

Antidepressants might work for people with major depression: where do we go from here? – Author’s reply

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We agree with Erlend Faltinsen and colleagues that standardised mean differences can be difficult to translate into clinical practice. As reported in the Cochrane handbook, the mean difference (or more correctly, difference in means) measures the absolute difference between the mean value in two groups and then estimates the average amount that the experimental intervention changes in the outcome compared with that of the control intervention. Mean difference can be used in meta-analysis as a summary statistic only when outcome measurements in all studies are made on the

same scale. By contrast with standardised mean differences, the overall intervention effect can be difficult to interpret because it is reported in units of SD rather than in units of a specific rating scale. Although, in some circumstances, it is possible to transform the effect back to the units used in a specific study, the problem with standardised mean differences is that this method assumes that differences in SD between studies reflect differences in measurement scales and not real differences in variability among study populations. This assumption could be problematic in circumstances in which there might be real differences in variability between the participants in different studies (for instance, pragmatic vs explanatory studies). For this reason, we paid careful attention when we drafted the inclusion and exclusion criteria in the protocol of our review^{1,2} and selected only trials that were similar in design, population, and interventions to reduce heterogeneity and inconsistency.³ This selection led to the inevitable exclusion of several trials. Even though we did an extensive search for published and unpublished data and contacted all study authors and pharmaceutical companies for additional data, we might, as is typically the case in systematic reviews, have missed some relevant studies. However, we do not agree that we should have included all the studies in the 2015 Cochrane review.⁴ Before finalising our list of included studies, we screened existing systematic reviews for any relevant reference in their lists of included (and excluded) studies. As detailed in the appendix of our review, we had to exclude several studies that were included by Ole Jakob Storebø and colleagues:⁴ 51 studies with less than 7 days of treatment, 38 crossover studies without washout period and no pre-crossover data (even after contacting the authors), 18 studies in which patients were responders to previous treatment, 14 studies where treatment was not as monotherapy, and a range of other studies without appropriate randomisation, with single-blind design, that included preschool children, or that administered non-oral formulation of the investigational drug. Including these trials would have been a clear violation of our published protocol and a material risk for the transitivity of the network.³

As prespecified in our peer-reviewed protocol,^{1,2} tolerability (proportion of patients who dropped out of studies because of side-effects) was chosen as primary outcome because it is consistently reported across studies and it is a hard outcome used in other similar reviews.⁵ We also analysed all-cause discontinuation as a pre-defined secondary outcome. It is an important measure of treatment acceptability and full results are reported in the main text of our review and in the online appendix.

We did not include edivoxetine because, when we drafted the protocol, we focused only on the drugs that were licensed or mentioned in international clinical guidelines at the time. We agree with Shuai Wang and Yi Zheng that systematic reviews should be as comprehensive as possible. We are aware that many new drugs for attention deficit hyperactivity disorder (ADHD) will be on the market in the near future. As we did with another network meta-analysis,⁶ we plan to publish the update of this review in a few years' time and will include in the network, as appropriate, all the relevant medications that will be available at that time.

In our network meta-analysis, we summarised the best available evidence about efficacy and acceptability of ADHD medications. In the protocol, we planned analyses of clinical outcomes at different time-points (acute and long term) but, unfortunately, there are not enough randomised controlled trials in the field. More long-term data and higher quality studies are urgently needed. We totally agree with John Warren that it is important to consider reliable information also about safety and harms when choosing a pharmacological treatment for ADHD (of course, this applies to any intervention in any disorder in any field of medicine). We are working on this question and have almost completed the data collection for a parallel project (based on the same protocol), which investigates the profile of specific adverse events for each drug, including—among others—psychotic symptoms, suicidality, sleep problems, headache, loss of appetite, and tics.

This information about tolerability will complete the clinical picture of the safety profile of ADHD medications and will better inform patients, carers, clinicians, and treatment guidelines.

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