



Advertisements for SSRIs May Be Misleading

Laurie Barclay, MD

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Nov. 8, 2005-- Advertisements in the U.S. for selective serotonin reuptake inhibitors (SSRIs) are not based on science, according to an essay published in the December issue of the *Public Library of Science (PLoS) Medicine*. Since the 1960s, investigators have proposed the "serotonin hypothesis," which implicates low brain levels of serotonin in depression. However, extensive research to date has failed to confirm this theory.

In 1965, Joseph Schildkraut suggested that depression was linked to low levels of norepinephrine, but investigators subsequently proposed that serotonin was the responsible neurotransmitter. Numerous studies to identify reproducible changes in neurotransmitter levels in the cerebrospinal fluid of clinically depressed patients, or to induce or correct depression by manipulating brain serotonin levels, were inconclusive and fraught with methodological limitations. Contemporary research has failed to prove any serotonergic lesion in any mental disorder, according to the *PLoS Medicine* essay.

Consumer advertisements for SSRIs in the U.S. "typically claim that depression, or other psychiatric condition, is probably caused by a chemical imbalance of the neurotransmitter serotonin, and that SSRIs correct this imbalance," lead author Jeffrey R. Lacasse, MSW, a PhD candidate at Florida State University College of Social Work in Tallahassee, told Medscape. "They routinely use visual portrayals of a nerve synapse demonstrating the action of SSRIs, showing a 'chemical imbalance' which is then 'corrected' by the medication."

Gordon McCarter, PhD, an assistant professor of biological sciences at the College of Pharmacy of Touro University in Vallejo, California, agreed that the evidence for an "imbalance" in neurotransmitters causing depression is "circumstantial" and "more and more tenuous." He noted the dearth of studies showing any measurable difference in serotonin or norepinephrine between depressed patients and controls, with the limited positive findings based on suicide victims. Dr. McCarter was not involved in the *PLoS Medicine* essay.

"This doesn't mean there isn't a difference, [but] it may be too localized and too small to measure with current techniques," Dr. McCarter told Medscape.

"Serotonin clearly plays a role in some [cases of] depression and blocking its

reuptake clearly helps many depressed patients, but this may be a symptomatic approach. Current thinking is that genetics, perhaps regarding serotonin-handling molecules in some cases, combined with life history affects the likelihood that stressful life events will trigger a depressive episode. Stating that depression is caused by a chemical imbalance is extremely simplistic."

The evidence that is usually used to support the claim of a serotonin imbalance, according to Mr. Lacasse, is the efficacy of SSRIs. Because SSRIs have an effect on depression, and SSRIs affect serotonin, the conclusion touted in the ads is that depression is due to serotonin imbalance. However, this line of reasoning may be inherently flawed; aspirin may relieve headache, but we do not therefore conclude that headaches are caused by low levels of aspirin in the brain.

Another difficulty with using the efficacy of SSRIs in depression to bolster the serotonin hypothesis is that the efficacy itself is problematic. A meta-analysis cited in the *PLoS Medicine* essay reviewed all clinical trials of antidepressants submitted to the U.S. Food and Drug Administration (FDA). This meta-analysis showed that placebo duplicated about 80% of the antidepressant response, and that more than half of pharmaceutical company-sponsored trials failed to show a statistically significant difference between antidepressant and placebo. Moreover, antidepressants that do not affect serotonin are as effective as SSRIs in reducing symptoms of depression, and even placebo and nonpharmacologic treatments have been shown to have robust effects.

"The etiology of depression and anxiety is still a mystery, and this is reflected in the scientific literature," senior author Jonathan Leo, PhD, a professor of neuroanatomy at Lake Erie College of Osteopathic Medicine in Bradenton, Florida, told Medscape. "The Diagnostic and Statistical Manual of Mental Disorders does not list serotonin as a cause of any mental disorder; it is simply one neurotransmitter that continues to be investigated. And the prescribing information for the SSRIs does not claim that their mechanism of action is to correct a chemical imbalance, although this is exactly what the advertisements claim."

The *PLoS Medicine* essay cites a recent review article on depression published by John Mann in the *New England Journal of Medicine*, which lists a dozen chemicals potentially involved in depression, and several pharmacologic interventions that do not affect serotonin; and a Cochrane review showing no major difference in efficacy between SSRIs and tricyclic antidepressants. Bupropion and reboxetine, which do not significantly affect serotonin, were shown to be as effective as SSRIs in the treatment of depression. In recent randomized controlled trials, St. John's wort and placebo were each more effective for depression than SSRIs, and exercise was as effective as the SSRI sertraline.

"The pharmaceutical industry has managed to convey a misleading picture," Joanna Moncrieff, MD, a senior lecturer in psychiatry at University College London, U.K., told Medscape. "I speak to quite a few journalists, and they are shocked to hear that the link between serotonin and depression is very tenuous and the research conflicting and not convincing. The psychiatric profession and academic researchers are probably also partly to blame for glossing over the weakness of the research."

The FDA is charged with the duty of regulating direct-to-consumer advertising (DTCA), and with ensuring that it is grounded in scientific evidence. However, the *PLoS Medicine* essay points out the "remarkable, and possibly unparalleled" disconnect between the scientific literature and the SSRI ads.

"All prescription drug advertising is to be fair and balanced, with an accurate portrayal of the benefits versus the risks," FDA spokesperson Crystal Rice, from the Trade Media and Exhibits Center for Drug Evaluation and Research, told Medscape. "There would be no difference with regard to these drugs ? as with any drug, these same rules apply. Concerning what information must be disclosed and in what manner, and how that would apply specifically to this situation, this is done on a case-by-case basis and dependent on the specific product and specific promotional piece."

The FDA requires that drug advertising present the most serious risks and the most common risks, according to Ms. Rice. The Division of Drug Marketing, Advertising, and Communications works closely with the medical review divisions and others in the FDA in determining which specific risks should be presented. The FDA has requested a labeling change for antidepressants, now requiring that drug companies include the warning about increased risk of suicidality in their advertising promotion. Until Feb. 28, 2006, the FDA has an open docket seeking the public's input on DTCA.

"I don't really think [DTCA statements about serotonin in depression] are untrue, especially if they are presented with qualifiers such as 'research suggests' and 'scientists believe,' but they might be bordering a little on unbalanced, so I think the FDA could be doing a little better in this regard," Dr. McCarter said. "By implying that depression is 'only' a chemical imbalance, [the ads] are leaving out very important aspects of the depression story. A 'balanced' statement on the etiology and treatment of depression directed at consumers should note that certain forms of counseling or psychotherapy, in particular cognitive-behavioral therapy, is equally effective in the treatment of major depression as antidepressant medication, and that together they are even better."

The *PLoS Medicine* essay notes that SSRIs are now among the best-selling drugs in medical practice, thanks in large measure to successful advertising campaigns. The marketing emphasis in SSRI ads on a theoretical serotonin imbalance appears to be specific to the U.S., causing "striking differences" from

advertising in the EU. Unlike the U.S., the EU does not allow DTCA.

"Two very different pictures emerge of the same exact medication, depending on government regulation and marketing practices," Dr. Leo said. "It's two very different political climates. We suspect that one important factor is the amount of influence that pharmaceutical companies hold in a particular society."

The British equivalent of the FDA, known as the Medicines and Healthcare products Regulatory Agency (MHRA), and U.K. medical literature published in the *British Medical Journal* and elsewhere have preceded the FDA in their open criticism of U.S. marketing practices for SSRIs.

"I personally feel that all drug advertising should be banned both to professionals and patients," said Dr. Moncrieff, who is also a founding member and cochair of the Critical Psychiatry Network. "Information about drugs should come from independent sources that people can access if required, and not be constantly shoved into people's faces. We currently have a manufactured epidemic of psychological disorders, and the drug industry is at least partly to blame."

However, Dr. Leo and Mr. Lacasse are not convinced that a ban on DTCA would eliminate misinformation about the serotonin theory.

"We suspect that this theory is repeated to patients by physicians, and that the problem is not limited to DTCA," they explain. "Depression and anxiety are complicated issues that cannot be explained in a 30-second commercial.... When the serotonin theory is portrayed with clever visual portrayals that do not accurately represent the neuroscience research, consumers are led to believe that medication is necessary for the treatment for depression."

Ostensibly absent from commercials is information concerning alternatives to medication, including evidence from randomized controlled trials that psychotherapy and exercise are effective in the treatment of depression; and significant adverse effects from SSRIs, including very high rates of sexual dysfunction. Other issues typically omitted from DTCA are difficulty in withdrawing from SSRIs in some patients; the self-limited nature of depression for many people, in whom it lasts for only several months; and the robust placebo effect documented in the overwhelming majority of clinical trials.

Dr. McCarter suggests that the FDA or even the National Institutes of Health might provide clear and concise information on the issues surrounding specific prescription drug classes, and treatments for diseases in general.

"Perhaps drug companies could be required, whenever they wish to advertise a prescription drug, to pay into a fund that provides public service announcements regarding that particular therapeutic area," he said. "Maybe there should be required a general 'balance statement,' produced by the FDA to accompany any

advertising; short and sweet, not like the notorious 'brief summaries' that were fired out in staccato or squished into microscopic text on the next page."

Another important concern embedded in DTCA is the issue of informed consent, which Mr. Lacasse and Dr. Leo believe is essential to an ethical and productive physician-patient relationship.

"If a patient comes into the office believing the serotonin theory and the doctor doesn't take the time to correct them, we wonder where that leaves the issue of informed consent, and especially the issue of potential risks and benefits," they point out. "We suspect that many consumers believe the serotonin theory to be more scientifically based than it is, and that they might have chosen an alternative approach to their distress if they were fully informed. These ads work to confound informed consent, essentially."

One example is a television ad for sertraline (*Zoloft*), which portrays a serotonin imbalance and claims, "Prescription Zoloft works to correct this imbalance." DTCA for fluoxetine (*Prozac*), Paxil, escitalopram (*Lexapro*), and other SSRIs has voiced comparable messages.

"In terms of real-life effects of this advertising, we are concerned that this oversimplified theory has become the intellectual justification for 10-minute office visits which result in the prescription of antidepressants for a variety of ill-defined conditions," Mr. Lacasse concluded. "In general, people need to be more skeptical regarding claims of chemical imbalance as explanation for psychological distress."

On the other hand, Dr McCarter believes that heightening consumer awareness of depression may produce some positive effects.

"While the 'chemical imbalance' message is overly simplistic and may mislead the audience away from an understanding of the cognitive and behavioral aspects of depression, if it gets someone who is suffering from this disease to think about seeing a doctor or even just to consider for the first time that there is a biological aspect to it, then some overall benefit has been achieved," he said. "I just wish there were other equally prominent information sources that were not produced under a profit motive."

Drs. Lacasse and Leo report no competing interests and no commercial funding for this work.

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Reviewed by Gary D. Vogin, MD
