

Los Angeles Times

Depressed brain can be 'primed'

By Susan Brink, Times Staff Writer

August 7, 2006

Before the antidepressant ever gets swallowed, before it dissolves and makes its way through the bloodstream and deep within the gray matter of the brain, some depressed patients start feeling better because they think they will. Experiments have shown that healing from depression starts in some people, called placebo responders, even when the drug given is just a sugar pill.

That, of course, is not enough to completely cure depression. But if a placebo can trick the brain into starting to get better, it's actually a pretty good predictor of who will continue to improve with antidepressant treatment.

A new study released last week in the American Journal of Psychiatry shows that the placebo effect may provide a head start for actual drug treatment by beginning to change the brain pathways that antidepressants will then follow.

The finding is an important step in helping scientists further refine who might be helped by drugs and what other factors might be involved in helping depressed patients get better.

The setting most likely matters too. Feeling free to talk openly about how he felt, along with a belief that he was going to be helped, set Chuck Park, 32, of Culver City on a path to healing. He was a participant in the 51-person study and one of 26 volunteers who received a placebo for the entire nine weeks of the trial. Another 25 volunteers received antidepressants for eight of the nine weeks. "After a few weeks, I started to feel a little better," he says. "The nurse, Michelle, would ask me how I was feeling, and I knew it wasn't just a superficial question. I could really tell her."

Activity measured by electroencephalogram in an area of the brain that is especially active in depressed patients, called the dorsolateral prefrontal cortex, slows down in some people shortly after they begin getting a placebo. The slowdown is not enough to overcome depression, but those people whose brains responded to sugar pills ended up also responding to antidepressants in the new study. And Park, who improved slightly on a

placebo, saw his depression lift completely after the trial ended and he started taking antidepressants.

"It's a very dramatic and clear example demonstrating that medication itself isn't the whole story," says Aimee M. Hunter, UCLA psychologist and lead author of the study. "If there is an actual formula or recipe for getting better, it may include medication, but it's very clear that it includes other factors or ingredients."

The placebo response, as the study measured it, appears to be a significant ingredient. Researchers attributed about 19% of the mood improvements measured on a depression scale after the trial to the placebo effect.

Psychiatric research is different from other kinds of medical research in that almost all depressed patients are given a placebo for about a week before the trial starts. Called the placebo lead-in, it is done to clear the body of other medications the patient might have been taking, but it is also done to get people used to filling out forms measuring their feelings and to allow them to meet the doctors and nurses who will be working with them. "Psychiatric studies are a lot more personal," says Dr. Andrew Leuchter, director of the laboratory of brain, behavior and pharmacology at UCLA.

"This is the first study to look at succession," Leuchter says. "There are brain changes due to placebo, and changes due to the medication." But that still leaves 81% of the formula predicting treatment success yet to be sorted out. A patient's beliefs, hopes, expectations and relationship with the doctor might also play a role.

Leuchter is part of a team of researchers in 10 centers throughout the country who are beginning to further sort out the elements that go into treating depression. They will study 300 patients to see if they can use similar EEG testing to predict which patients will do well on specific antidepressants.

There are about 20 antidepressants available by prescription, and patients can fail on several before finding one that works. In fact, a National Institute of Mental Health sponsored study of 4,000 patients found that only about half of depressed patients got relief from their symptoms following a first round of treatment with either an antidepressant or talk therapy. "Right now, trial and error is the rule, and it can take months to find the right medication," says Leuchter.

The new study he's involved with, called the Biomarkers for Rapid Identification of Treatment Effective in Major Depression trial, will look at brain changes following one week of treatment with any one of a number of antidepressants. That won't be enough time for the drugs to work clinically, but researchers will be looking for early brain changes. Volunteers will again be tested with EEGs after about three months of treatment. "We can look at early EEG changes to see if any of those changes predict how they did later," he says.

If early brain changes can alert physicians to patients who are on the right track for treatment, Leuchter says, it could cut down on the time needed to find the right drug for the right patient. "We're hoping that within three years, this might be a test available in doctors' offices," he says.

It's not just the right drug, either, that has yet to be sorted out. Depression is complicated and the NIMH is conducting a seven-year study, called the Sequenced Treatment Alternatives to Relieve Depression, to determine the effectiveness of various treatments, including drugs and psychotherapy and combinations of both.

"We know from other studies that psychotherapy also causes certain brain changes," Leuchter says. "I believe that engagement with physicians and attention is a form of supportive therapy."

It could be, he says, that just as drugs, placebo and talk therapy can change the brain's circuitry, so can wanting to get better, believing one will get better, or hearing a physician say there is great hope that you'll get better.

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