

The Serotonin Balance Myth VII

At the very least, we need to stop thinking of psychoactive drugs as the best, and often the only, treatment for mental illness or emotional distress. Both psychotherapy and exercise have been shown to be as effective as drugs for depression, and their effects are longer-lasting, but unfortunately, there is no industry to push these alternatives and Americans have come to believe that pills must be more potent. (Marcia Angell, M.D. former editor-in-chief New England Journal of Medicine)

No one has made the case against these brain drugs better than Irving Kirsch, a researcher at Harvard. Kirsch argues that anti-depressants (ADMs) are active placebos. The physical symptoms ADMs cause, like headache, stomach-ache, and sexual problems, create a belief in the patient that they are getting a powerful treatment and this belief is *the mechanism of change* for the person reporting depression.

His evidence is simple. When compared to sugar pills (placebos), ADMs consistently produce rates of improvement over placebo “so small that they did not qualify as clinically significant” (p. 53). That is, mood changes were so small that the rating scales did not show meaningful changes. The patients taking ADMs rated their depression as only slightly lower than those taking sugar pills, with no real-life difference in how they felt.

Many objections were raised to his research but he responds ably to each and, in the process, demolishes the whole notion that ADMs treat depression.

- For example, to the objection that ADMs do reduce depression symptoms in some he responds that all sorts of placebos reduce various symptoms including, famously, sham surgeries for knee pain. He cites a study in the prestigious Journal of the American Medical Association in 2002 that compared an SSRI (Zoloft), to an herbal remedy, and a sugar pill. After two months, “there was still no difference between groups” (p. 66). All three groups got better and stayed better, including those taking the sugar pill.
- Many would also find it shocking to know that the FDA “acknowledged the failure (of ADMs) to show a clinically significant benefit” (p. 74).
- There is also little doubt that the simple action of taking a sugar pill affects us and the mechanism appears to be a reduction in the way pain is signaled in the brain (Pecina). All of this undermines the simplistic and incorrect idea that ADMs correct a “chemical imbalance” in the brain.
- To the idea that depression is caused by too little serotonin, norepinephrine, or dopamine in the brain, Kirsch observes that “at least 90” studies designed to show this outcome have failed to do so (p. 91).
- Finally, a drug called tianeptine works opposite to common ADMs like Prozac or Paxil to *decrease the amount of serotonin* in the brain. Summing up, “if depression can be equally affected by drugs that increase serotonin . . . decrease [it] . . . and drugs that do not affect it at all, then the benefits of these drugs cannot be due to their specific chemical activity” (p. 97).

But don’t medical scientists find biological differences in the brains of people with depression?

- No, not all. Two of the last three heads of the National Institute of Mental Health (the psychiatry arm of the federal government’s National Institute of Health) and the psychiatrist who chaired the committee that created “psychiatry’s bible” the DSM 5 have stated variously that there are

no “biomarkers” for mental illness, that current diagnosis of “mental illness” is an impediment to “progress,” “lacks validity,” and constitutes “an absolute scientific nightmare” (NYT).

Dr. Joanna Moncrieff, Senior Lecturer in Psychiatry at University College London, said of the serotonin balance theory: *"It is high time that it was stated clearly that the serotonin imbalance theory of depression is not supported by the scientific evidence . . . Through misleading publicity the pharmaceutical industry has helped to ensure that most of the general public is unaware of this"* (PLOS).

Despite this, prescribing ADMs is still a roughly \$12 billion industry in the U.S. alone. Alan Frazer, the chair of pharmacology at University of Texas-San Antonio, in an interview with NPR says of the serotonin balance myth, "I don't know of any story that has supplanted it" and Pedro Delgado who chairs the psychiatry department at UT adds, “it definitely continues to live-absolutely . . . If you go to your community doctor, you’re likely to hear some version of that” (NPR). The takeaway for NPR’s Alix Spiegel was this, “Researchers don’t really know what causes depression” and a non-story like that is not going to create the next blockbuster drug.

In some ways, the prescribing of ADMs reflects our whole culture of pill-taking. Sadly, the pill-prescribing action by a physician pays three or four times more than talking to patients. Doctors in training at leading medical schools (Harvard and Johns Hopkins) are taught to tell their patients that they have a chemical imbalance that needs treatment with ADMs in the same the way a diabetic needs insulin.

Can ADMs cause harm? Yes. Leaving aside the common, but not insignificant, issues around appetite, weight, and sexual dysfunction, there is research suggesting that anti-depressants can disrupt the body’s complex balance. In this view, down moods are normal and adaptive rather than pathological. If the body’s store of serotonin is increased over time by drugs like Prozac and then the drug is taken away, the body’s response may be to fall into a depressed state (Andrews).

The takeaway for anyone on ADMs: If you’ve been on them a while, *you are best advised to stay on them while finding as many other healthy ways to handle stress as you are able*. If you wish to taper, begin by talking it over with the prescribing physician. Two good resources are The Antidepressant Solution written by a Harvard physician and Laura Delano’s website “The Withdrawal Project.” Delano offers an approach to tapering drugs from stimulants to sedatives that is very conservative (slow-paced) and respectful of physician engagement.

The site answers questions about how slow to go, what’s a “cut and hold” approach to tapering, how to change the dosage of pills, where to get liquid forms of the common psychotropics, etc. Again, there is no need to rush. Build your skills using the advice of your therapist and approach the taper with calm and confidence.

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- Joseph Glenmullen, M.D. (2006). The Antidepressant Solution: A Step-by-Step Guide. N.Y.: Free Press.
- NPR at: <http://www.npr.org/blogs/health/2012/01/23/145525853/when-it-comes-to-depression-serotonin-isnt-the-whole-story>
- NYT at: www.nytimes.com/2013/05/07/health/psychiatrys-new-guide-falls-short-experts-say.html
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No one has made the case any better than Irving Kirsch, a researcher at Harvard. Kirsch argues that antidepressants (ADMs) are active placebos. The physical symptoms ADMs cause, like headache, stomach-ache, and sexual problems, create a belief in the patient that they are getting a powerful treatment and this belief is *the mechanism of change* for the person reporting depression.

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The Irish equivalent of the FDA, the Irish Medicines Board, has banned GlaxoSmithKline from claiming in their patient information leaflets that paroxetine (Paxil) corrects a chemical imbalance. Dr Joanna Moncrieff, Senior Lecturer in Psychiatry at University College London, said of serotonin balance theory: *"It is high time that it was stated clearly that the serotonin imbalance theory of depression is not supported by the scientific evidence . . . Through misleading publicity the pharmaceutical industry has helped to ensure that most of the general public is unaware of this"* (PLoS).

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In some ways, *the prescribing of ADMs is more of a treatment for the busy, stressed physician or nurse than for the patient*. Pressed into ever smaller amounts of time, the doctor is confronted by a patient who each year is subjected to billions of dollars of advertising emphasizing the utility of drugs such as ADMs. The patient has been trained to want a pill, not advice about exercise, or suggestions to improve problem-solving skills. Furthermore, the pill-prescribing action by the doctor pays three or four times more than talking to patients. Doctors in training at leading medical schools (Harvard and Johns Hopkins) are taught to tell their patients that they have a chemical imbalance that needs treatment with ADMs in the same the way a diabetic needs insulin.

On NPR, psychiatrist Dr. Delgado sums up the placebo effect by saying, "When you feel that you understand it (depression), a lot of the stress levels dramatically are reduced . . . so stress, hormones, and a lot of biological factors change" (NPR). The takeaway for NPR's Alix Spiegel was this, "Researchers don't really know what causes depression" and a non-story like that is not going to create the next "blockbuster" drug (NPR).

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The takeaway for anyone on depressants: If you've been on them a while, *you are best advised to stay on them while finding as many other healthy ways to handle stress as you are able*.

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His research concludes that there is evidence to support this theory since depression relapse increases in depressed patients treated with anti-depressants compared to those treated with sugar pills.

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Some countries have taken action to address the misleading advertising around ADMs. The Irish equivalent of the FDA, the Irish Medicines Board, recently banned GlaxoSmithKline from claiming in their patient information leaflets that paroxetine (Paxil) corrects a chemical imbalance, the FDA has never taken any similar action on this issue.

Dr Joanna Moncrieff, Senior Lecturer in Psychiatry at University College London, said of the serotonin balance theory: *“It is high time that it was stated clearly that the serotonin imbalance theory of depression is not supported by the scientific evidence or by expert opinion. Through misleading publicity the pharmaceutical industry has helped to ensure that most of the general public is unaware of this”* (PLOS).

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In some ways, *the prescribing of ADMs is more of a treatment for the busy, stressed physician or nurse than for the patient*. Pressed into ever smaller amounts of time, the doctor is confronted by a patient who each year is subjected to more than \$3 billion dollars of advertising emphasizing the utility of ADMs. The patient has been trained to want a pill, not advice about exercise, or suggestions to improve their problem-solving skills. Furthermore, the pill-prescribing action by the doctor pays three or four times more than talking to patients. Doctors in training at our most prestigious medical schools (think Harvard and Johns Hopkins) are taught to tell their patients that they have a chemical imbalance that needs treatment with ADMs in the same the way a diabetic needs insulin.

Psychiatrist Dr. Delgado sums up the placebo effect in part by saying, “When you feel that you understand it (depression), a lot of the stress levels dramatically are reduced . . . so stress, hormones, and a lot of biological factors change” (NPR). The takeaway for NPR’s Alix Spiegel was this, “Researchers don’t really know what causes depression” and a non-story like that is not going to create the next “blockbuster” drug (NPR).

Finally, the question remains as to whether anti-depressants cause harm. Leaving aside the common, but not insignificant, issues of weight gain and sexual dysfunction, there is research suggesting that anti-depressants can disrupt the body’s complex balance. In this view, down moods are normal and adaptive rather than pathological. If the body’s store of serotonin is increased over time by drugs like Prozac and then the drug is taken away, the body’s response may be to fall into a depressed state. Paul Andrews of Canada’s McMaster University puts it this way.

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His research concludes that there is evidence to support this theory since depression relapse increases in depressed patients treated with anti-depressants compared to those treated with sugar pills. The takeaway for anyone on depressants: If you’ve been on them a while, you may be best advised to stay on them while finding as many other healthy ways to handle stress as you are able.

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Below are excerpts from the online journal PLoS at: <http://www.plosmedicine.org>

Consumer ads for a class of antidepressants called SSRIs often claim that depression is due to a chemical imbalance in the brain, and that SSRIs correct this imbalance, but these claims are not supported by scientific evidence . . . For instance, the widely televised animated Zoloft (setraline) commercials have dramatized a serotonin imbalance and stated, "Prescription Zoloft works to correct this imbalance." Advertisements for other SSRIs, such as Prozac (fluoxetine), Paxil (paroxetine), and Lexapro (escitalopram), have made similar claims.

In the US, the FDA is responsible for regulating consumer advertisements, and requires that they be based on scientific evidence. [The authors] claim the mismatch between the scientific literature and the SSRI advertisements is "remarkable, and possibly unparalleled."

Meanwhile, the Irish equivalent of the FDA, the Irish Medicines Board, recently banned GlaxoSmithKline from claiming in their patient information leaflets that paroxetine (Paxil) corrects a chemical imbalance, the FDA has never taken any similar action on this issue.

Dr Joanna Moncrieff, Senior Lecturer in Psychiatry at University College London, said of the serotonin balance theory: *"It is high time that it was stated clearly that the serotonin imbalance theory of depression is not supported by the scientific evidence or by expert opinion. Through misleading publicity the pharmaceutical industry has helped to ensure that most of the general public is unaware of this"* (PLoS).

To say that misleading publicity has kept this theory alive is a vast understatement. Alan Frazer, the chair of pharmacology at UT-San Antonio in an interview with NPR says of the serotonin balance myth, "I don't know of any story that has supplanted it" and Pedro Delgado who chairs the psychiatry department at UT adds, "it definitely continues to live-absolutely . . . If you go to your community doctor, you're likely to hear some version of that" (NPR).

Dr. Joseph Coyle, professor of neuroscience at Harvard Medical School and editor of the journal Archives of General Psychiatry comments that "chemical imbalance is sort of last-century thinking. It's much more complicated than that" and further that although "serotonin plays a role in depression, low serotonin is likely not the cause . . . It's (serotonin balance theory) *really an outmoded way of thinking*" (NPR). This admission regarding serotonin is rather like saying we know that the brain has something to do with thinking but we're really not sure what.

The serotonin balance myth is linked to the history of tricyclic antidepressants (an earlier type of antidepressant) and Parkinson's disease. It did turn out that Parkinson's was caused by a deficit in dopamine. Unsurprisingly, the hope was depression could be similarly explained as a deficit. But science could never prove this. Nevertheless, when Prozac hit the market in 1987, the mild side-effect profile made it instantly popular and since it affected only one neurotransmitter, serotonin, the stage was set for the serotonin deficit myth to take hold.

Pharmacologist Frazer comments, "I don't think there's any convincing body of data that anybody has ever found that depression is associated to a significant extent with a loss of serotonin." Dr. Delgado himself carried out a study in the 1990's showing "that if you take a normal person and deplete them of serotonin, they will not become depressed" (NPR). And Harvard's Coyle notes that the field has moved on from the serotonin balance myth to questions around genes and depression. He says, "What's being looked at are processes that are much more fundamental than just serotonin levels," he says. "We need to move beyond serotonin . . ." (NPR).

The utility of the myth is obvious. When a physician or pharmacist tells a patient that a pill is correcting a deficit in the body it is easy to understand and sell to people. The side effects only add to the power of the placebo. The patient surmises that something big is happening inside of his or her body, but not too big. Since the doctor said it would help, the suggestion often tilts the patient's thinking in a better direction. Hope is restored, thus changing a person's thinking regarding the down mood.

Psychiatrist Dr. Delgado sums up by saying, “When you feel that you understand it (depression), a lot of the stress levels dramatically are reduced . . . so stress, hormones, and a lot of biological factors change” (NPR). The takeaway for NPR’s Alix Spiegel was this, “Researchers don’t really know what causes depression” and a non-story like that is not going to create the next “blockbuster” drug (NPR). Finally, the question remains as to whether anti-depressants cause harm. Leaving aside the common, but not insignificant, issues of weight gain and sexual dysfunction, there is research suggesting that anti-depressants can disrupt the body’s complex balance. In this view, down moods are normal and adaptive rather than pathological. If the body’s store of serotonin is increased over time by drugs like Prozac and then the drug is taken away, the body’s response may be to fall into a depressed state. Paul Andrews of Canada’s McMaster University puts it this way.

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Front. Psychol., 24 April 2012 | doi: 10.3389/fpsyg.2012.00117

Primum non nocere: an evolutionary analysis of whether antidepressants do more harm than good At: <http://www.frontiersin.org/Journal/10.3389/fpsyg.2012.00117/full>

Also: Marcia Angell <http://www.nybooks.com/articles/archives/2011/jun/23/epidemic-mental-illness-why/>

Big think at: <http://bigthink.com/devil-in-the-data/the-chemical-imbalance-myth>

We live in a time of information abundance, which far too many of us see as information overload. With the sum total of human knowledge, past and present, at our fingertips, we're faced with a crisis of attention: which ideas should we engage with, and why? Big Think is an evolving roadmap to the best thinking on the planet — the ideas that can help you think flexibly and act decisively in a multivariate world.

A word about Big Ideas and Themes — The architecture of Big Think

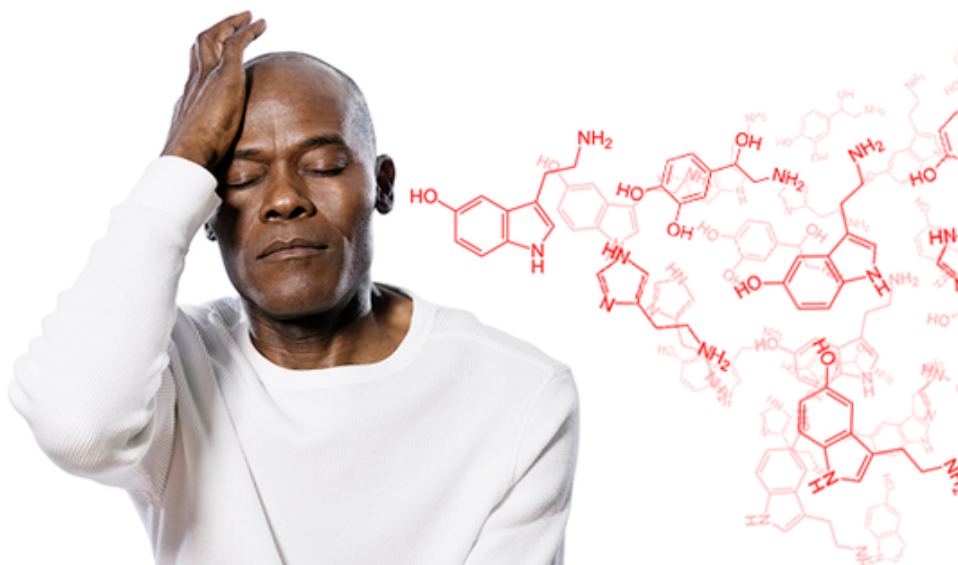
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The Chemical Imbalance Myth

by [Kas Thomas](#)

May 8, 2013, 10:09 AM



Very few countries allow direct-to-consumer advertising by drug companies, but in those that do (New Zealand, Canada, and the U.S.), the medicine-buying public has been brainwashed to believe that mental illnesses, particularly those involving depression, are caused by a "chemical imbalance in the brain." Hundreds of billions of dollars of Prozac, Zoloft, Paxil, Celexa, and other popular antidepressants have been sold on the basis of their being able to restore normal serotonin levels to out-of-whack brain cells.

The trouble is, there's no evidence that depression is caused by a serotonin imbalance. And there's no simple blood or urine test that will tell you if neurotransmitter levels in your brain are out of whack. (Serotonin doesn't cross the [Blood Brain Barrier](#). Hence, a blood test would be meaningless.) Even if there were such a test, the mere finding that serotonin is too low (or too high) in your brain isn't enough, by itself, to establish a causal connection with how you feel. Saying that because serotonin reuptake inhibitors help treat depression, *therefore* depression is a disorder of serotonin imbalance in the brain, is like saying that because I'm unfocused in the morning until I have coffee, *therefore* I have Morning Attention Deficit Disorder caused by an imbalance of purines in my brain. (Caffeine is an [antagonist of adenine receptors](#).) From there, it's only one step away to the chocolate-imbalance theory of lovesickness, the Red Bull imbalance theory of fatigue, and equally cockamamie theories.

As the authors of a [paper](#) in *PLoS Medicine* noted: "To our knowledge, there is not a single peer-reviewed article that can be accurately cited to directly support claims of serotonin deficiency in any mental disorder, while there are many articles that present counterevidence."

Advertising

Serotonin-imbalance theorists have yet to reconcile the fact that while some depressed patients respond to SSRIs, some also respond to SNRIs (drugs that affect norepinephrine and serotonin levels), whereas others respond to drugs like [mirtazapine](#) that affect norepinephrine and dopamine and serotonin (or dopamine and norepinephrine in the case of bupropion), whereas for other patients (namely those who respond to [tricyclics](#)) therapeutic action involves an intricate combination of imbalances related to serotonin, norepinephrine, and dopamine *transporters* (SERT and NET and DAT) as well as the H1 histamine receptor, the 1A and 2A serotonin *receptors*, $\alpha 1$ and $\alpha 2$ adrenergic receptors, the D2 dopamine receptor, and the muscarinic acetylcholine receptor. That's an awful lot of different types of "chemical imbalance," for one illness. The literature shows that depressed patients tend to respond more-or-less equally well to *any* of the major categories of antidepressants (this was the major finding of the six-year, \$35 million [STAR*D study](#)), basically proving that these drugs are *not* highly specific in their effects. If they were indeed highly specific to certain types of depression (if some patients specifically *needed* an SNRI, whereas others specifically *needed* an SSRI, whereas others *needed* a tricyclic, etc.) then the patient subpopulations would add up to more than 100% of the total patient population, based on how many people tend to respond to each type of drug.

Then there's the somewhat curious fact that [tianeptine](#), an antidepressant marketed for many years under the name Coaxil in Europe and South America, is actually a selective serotonin reuptake *enhancer* (not inhibitor). So apparently, some depression is caused by too *much* serotonin.

Researchers who've tried to induce depressive symptoms in normal subjects by lowering their endogenous serotonin levels (through a well-known dietary trick) have consistently been unable to do so. (E.g., [Salomon et al.](#), "Lack of behavioral effects of monoamine depletion in healthy subjects," *Biological Psychiatry*, 1 January 1997, 41:1, 58–64.) This elementary result is rarely discussed.

The [Zoloft web site](#) promotes Zoloft (an SSRI) as a treatment for Major Depressive Disorder (MDD), Obsessive-Compulsive Disorder (OCD), Panic Disorder, Posttraumatic Stress Disorder (PTSD), Premenstrual Dysphoric Disorder (PMDD), and Social Anxiety Disorder (SAD). As the authors of one paper noted: "For the serotonin hypothesis to be correct as currently presented, serotonin regulation would need to be the cause (and remedy) of each of these disorders. This is improbable, and no one has yet proposed a cogent theory explaining how a singular putative neurochemical abnormality could result in so many wildly differing behavioral manifestations." See [Lacasse, J.R., and Leo, J. \(2005\), "Serotonin and Depression: A Disconnect between the Advertisements and the Scientific Literature," PLoS Med 2\(12\):e392.](#)

The [Code of Federal Regulations under which direct-to-consumer drug advertising is regulated](#) states that an advertisement may be cited as false or misleading if it "[c]ontains claims concerning the mechanism or site of drug action that are not generally regarded as established by scientific evidence by experts qualified by scientific training and experience *without disclosing that the claims are not established and the limitations of the supporting evidence...*" Direct-to-consumer advertisements are also forbidden to include content that "contains favorable information or opinions about a drug previously regarded as valid but which have been rendered invalid by contrary and more credible recent information." Despite this, we still find the [Paxil website](#) saying (quite falsely): "Paxil can help restore the balance of serotonin (a naturally occurring chemical in the brain) -- which helps reduce the symptoms of anxiety and depression." Oddly, the FDA has never once cited a pharmaceutical company for these sorts of falsehoods, which have been presented over and over again in direct-to-consumer advertising about antidepressants.

It would be easier to accept neurotransmitter-imbalance theories of depression if the drugs in question worked with the same high degree of efficacy that, say, aspirin works for a headache or that insulin does for diabetes, but in fact the drugs work so poorly that the [number one bestselling drug in America](#) right now is an adjunctive drug sold on the basis of helping antidepressants work better (Abilify). When I mentioned this to a (non-depressed) friend of mine, and told him the [retail price of a month's worth of Abilify](#) (5mg, 30 pills) is a whopping **\$683** (making Abilify many times more valuable, ounce for ounce, than pure gold), his comment was: "Why don't you just go lease a new Acura and see if that doesn't cheer you up? It'd be cheaper, and more satisfying."

Personally, I think my friend is right. Everybody on Medicare, Medicaid, or private insurance who's receiving Abilify at subsidized rates should be offered a choice: continue to receive Abilify, or start driving a new Acura at no cost.

I wonder which one people would choose?

Additional Reading

For more on this subject, I recommend: "The Chemical Imbalance Explanation for Depression: Origins, Lay Endorsement, and Clinical Implications" by Christopher M. France, Paul H.

Lysaker, and Ryan P. Robinson, in *Professional Psychology: Research and Practice*, 2007, 38:4, 411–420, full version [here](#).

Also see Lacasse, Jeffrey R., and Leo, Jonathan, "Serotonin and Depression: A Disconnect between the Advertisements and the Scientific Literature," *PLoS Med* 2(12): e392, full version [here](#).

We find that the risk of relapse after ADM discontinuation is positively associated with the degree to which ADMs enhance serotonin and norepinephrine in prefrontal cortex, after controlling for covariates.

Serotonin Balance Myth

Ads for SSRI antidepressants are misleading, say researchers

12 Nov 2005

Consumer ads for a class of antidepressants called SSRIs often claim that depression is due to a chemical imbalance in the brain, and that SSRIs correct this imbalance, but these claims are not supported by scientific evidence, say researchers in *PLoS Medicine*.

Although scientists in the 1960s suggested that depression may be linked to low brain levels of the chemical serotonin (the so-called "serotonin hypothesis"), contemporary research has failed to confirm the hypothesis, they say.

The researchers--Jeffrey Lacasse, a doctoral candidate at Florida State University and Dr. Jonathan Leo, a neuroanatomy professor at Lake Erie College of Osteopathic Medicine--studied US consumer advertisements for SSRIs from print, television, and the Internet. They found widespread claims that SSRIs restore the serotonin balance of the brain. "Yet there is no such thing as a scientifically established correct 'balance' of serotonin," the authors say.

According to Lacasse and Leo, in the scientific literature it is openly admitted that the serotonin hypothesis remains unconfirmed and that there is "a growing body of medical literature casting doubt on the serotonin hypothesis," which is not reflected in the consumer ads.

For instance, the widely televised animated Zoloft (setraline) commercials have dramatized a serotonin imbalance and stated, "Prescription Zoloft works to correct this imbalance." Advertisements for other SSRIs, such as Prozac (fluoxetine), Paxil (paroxetine), and Lexapro (escitalopram), have made similar claims.

In the US, the FDA is responsible for regulating consumer advertisements, and requires that they be based on scientific evidence. Yet, according to Lacasse and Leo, the mismatch between the scientific literature and the SSRI advertisements is "remarkable, and possibly unparalleled."

And while the Irish equivalent of the FDA, the Irish Medicines Board, recently banned GlaxoSmithKline from claiming in their patient information leaflets that paroxetine (Paxil) corrects a chemical imbalance, the FDA has never taken any similar action on this issue.

Commenting on Lacasse and Leo's work, Professor David Healy of the North Wales Department of Psychological Medicine, said: "The serotonin theory of depression is comparable to the masturbatory theory of insanity. Both have been depletion theories, both have survived in spite of the evidence, both contain an implicit message as to what people ought to do. In the case of these myths, the key question is whose interests are being served by a widespread promulgation of such views rather than how do we test this theory."

Dr Joanna Moncrieff, Senior Lecturer in Psychiatry at University College London, said: "It is high time that it was stated clearly that the serotonin imbalance theory of depression is not supported by the scientific evidence or by expert opinion. Through misleading publicity the pharmaceutical industry has helped to ensure that most of the general public is unaware of this."

Citation: Lacasse JR, Leo J (2005) Serotonin and depression: A disconnect between the advertisements and the scientific literature.
PLoS Med 2(12): e392.

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Main News Category: Depression



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