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Can the Placebo Treat Depression? That Depends

By RICHARD A. FRIEDMAN

A patient of mine who had been depressed gleefully announced that he was going to stop his antidepressant because he had just read in the news that placebos were as effective as antidepressants. A provocative simple claim, but is it true?

Suddenly, the placebo effect has made a comeback after having been supposedly debunked last year by a group of Danish researchers. In a study published in The New England Journal of Medicine, Dr. Asbjorn Hrobjartsson reported that placebos were no more effective than doing nothing in a variety of medical illnesses like hypertension, asthma and obesity. As a result, many researchers pronounced the placebo effect a myth. Perhaps this is true for the medical disorders in this study, but what about the placebo response in depression, which was unexamined in this meta-analysis?

In a soon to be published study, Dr. Arif Khan, a psychiatrist at the Northwest Clinical Research Center in Washington, analyzed the Food and Drug Administration's database of 52 clinical trials in depression, involving nine new antidepressants, conducted from 1985 to 2000. Since the agency requires drug companies to report all data from all studies for drugs under development, the database can give a more accurate picture of a new drug's efficacy than the medical journals, where positive findings are far more likely to be reported than negative ones.

Dr. Khan found that in only 48 percent of the 52 clinical trials was the antidepressant superior to the placebo. Does this really mean that antidepressants are on average no better than placebos for depression?

In a word, no. It all depends on how depression is defined and what kind of depressed patients are included in the clinical trials. Unlike a disease like H.I.V., which can be diagnosed by a simple blood test, the cause of depression is unknown; it is a syndrome that is diagnosed based on a cluster of symptoms like sad mood, low self-esteem, suicidal ideation and insomnia. So two depressed patients who appear the same in terms of their symptoms may be biologically very different.

To get into a study, a subject needs both to meet diagnostic criteria for depression and to have the requisite symptom severity, which varies from study to study. But depressed people who enroll in antidepressant clinical trials are a very select group who are not representative of depressed patients in general. For example, they tend be only mildly or moderately depressed and are never actively suicidal. And they also are usually free of other psychiatric or medical illness that are common in the general population.

It turns out that the more severely depressed people are, the less likely they are to respond to a placebo. And people with more mild depressions get better with just about all treatments, including placebos. Since most clinical trials enroll less severely depressed patients, the observed difference between the response to an antidepressant and a placebo can be misleadingly small.

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So placebo response rates vary a lot depending on the characteristics of the study subjects; it is easy to pick a group of mildly depressed patients and show that a placebo is equivalent to an antidepressant.

There are other reasons that researchers may mistakenly conclude that placebos are as effective as antidepressants. For example, at least nine clinical trials included in Dr. Khan's meta-analysis lasted only four to five weeks. Yet we know that it can take up to six weeks and more for someone with depression to respond to an antidepressant. For example, studies have shown that about half of patients who had not improved after four weeks of antidepressant treatment responded by Week 6. So studies of short duration can exaggerate the efficacy of placebos.

But why does it matter whether a depressed patient gets better on a placebo or an antidepressant? Isn't the mere fact of improvement proof of efficacy? Well, the problem is that the placebo effect is only short-lived, while depression tends to be a chronic illness with a variable rate of recurrence. Patients who continue on placebos have more than double the risk of relapse to depression than those who stay on antidepressant medication.

But the real problem with the so-called placebo effect in depression is that no one really knows what it is. The reason is that when people are given placebos, there are two reasons why they may get better. One is suggestibility or enthusiasm on the part of the patient who wishes to get better. The other is spontaneous change: they might have gotten better if nothing was done.

Spontaneous remission occurs naturally in many diseases, like the common cold, ulcers and asthma, as well as depression. Without comparing a group of depressed patients followed on neither drug nor placebo with a group taking a placebo, it is impossible to tell how much of the placebo response rate is due to suggestibility and how much is due to spontaneous change. And this is not done in clinical trials for depression.

So when it comes to depression, no one knows if placebos are really better than doing nothing. At best, a placebo may give the patient a temporary boost if he is mildly depressed, but in a seriously depressed patient, it is right in more ways than one to call it a dummy pill.