Withdrawal symptoms of antidepressants

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Withdrawal symptoms when antidepressants are stopped has sparked heated discussion, both on social media and in the general public press. In the scientific literature, there is a more restrained debate about their frequency and severity and the best way to deprescribe.

The linked paper by [Henssler et al ….] has provided some important numbers that will help part of this debate. In their systematic review they found that 31% (95% CI 27-35) reported at least one withdrawal symptom when stopping antidepressants compared to 17% (95% CI 14-21) who reported symptoms after stopping a placebo, a difference of about 14%. There is the potential of a selection bias when comparing these two populations, so the authors also looked at the subset where individuals were randomised to active or placebo so that a comparison could be made with more validity. The difference was then 8% (95% CI 4-12) between active and placebo. They also estimated that 2.8% (95% CI 1.4-5.7) of people reported “severe withdrawal” syndromes after antidepressants compared to 0.6% (95% CI 0.2-1.3) on stopping placebo.

There are some important implications here. First, that withdrawal symptoms and syndromes are reported after stopping a placebo so in clinical practice we must be careful when we infer that any symptom is causally related to stopping the medication. It is also important to reassure and sometimes challenge patients about this as well. The second point is that the difference between the active and placebo arms is the important one from a scientific point of view. A rough estimate of the "real" prevalence of withdrawal syndromes is about 10% and of severe withdrawal syndromes about 2%. Reports of withdrawal symptoms that do not compare with a placebo will give a large overestimate of the frequency of such symptoms. [1] Future study of withdrawal symptoms should ensure that comparisons are made with a placebo when possible.

These results can explain some of the controversy. Given that antidepressants are prescribed to many millions of people, the relatively uncommon severe withdrawal symptoms will still affect a substantial number of people. Organisations that help people stop prescription drugs have many members who have difficulty in stopping antidepressants.[2] On the other hand, for individual clinicians, severe withdrawal symptoms will seem uncommon and most patients will not be troubled by antidepressant withdrawal especially when medication is tapered over a few weeks.

All systematic reviews are limited by the strength of the constituent papers. In this case a major limitation is how withdrawal syndromes were defined and operationalised. The authors relied upon the definitions provided by the studies themselves and this likely contributed to the high levels of heterogeneity. As expected, structured assessments provided higher estimates than those relying upon self-report. We should also note that many of the studies were small, often using antidepressants not commonly used now and studying people who had not taken the antidepressants for a very long time. Despite these limitations, the results here are a substantial improvement on anything that has gone before.

The paper does not inform the ongoing debate about the relationship between withdrawal symptoms and the depressive and anxious symptoms of relapse, but this debate underpins any interpretation of these data.[3] The evidence that long term maintenance antidepressants prevent relapse of depression is very strong. [4] The more recent ANTLER study[5] has further strengthened this evidence by examining long term maintenance and reported a doubling of relapse rate in those who discontinue. So cessation of antidepressants will lead, on average, to an increase in depressive and anxious symptoms. Withdrawal symptom scales such as the Discontinuation-Emergent Signs and Symptoms (DESS) scale [6] include symptoms that are identical to those expected in depression and anxiety. For example, some of the most common symptoms reported using the DESS are: fatigue, nervousness or anxiety, irritability, sudden worsening of mood, bouts of crying, dizziness and trouble sleeping.[3] [6] Distinguishing between relapsing symptoms and withdrawal is difficult to do.

For the patient and clinician, the main issue is how to manage the discontinuation of medication, and to decide if the medication was, or more importantly, will be a net benefit. Short term symptoms that go away quickly and on their own are best thought of as “withdrawal” even if those symptoms might be similar or identical to the symptoms of depression and anxiety. More serious and longer term symptoms might best be managed by tapering more slowly[7] or even deciding to remain on the antidepressant. Of course, shared decision making is essential and psychotherapy might help.[8] Arguing about whether these should be called relapses or withdrawals will help no one.

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