after starting on the pills. Yet changes in brain activity registered in just a few days in the medication responders, Dr. Leuchter says – vs. one to two weeks in placebo responders.

His study showed that the placebo effect "seems to be an effect that grows over time."

But factors other than an inert pill may play a role, Dr. Leuchter says. A patient who has been depressed for months, then resolves to seek help, may be primed for treatment. Patients in a study also receive personal attention that could improve their mood – for the duration of the study, anyway. And they have the study's schedule and expectations to meet.

"Whatever process is going on may be additive over time, and that may be why these processes have a certain latency that you don't see with medication," says Dr. Leuchter, director of adult psychiatry at UCLA's Neuropsychiatric Institute and Hospital.

Still, he says, the study suggests that among depression patients, there are different brain pathways to improvement. He wonders whether the pathways would be similar in people given psychotherapy vs. a placebo form of therapy – or whether results from the psychotherapy group would look more like the group who responded to the placebo in the current study.

Dr. Leuchter also notes that patients with many other illnesses respond to a placebo. "If someone gets better on a placebo for their hypertension or asthma or chronic pain, would we see the same changes in the prefrontal regions of the brain?" he asks.

In the current study, the effects were not lasting among those who responded to the placebo, Dr. Leuchter says. "At the end of eight

weeks, we told people what they were getting, and ... within a month of the end of the study, most of the placebo responders required medication. I don't want people to think ... we don't need medication anymore."

Indeed, that would be the wrong message, says UT Southwestern's Dr. Nestler. "People who are seriously ill with depression really need treatment."

The UCLA study involved patients who met the diagnostic guidelines for major depression but whose degree of illness was not severe, Dr. Nestler points out. "So the placebo responses they're seeing are high, but they're placebo responses for people with mild depression.

"The kind of person who can't get out of bed in the morning, is despondent, can't work, can't do anything – that person's not going to show a placebo response."

Placebo response is "a tougher issue to tease out in depression," agrees Dr. Drevets of the NIMH. "If you look at a depressed patient today and again in three or four weeks ... depressive symptoms fluctuate. They're intermittent."

The fluctuations can be dramatic, he says. "It's not like cancer ... where the tumor is persistent over time."

Because depression has varied forms, Dr. Drevets takes extra steps in his brain imaging studies to find subjects whose disease is more likely to be biologically based. For instance, he considers whether depression or manic depression runs in subjects' families, and whether bouts of depression have recurred.

Other studies often don't take such steps, "so they get a much more heterogeneous group of people. And this just increases the placebo effect by washing out the true differences," Dr. Drevets says. "I get much more dramatic responses to medicines. My bet is because I'm getting such a robust medication effect that they would also not have so much of a placebo effect."

Still, the new study is noteworthy because it examined the brain's reaction to treatment over time, says Dr. Pizzagalli. The repeated glimpses of brain activity were possible because the research used a technique called quantitative electroencephalography, or QEEG – a relatively inexpensive, noninvasive method that Dr. Pizzagalli expects scientists to continue to exploit.

QEEG involves taking the electrical brain data from a standard EEG and digitizing it, Dr. Leuchter says; from this, researchers can better quantify the intensity of the electrical signal.

With a technique such as PET (positron emission tomography) scanning, Dr. Pizzagalli says, "it's not always possible to make assessments [over time], for health reasons, because you use a radioactive tracer."

In addition, at a time when some studies are questioning whether the placebo effect even exists, the new research shows that placebo has a "very important and remarkable effect" on the brain, Dr. Pizzagalli says. "It shows the power, so to speak, of the mind for affecting biology."

Such research may someday yield an important diagnostic tool, Dr. Nestler says.

"If there's a high school student, for example, who's having a tough time with a girlfriend, do they have bad depression, or is it one of those lifetime things that takes time and experience to get used to?" he says. "We have no way to distinguish that right now."

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