

Antidepressant Medications: Placebo Effects of Various Drugs

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Received date: July 25,2018 ;**Accepted date :** August 17,2018; **Published date:** September 12 ,2018.

Citation : Timefey Palus , Antidepressant Medications: Placebo Effects of Various Drugs , Doi:10.31579/2578-8868/045

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Abstract

Antidepressants are supposed to work by fixing a chemical imbalance, specifically, a lack of serotonin in the brain. Indeed, their supposed effectiveness is the primary evidence for the chemical imbalance theory. But analyses of the published data and the unpublished data that were hidden by drug companies reveals that most (if not all) of the benefits are due to the placebo effect. Some antidepressants increase serotonin levels, some decrease it, and some have no effect at all on serotonin. Nevertheless, they all show the same therapeutic benefit. Even the small statistical difference between antidepressants and placebos may be an enhanced placebo effect, due to the fact that most patients and doctors in clinical trials successfully break blind. The serotonin theory is as close as any theory in the history of science to having been proved wrong. Instead of curing depression, popular antidepressants may induce a biological vulnerability making people more likely to become depressed in the future.

Keywords

Depression, Antidepressants, Effectiveness, Serotonin, Placebo

Introduction

In the early 1950s, the mood-elevating effects of the monoamine oxidase inhibitors (MAOIs) were discovered serendipitously. Further investigations of these compounds and the tricyclic antidepressants (TCAs) led to early theories relating brain chemistry and mood. These discoveries in the 1950s and 1960s sparked further interest in antidepressant drug therapy and in developing new and better medications for patients suffering from depression.

TCAs nonselectively inhibit the reuptake of serotonin, norepinephrine, and dopamine into presynaptic storage vesicles in the brain. Although they are effective in treating depression, their effects on other receptor systems, including histaminic, cholinergic, adrenergic, and postsynaptic serotonin receptors unrelated to depression, led to the development of significant, often intolerable adverse effects that limited their use in clinical practice.

Severity of Depression and Antidepressant Effectiveness

Critics of our 2002 meta-analysis argued that our results were based on clinical trials conducted on subjects who were not very depressed. In more depressed patients, they argued, a more substantial difference might be found. This criticism led my colleagues and I to reanalyze the FDA data in 2008. We categorized the clinical trials in the FDA database according to the severity of the patients' depression at the beginning of the trial, using conventionally used categories of depression. As it turns out, all but one of the trials were conducted on moderately depressed patients, and that trial failed to show any significant difference between drug and placebo. Indeed, the difference was virtually nil (0.07 points on the HAM-D). All of the rest of the trials were conducted on patients whose mean baseline scores put them in the "very severe" category of depression, and even among these patients, the drug-placebo difference was below the level of clinical significance.

Still, severity did make a difference. Patients at the very extreme end of depression severity, those scoring at least 28 on the HAM-D, showed an average drug-placebo difference of 4.36 points.

To find out how many patients fell within this extremely depressed group, I asked Mark Zimmerman from the Brown University School of Medicine to send me the raw data from a study in which he and his colleagues assessed HAM-D scores of patients who had been diagnosed with unipolar major depressive disorder (MDD) after presenting for an intake at a psychiatric outpatient practice. Patients with HAM-D scores of 28 or above represented 11% of these patients. This suggests that 89% of depressed patients are not receiving a clinically significant benefit from the antidepressants that are prescribed for them.

Yet this 11% figure may overestimate the number of people who benefit from antidepressants. Antidepressants are also prescribed to people who do not qualify for the diagnosis of major depression. My neighbor's pet dog died; his physician prescribed an antidepressant. A friend in the US was diagnosed with lumbar muscle spasms and was prescribed an antidepressant. I have lost count of the number of people who have told me they were prescribed antidepressants when complaining of insomnia – even though insomnia is a frequently reported side effect of antidepressants. About 20% of patients suffering from insomnia in the United States are given antidepressants as a treatment by their primary care physicians, despite the fact that "the popularity of antidepressants in the treatment of insomnia is not supported by a large amount of convincing data, but rather by opinions and beliefs of the prescribing physicians".

Predicting Response to Treatment

Although type of medication does not make a clinically significant difference in outcome, response to placebo does. Almost all antidepressant trials include a placebo run-in phase. Before the trial begins, all of the patients are given a placebo for a week or two. After this run-in period, the patients are reassessed, and anyone who has improved substantially is excluded from the trial. That leaves patients who have not benefitted at all from placebo and those who have benefitted only a little bit. These are the patients who are randomized to be given drug or kept on placebo.

As it turns out, the patients who show at least a little improvement during the run-in period are the ones most likely to respond to the real drug, as shown not only by physician ratings, but also by changes in brain function.

The Serotonin Myth

Over the years, I have noticed something very strange in the antidepressant literature. When different antidepressants are compared with each other, their effects are remarkably similar. I first noticed this when Guy Sapirstein did our 1998 meta-analysis of the published literature. When we first saw how small the actual drug effect was, we thought we might have done something wrong. Perhaps we had erred by including trials that had evaluated different types of antidepressants. Maybe we are underestimating the true effectiveness of antidepressants by including clinical trials of drugs that were less effective than others.

Before submitting our paper for publication, we went back to the data and examined the type of antidepressant used each trial. Some were selective serotonin reuptake inhibitors (SSRIs), others were tricyclic medications, we lumped together the trials on antidepressant drugs that were neither SSRIs nor tricyclics and called them “other antidepressants.” And then we noticed that there was a fourth category of drugs in the trials were had analyzed. These were trials in which drugs that are not thought to be antidepressants at all – tranquilizers and thyroid medications, for example – were given to depressed patients and evaluated for their effect on depression.

When we analyzed the drug and placebo response for each type of drug, we found another surprise awaiting us. It did not matter what kind of drug the patients had been given in the trial. The response to the drug was always the same, and 75% of that response was also found in the placebo groups. I recall being impressed by how unusual the similarity in results was, but I have since learned that they are not unusual at all. I have since encountered this phenomenon over and over again. In the STAR*D trial, which, at a cost of \$35,000,000, is the most costly clinical trial of antidepressants ever conducted, patients who did not respond to the prescribed SSRI were switched to a different antidepressant. Some were switched to a SNRI (serotonin-norepinephrine-reuptake-inhibitor), a drug that is supposed to increase norepinephrine as well as of serotonin in the brain. Others were switched to an NDRI (norepinephrine-dopamine reuptake inhibitor), which is supposed to increase norepinephrine and dopamine, without affecting serotonin at all. And still others were simply given a different SSRI. About one out of four patients responded clinically to the new drug, but it did not matter which new drug they were given. The effects ranged from 26% to 28%; in other words, they were exactly the same regardless of type of drug.

Antidepressants as Active Placebos

All antidepressants seem to be equally effective, and although the difference between drug and placebo is not clinically significant, it is significant statistically. This leads to the obvious question: What do all of these active drugs have in common that make their effect on depression slightly, but statistically significantly, better than placebo?

One think that antidepressants have in common is that they all produce side effects. Why is that important? Imagine that you are a subject in a clinical trial. You are told that the trial is double blind and that you might be given a placebo. You are told what the side effects of the medication are. The therapeutic effects of the drug may take weeks to notice, but the side effects might occur more quickly. Would you not wonder to which group you had been assigned, drug or placebo? And noticing one of the listed side effects, would you not conclude that you had been given the real drug? In one study, 89% of the patients in the drug group correctly “guessed” that they had been given the real antidepressant, a result that is very unlikely to be due to chance.

Conclusion

Based on their tolerability profile, the SSRIs are a significant advancement over the TCAs for the treatment of depression.

Although some SSRI-associated adverse effects can be intolerable or troubling, except for the serotonin syndrome, they are not life-threatening. As with other classes of antidepressants, SSRIs induce side effects that can be predicted by receptor physiology. Through the broad-based experience with the SSRIs, the frequency of side effects such as sexual dysfunction and sleep disturbance has increased. Therefore, selectivity for serotonergic receptors does not ensure freedom from adverse effects. The shift of treatment of depression to primary care practitioners, who manage heavy patient schedules across all therapeutic areas, has created the need to enhance the successful treatment of depression. The wealth of experience with SSRIs has set the stage for a next generation of antidepressants that are at least as effective, but better tolerated and safer than their predecessors. The search for the magic bullet continues.

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