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SCIENCE JOURNAL
 By SHARON BEGLEY



Some Drugs Work To Treat Depression, But It Isn't Clear How

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Hardly any patients know how Lipitor lowers cholesterol, how Lotensin reduces blood pressure, or even how ibuprofen erases headaches. But when it comes to Prozac, Zoloft and Paxil, ads and glowing accounts in the press have turned patients with depression into veritable pharmacologists, able to rattle off how these "selective serotonin reuptake inhibitors" keep more of the brain chemical serotonin hanging around in synapses, correcting the neurochemical imbalance that causes depression.

There is only one problem. "Not a single peer-reviewed article ... support[s] claims of serotonin deficiency in any mental disorder," scientists write in the December issue of the journal PLoS Medicine.

Indeed, a steady drip of studies have challenged the "serotonin did it" hypothesis. A 2003 mouse experiment suggested that SSRIs work by inducing the birth and growth of new brain neurons, not by monkeying with serotonin. In March, a review of decades of research concluded that something other than "changes in chemical balance might underlie depression." And as Jeffrey Lacasse and Jonathan Leo write in PLoS Medicine, although ads for SSRIs say they correct a chemical imbalance, "there is no such thing as a scientifically correct 'balance' of serotonin."

How did so many smart people get it so wrong? Medicinal chemist Derek Lowe, who works in drug development for a pharmaceutical firm, offered an explanation in his "In the Pipeline" blog. "I worked on central nervous system drugs for eight years, and I can confidently state that we know just slightly more than jack" about how antidepressants work.

It is not for lack of trying. In 1965, psychiatrist Joseph Schildkraut of Harvard University suggested that a deficiency of a brain chemical causes depression. With the

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success of drugs that block the reuptake of these chemicals, that idea started to look pretty good.

Yet the evidence was always circumstantial. You can't measure serotonin in the brains of living human beings. The next best thing, measuring the compounds that serotonin breaks down to in cerebrospinal fluid, suggested that clinically depressed patients had less of it than healthy people did. But it was never clear whether depression caused those low levels, or vice versa. A 2002 review of these early experiments took them to task for such flaws.

There had always been data that don't fit the serotonin-imbalance theory. Depleting people's serotonin levels sometimes changed their mood for the worse and sometimes didn't. Sending serotonin levels through the roof didn't help depression, a study found as early as 1975.

There is little doubt that the SSRIs do what their name says, keeping more serotonin in the brain's synapses. But the fact "that SSRIs act on the serotonin system does not mean that clinical depression results from a shortage of serotonin," says Dr. Leo, professor of anatomy at Lake Erie College of Osteopathic Medicine, Bradenton, Fla. No more so, anyway, than the fact that steroid creams help rashes means that rashes are caused by a steroid shortage.

A clue to how SSRIs do work comes from how long they take to have any effect. They rarely make a dent in depression before three weeks, and sometimes take eight weeks to kick in. But they affect serotonin levels right away. If depression doesn't lift despite that serotonin hit, the drugs must be doing something else; it's the something else that eases depression.

The best evidence so far is that the something else is neurogenesis -- the birth of new neurons. When scientists led by Rene Hen of Columbia University and Ronald Duman of Yale blocked neurogenesis in mice, SSRIs had no effect. When neurogenesis was unimpeded, SSRIs made the mice less anxious and depressed -- for rodents. As best scientists can tell, SSRIs first activate the serotonin system, which is somehow necessary for neurogenesis. That is what takes weeks.

Claiming that depression results from a brain-chemical imbalance, as ads do, is problematic on several fronts. Patients who believe this are more likely to demand a prescription. If you have a disease caused by too little insulin, you take insulin; if you have one caused by too little serotonin, you take serotonin boosters.

Most people treated for depression get pills rather than psychotherapy, and this week a study from Stanford University reported that drugs have been supplanting psychotherapy for depressed adolescents. Clinical guidelines call for using both, and for psychotherapy to be the first-line treatment for most kids. Psychotherapy "can be as effective as medications" for major depression, concluded a study in April of 240 patients, in the Archives of General Psychiatry. Numerous other studies find the same.

The hegemony of the serotonin hypothesis may be keeping patients from a therapy that will help them more in the long term. The relapse rate for patients on pills is higher than for those getting cognitive-behavior psychotherapy.

Some 19 million people in the U.S. suffer from depression in any given year. For many, SSRIs help little, if at all. To do better, we have to get the science right.

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