

What does the latest meta-analysis really tell us about antidepressants?

Abstract

A recent meta-analysis of antidepressant trials is the largest conducted to date. Although it claims to prove antidepressant effectiveness beyond dispute, the main outcome is response rates, which are derived from continuous data in a process that can inflate differences between groups. The standardised mean difference of 0.3 is in line with other meta-analyses that show small differences between antidepressants and placebo that are unlikely to be clinically significant. Other factors likely to exaggerate effects are discussed, and evidence on associations between antidepressant effects and severity, and outcomes of long-term treatment is considered. Clinicians need to have open discussions with patients about the limitations of antidepressant research, the lack of evidence that they correct a chemical imbalance or other brain abnormality, and the range of adverse effects and mental and physical alterations antidepressants can produce.

Keywords: antidepressants; meta-analysis; antidepressant efficacy

A recent meta-analysis of antidepressant trials (Cipriani *et al.*, 2018) was greeted by media coverage declaring that 'the drugs do work' and that doubts about their usefulness should be 'put to rest.' Some of the authors called for wider prescribing, suggesting that 1 million more people in the UK should be prescribed antidepressants (Boseley, 2018).

The latest meta-analysis, undertaken by Andrea Cipriani and colleagues, is the largest to have been undertaken, and included some unpublished as well as published studies. It employed a network analysis method, including data from comparative trials that did not include a placebo group. Included trials evaluated short-term treatment with antidepressants for an average of eight weeks. The principal efficacy outcome, 'response' rate, showed odds ratios of between 2.13 for amitriptyline and 1.37 for reboxetine, indicating that patients treated with antidepressants were approximately one and a half to

two times more likely to show a response than patients treated with a placebo (Cipriani *et al.*, 2018).

'Response' is an artificial category, however. It is arbitrarily constructed out of scores on depression rating scales, such as the Hamilton Rating Scale for Depression (HRSD), which is the data that is actually collected from participants. The assumption that a 50% decrease in scores (the usual definition of response) represents a clinically meaningful improvement has not been validated. Moreover, categorising data can inflate small differences in raw scores, especially if the cut-off is close to the mean score, which it frequently is (Kirsch & Moncrieff, 2007).

The Standardised Mean Difference for the difference in rating scale scores in the Cipriani *et al.* (2018) meta-analysis was 0.3, which is comparable with several other meta-analyses conducted over the last two decades. These show that SMDs of around 0.3 translate into differences in HRSD scores of around 2 points (Kirsch *et al.*, 2002), which is unlikely to be clinically relevant. Research comparing HRSD scores with scores on the Clinical Global Impressions (CGI) scale suggest that such a difference would not even be noticed, with a difference of at least 8 points being required to register as 'mild improvement' (Moncrieff & Kirsch, 2015).

However, even these small differences are easily accounted for by the fact that antidepressants produce more or less subtle mental and physical alterations (e.g. nausea, dry mouth, dizziness, drowsiness and emotional blunting) irrespective of whether or not they treat depression. These alterations enable participants to guess whether they have been allocated to antidepressant or placebo better than would be expected by chance. Participants receiving the active drugs may therefore experience amplified placebo effects. This may explain why antidepressants that cause the most noticeable alterations, such as amitriptyline, appeared to be the most effective in the Cipriani *et al.* (2018) meta-analysis. Another problem is that antidepressant trials often include people who are already on antidepressants, and who are withdrawn from them prior to the trial. Although there is usually a 'placebo washout' period during which participants are withdrawn from previous medication, we know that withdrawal effects can persist for longer than the one to two weeks that such periods usually last. Since trials do not try to identify antidepressant

withdrawal effects, they may be misclassified as symptoms of depression in people who are subsequently randomised to placebo.

The use of network meta-analysis is also likely to have inflated differences between antidepressants and placebo. People treated with antidepressants in placebo-controlled trials show lower response rates than participants in comparative trials that lack a placebo group, indicating how outcomes are influenced by expectations of receiving active therapy (Sinyor *et al.*, 2010). Therefore network analysis includes data on antidepressants that is collected in more favourable circumstances than the data on placebo.

The Cipriani meta-analysis only looked at data on short-term treatment, whereas in real life people increasingly take antidepressants for years. Few randomised, placebo-controlled trials have investigated long-term effects. In the large longitudinal STAR-D study, the proportion of people who adhered to recommended treatment, recovered and did not relapse was startlingly low (only 108 out of the 3110 people who satisfied inclusion criteria) (Pigott *et al.*, 2010).

Some evidence indicates that people with more severe depression show greater relative differences between antidepressants and placebo than those with less severe symptoms. However, other studies have not detected an association with severity (Gibbons *et al.*, 2012, Walsh *et al.*, 2002). In one meta-analysis that detected a severity effect, the difference between drug and placebo among those with severe depression was 4 points on the HRSD, which still falls well below the level that would indicate minimal improvement on the CGI (Kirsch *et al.*, 2008).

The recent meta-analysis does not resolve recent debates about the utility of antidepressants, but clinical guidelines continue to recommend them, and many people expect to be offered them. Much of the general public has also been persuaded that depression is caused by a chemical 'imbalance' that antidepressants correct, even though the evidence for this idea was never convincing. Indeed, despite speculation about a number of physiological processes, the mechanism through which antidepressants might affect symptoms of depression remains unknown.

Antidepressants are not placebos, however. They are active drugs that produce a range of physical and mental alterations. Some of the alterations they produce, such as the sedation induced by tricyclics, or the emotional blunting associated with SSRIs, may plausibly be useful for various psychological symptoms. However, the evidence reviewed above suggests the utility of these effects for the treatment of depression specifically is minimal. Moreover, some alterations are harmful or unpleasant, such as sexual dysfunction, which in some cases seems to persist after discontinuation of the drug (Farnsworth & Dinsmore, 2009) and agitation, suicidal and aggressive behaviour which can occur among younger users in particular (Sharma *et al.*, 2016). Although serious adverse effects are probably rare, we have little data on the frequency or mechanisms of such effects, or how to treat them.

Patients and clinicians need to consider all these factors if they are to make informed decisions about whether to use antidepressants or not. In particular, clinicians need to discuss the limitations of research on the efficacy and effectiveness of antidepressants, the lack of support for the idea that antidepressants correct a chemical imbalance or other brain abnormality and the range of adverse effects and mental and physical alterations that antidepressants can produce.

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Ethical standard: the authors assert that all procedures relating to this work comply with the standards of the relevant national and international committees on human experimentation and with the Helsinki Declaration of 1975 as revised in 2008.

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