Should we continue to trust antidepressants?

"It's caused by a chemical imbalance in my brain, so that's why I take antidepressants – to correct that imbalance." We were talking about his depression; my friend had been taking antidepressants for years and this was his perspective on his situation. I wanted to push, but who was I to tell him he may wrong about himself? I could tell him that chemical imbalance theory was an outdated, reductive, and unscientific theory of depression, and that the evidence for the effectiveness of antidepressants was shaky at best, but who wants to hear that the drug they rely on for their happiness, maybe even their survival, may actually be ineffective? People seem to sort of know this, and yet chemical imbalance theory and antidepressants continue to be treated as though there were solid scientific consensus surrounding them. Unfortunately though, the truth is that there isn't. Chemical imbalance theory was loosely derived through an accident, and the effectiveness of antidepressants hasn't been established outside of the bounds of what may simply be placebo… Could it really be true that our number one cure for our current mental health crisis is just a placebo effect?

Viewing depression as primarily a biochemical issue has taken over in many people's minds, but as Chris Wojdack, a therapist licensed in the state of Michigan currently completing his PhD in psychology puts it, "there seem to be some attendant dangers in just believing in chemical imbalance theory. I was asked not too long ago about this: do you think depression is a biochemical issue? Why can't we say – yes – yes and it's *more* than that. It's a levels of analysis problem. You could say that eating dinner is a biochemical event, but it's also a social event, and for some people, a spiritual event." The attendant danger he was referring to was that of a fixed mindset. If people believe their depression is purely a biochemical issue and is out of their control, it may inhibit them from recovery. Hans Schroder, a professor of psychiatry at the university of Michigan, has looked into how people's mindsets affect their mental health issues, finding that "individuals who believed their attributes could change reported fewer mental health symptoms."

Almost 1 in 5 Americans are now being treated for depression, and almost 1 in 7 take antidepressants, a staggering increase of almost triple just two decades ago. Globally, suicide rates have decreased over the past few decades, but in the Americas, they have been steadily climbing, and disproportionately so for younger people. More Americans are struggling with

their mental health than ever, disproportionately so for my generation, and along with therapy, antidepressant usage has been the response.

The most common antidepressants are SSRIs, or selective serotonin reuptake inhibitors, such as Prozac or Zoloft. There are also many other types of antidepressants, such as tricyclic antidepressants (TCA) and serotonin-norepinephrine reuptake inhibitors (SNRI). Antidepressants are most commonly prescribed to treat depression, (thus the name: anti-depressant), but can also be prescribed for a variety of different mental health conditions, such as generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and more. SSRIs function by altering the neurochemical mechanism of the brain, specifically the neurotransmitter serotonin. Different neurons in the brain release different neurotransmitters, which are substances released in the brain through synaptic transmission, or interactions between neurons. There are over 100 different identified neurotransmitters in the brain, such as dopamine, epinephrine, GABA, acetylcholine, and serotonin, and each have different effects depending on the receptor upon which they act. When serotonin is released, it binds with certain receptors, (5-HT1 through 5-HT7), which each have different functions associated with mood, anxiety, and sleep. Put briefly, SSRIs do exactly what their name suggests: they inhibit the reuptake of the neurotransmitter serotonin. Normally, having been released in the brain, serotonin would undergo reuptake into the presynaptic neuron, meaning that it would not continue its effects. But, since SSRIs block that reuptake, more serotonin remains in the synapse and can continue to bind with its receptors, continuing those effects.

Antidepressants are used to treat depression due to chemical imbalance theory, or the serotonin hypothesis of depression, which originated from doctors who were trying to treat patients for tuberculosis using the drug iproniazid in the 1950's. They observed that the drug caused significantly elevated mood, appetite, and energy in their patients, and found that it worked on the serotonergic system. An accidental discovery led to a loose conclusion that depression must be caused by a deficiency of serotonin in the brain. If patient's moods were elevated by an increase in serotonin, could it not be that depression was caused by a deficiency in serotonin? And so drugs that targeted the serotonergic system were developed to treat depression. But reverse causality without controls is no basis for a scientific theory, and to this day, no actual scientific evidence for chemical imbalance theory has been established except for the observed effectiveness of antidepressants, which itself is quite questionable.

Critics of the antidepressant and chemical imbalance theory dogma claim that having reviewed the evidence for both, there is no solid empirical ground to stand on. A meta-analysis published in *Nature* in 2022 says, "the main areas of serotonin research provide no consistent evidence of there being an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations." This is a positively alarming conclusion considering how much this theory continues to shape our approach to treating depression. And as far as the established scientific evidence for the effectiveness of antidepressant goes, things don't look much better. Another study says, "meta-analyses of FDA trials suggest that antidepressants are only marginally efficacious compared to placebos and document profound publication bias that inflates their apparent efficacy. These meta-analyses also document a second form of bias in which researchers fail to report the negative results for the pre-specified primary outcome measure submitted to the FDA, while highlighting in published studies positive results from a secondary or even a new measure as though it was their primary measure of interest." Troubling findings for the drug to which so many people are looking for support.

To understand the apparent contrast between the lack of scientific consensus and the continued usage of antidepressants, I looked to a psychiatrist for help. Dr. Alberto Cano is a Spanish psychiatrist (MD) currently completing his PhD in psychiatry in Boston. When I asked him about this psychiatric dilemma, he began by reminding me that antidepressants are not meant as a sole remedy to depression, but rather form a part of a care package given to people suffering from depression. Randomized, controlled clinical trials indeed do not show a "very big" effect for antidepressants, but there's more to consider. When people receive care for depression, they receive individual therapy, possibly group therapy, medical recommendations for diet, exercise, and sleep, and in addition to all this, perhaps an antidepressant. All of these factors combined can have a tremendous effect on people, but this tells a different story than the one my friend told me about his depression. The biochemical aspect of depression is only a small part, and one we seem to actually know very little about. Focusing on it by itself makes no sense, and could, as Chris Wojdack said above, carry real dangers. Dr. Cano also mentioned how despite the fact that antidepressants are supposed to take at least a few weeks to kick in, certain patients claim to feel the effects after a few days. Does this not scream placebo effect?

Jacob Stegenga, a professor of the philosophy of science, goes so far as to claim in a 2019 article in Aeon that "when analyzed properly, the best evidence indicates that antidepressants are not clinically beneficial." Stegenga's troubling conclusion is that when people self-report the beneficial effects of antidepressants, it is far more likely due to a placebo effect strengthened by confirmation bias than actual biochemical effectiveness. Having reviewed the methods and results of the trials used for the evidence, he concludes that "we have plenty of reasons to think that antidepressants have no clinically meaningful benefits for those suffering from depression," and beyond that, "we know that these drugs cause many harmful side-effects, including weight gain, sexual problems, fatigue and insomnia. Some studies have demonstrated a link between antidepressants and the risk of violence, suicide, childhood and teenage aggression, and psychotic events in women." Indeed, the negative side effects of antidepressants are widely reported, and beyond that, once someone has started taking the drug, it can be incredibly difficult to get off of. Patients are often prescribed antidepressants with no timeline and have no real plan for ending usage, which leads to people just taking them indefinitely. Failed attempts at quitting sometimes result in troubling episodes which can leave people in a worse state than they were before, even causing some to attempt suicide.

Not only is there a lack of solid scientific consensus surrounding antidepressants, they can also have incredibly concerning side effects, even potentially mortal for some people. If all this is the case, why? Why has their usage not only continued but increased? Well, at the end of the day the truth is that many people have found them beneficial. Placebo or not, care providers have observed positive outcomes in many patients. Maybe we should we sit back and not ask too many questions. After all, a critique like this may be at risk of ruining what turns out to be the only beneficial aspect of the drugs: the power of belief. Depression is incredibly complicated and difficult to address, and different people need different ways to do it. Some people may be able or want to take personal responsibility for their depression in hopes that they can truly overcome it and gain strength from that accomplishment, but for others, that responsibility may just be too much. If it *might* be true that it *is* caused by a neurochemical imbalance which *can* be treated with a drug – and believing that works for them, why ruin it? But only time will tell whether or not this is a real solution.

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