Diana D’Souza

Professor Granger

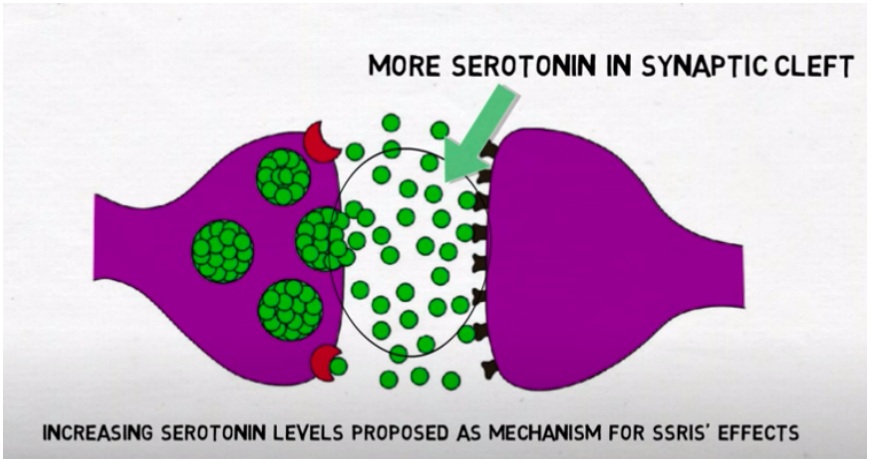
Psych 7 Brain Evolution

8 May 2020

Antidepressants: Scam or Cure?

Patient X suffered from depression for over 20 years. Although she was prescribed many medications, none of them worked (Healthline). Patient Y’s brother committed suicide, and she recently lost her job. However, she credited antidepressants for saving her life (New Scientist). Reactions to antidepressants vary drastically, as demonstrated by Patient X and Y.

Many popular antidepressants fall into a class of drugs called selective serotonin reuptake inhibitors (SSRIs). The name comes from the serotonin hypothesis of depression, which says that depression is caused by low levels of the chemical, serotonin. In a non-depressed person’s brain, a protein transports excess serotonin out of the synaptic cleft. In a depressed person’s brain, SSRIs prevent serotonin from leaving the synaptic cleft. In theory, the increased levels of serotonin treat the symptoms of depression.



SSRIs prevent serotonin (green circles) from leaving the synaptic cleft (circled gap). According to the serotonin hypothesis of depression, higher levels of serotonin should alleviate the symptoms of depression.

You've probably heard of some common SSRIs: fluoxetine (Prozac), paroxetine (Paxil, Pexeva), sertraline (Zoloft). But there are also other classes of antidepressants that increase or decrease the levels of other chemicals such as norepinephrine, which controls fight-or-flight. Other classes of drugs even decrease the level of serotonin.

In 2008, Dr. Kirsch and his team published a ground-breaking study on antidepressants that transformed him into a villain. Kirsch had always been intrigued by the placebo effect, a phenomenon where people feel better after receiving an inactive treatment. Were the antidepressants making patients feel better? Or did the action of taking medication convince them that they felt better? The team examined 35 controlled trials of FDA-approved antidepressants. In order for a drug to be FDA-approved, it needed at least two "positive" studies that showed a 50% reduction in symptoms, as compared to the placebo. One may say, "The FDA approved these drugs; of course, they are effective." However, positive studies are more likely to be published in journals and hailed by pharmaceutical companies, eager to sell more antidepressants. "Negative" studies are often unpublished, creating the false impression that antidepressants are effective.

Dr. Kirsch's study was unique in that he included both positive and negative studies. He performed a "meta-analysis" by using the compiled data to form new conclusions. The results were shocking: only 43% of the antidepressant trials showed a significant benefit over the placebo. The team performed a second meta-analysis with more FDA-approved antidepressants. This time, "82% of the drug response was duplicated by a placebo." Researchers tested the effectiveness of the antidepressant with the Hamilton Depression Rating Scale (HAM-D), a test that ranks patient depression on a scale of 0-53. The mean difference between the drug and the placebo was less than 2 points for both analyses. The media reported that antidepressants were a scam, but they failed to recognize the second part of Kirsch's study. Kirsch re-analyzed the data

according to the severity of the patient's depression. He concluded that antidepressants were no better than placebos for patients with mild to moderate depression, but were superior to placebos for patients with moderate to severe depression.

Another researcher and his team challenged Kirsch's findings with a much larger meta-analysis. Dr. Cipriani analyzed 522 randomized, double-blind, placebo-controlled trials. Similarly, to Kirsch, he included both positive and negative trials, but he also located many hard-to-find unpublished studies, older antidepressants, and antidepressants not available in the US. In a shocking twist, Cipriani found that all 21 antidepressants were more effective than the placebo; however, some antidepressants were more effective than others. (The study deemed an antidepressant effective if a patient's HAM-D score was reduced by 50% or more, post-medication.) Many deemed Cipriani's study as the "most comprehensive currently available evidence" on antidepressant effectiveness.

Even though Dr. Cipriani's study was more comprehensive (116,000+ patients) than Dr. Kirsch's (5000+), there are several red flags in Cipriani's meta-analysis that make Kirsch's argument more convincing. Cipriani argued that "all antidepressants were more effective than the placebo," but he admitted that their effects were "mostly modest." Researchers evaluated the effectiveness of the antidepressant with the Standardized Mean Difference (SMD) scale (0.2 = antidepressant had a small effect, 0.5 = antidepressant has a medium effect). Cipriani calculated SMD = 0.3; Kirsch calculated SMD = 0.32. These low SMD scores indicate that antidepressants may have an effect, but that effect is insignificant when compared to the placebo. This was the exact finding Kirsch published.

Another flaw in Cipriani's study was pharmaceutical bias. Many of the 522 studies he compiled were funded by pharmaceutical companies that manufactured the antidepressant being studied (*Time*). Furthermore, Cipriani did not divide the patients into subgroups depending on

the severity of their depression (mild, moderate, severe), as Kirsch did. Hence, it is possible that Cipriani's research could have yielded different results. Every year, the latest study published about antidepressants sends the media into a frenzy: “The drugs work,” “The debate is over,” “Think twice about SSRIs.” The debate signals that we must demand more transparency by limiting the presence of big pharma in research and publishing both positive and negative studies.

Works Cited

Cipriani, Andrea, et al. "Comparative Efficacy and Acceptability of 21 Antidepressant Drugs for the Acute Treatment of Adults with Major Depressive Disorder: A Systematic Review and Network Meta-Analysis." *The Lancet*, vol. 391, no. 10128, Apr. 2018, pp. 1357–66. *DOI.org (Crossref)*, doi:10.1016/S0140-6736(17)32802-7.

"Do Antidepressants Work? Yes, No, and Yes Again!" *Psychology Today*. https://www.psychologytoday.com/us/blog/psych-unseen/201802/do-antidepressants-work-yes-no-and-yes-again. Accessed 30 April 2020.

Kirsch, Irving. "Antidepressants and the Placebo Effect." *Zeitschrift Für Psychologie*, vol. 222, no. 3, Jan. 2014, pp. 128–34. *DOI.org (Crossref)*, doi:10.1027/2151-2604/a000176.

Nobody Can Agree about Antidepressants. Here's What You Need to Know | New Scientist. https://www.newscientist.com/article/mg23931980-100-nobody-can-agree-about-antidepressants-heres-what-you-need-to-know/. Accessed 30 April 2020.

"She Thought Antidepressants Would Treat Her Depression, They Didn't." *Healthline*. www.healthline.com. Accessed 30 April 2020.

"These Antidepressants Are Most Effective, Study Says." *Time*. *time.com*, https://time.com/5169013/antidepressants-more-effective-placebo-treating-depression/. Accessed 30 Apr. 2020.

YouTube. https://www.youtube.com/watch?v=uiXcAbrO8kU. Accessed 30 April 2020.