How do we determine whether antidepressants are useful or not?

We read with interest the Article by Fredrick Hieronymus and colleagues in *The Lancet Psychiatry*.[1] The authors showed that SSRIs significantly improve scores in a subset of items in the 17-item Hamilton Depression Rating Scale (HDRS-17), over and above placebo, after a treatment period of 6 weeks, irrespective of baseline depression severity. However, we think that some uncertainties exist that should temper the authors' conclusion that the "claim that antidepressants are useless for patients with non-severe depression has been premature and is misleading".[1]

To answer the question of whether SSRIs are useful or not, their relative benefits and harms need to be assessed over a time period that reflects the period for which patients are generally prescribed antidepressants. Because half of people using antidepressants in the UK have been on medications for more than 2 years,[2] and current guidelines recommend treatment for at least 6 months, the findings of Hieronymus and colleagues that significant effects are seen after 6 weeks might not be relevant for real-world use. For example, benzodiazepines appear effective for anxiety after a few weeks, whereas their effectiveness long-term is quite different. Short-term studies, such as those examined in this Article, still do not answer the question of whether antidepressants overall improve or worsen long-term outcomes in depression.

In appraising the overall usefulness of antidepressants, the harms of them also need to be considered, including severe and long-lasting withdrawal effects that are increasingly recognised,[3] alongside a wide variety of side-effects during long-term use. In this context, the beneficial effects of antidepressants on the HDRS-17, or a subset of items on the HDRS-17, should be deliberated. In the study by Hieronymus and colleagues, placebo—itself a complex treatment enhanced by patient visit, frequent assessments and expectation—produced a large effect on depression scores: a 7·2 point improvement on the HDRS-17 for the least depressed, increasing to 12·6 points for the most depressed (figure 1 in the Article).[1] Whether or not the small improvements additionally produced by antidepressants (1–2·8 points on HDRS-17, equating to 14–22% the size of the placebo response) are clinically significant is a matter of debate, given that changes in HDRS score of up to 3 points have been found to correspond with no change on a clinical global impression scale.[4]

Furthermore, we wonder whether consideration was given to the confounder of placebo run-in designs used in many placebo-controlled antidepressant studies.[5] In such studies, patients on antidepressants are abruptly taken off their existing treatment for up to 1 week and randomly assigned to either the placebo or antidepressant treatment group.[5] The withdrawal effects elicited in the run-in period, which are alleviated in the antidepressant group but not affected by placebo, could inflate the apparent differences between the two groups as measured by depression scores.[5]

What is needed to establish whether SSRIs are helpful or harmful in severe and non-severe depression are placebo-controlled studies in antidepressant-naive populations for time periods that reflect clinical use (months or years) and discontinuation studies that taper antidepressants slowly enough to remove the confounder of withdrawal effects to establish their efficacy as maintenance treatment for depression.

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Authors' reply

We appreciate the interest shown by Mark Horowitz and David Taylor in our Article[1] but note that their criticism largely deals with issues not addressed in the publication they question.

Authorities in many countries claim that SSRIs are useful for severe but less so for non-severe cases of depression. Our main finding was that meta-analyses inspiring this stance[2,3] have been misleading. We thus show that SSRIs reduce essential depression symptoms such as depressed mood and anxiety just as well in patients whose cases are defined as non-severe.

Horowitz and Taylor question our conclusion because they believe the analysed trials have been of insufficient duration and that some of them have applied the placebo run-in principle; however, the same can be said for most of the trials included in the meta-analyses that we rebut.[2,3] Hence, the difference between our results and those of the papers we question does not reside in the nature of the data included but in how these data are analysed. Moreover, if indeed