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Whether antidepressants are effective should be based on both statistical and clinical significance: Comment on Cipriani et al. 2018

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Cipriani et al.¹ conclude from their meta-analysis that antidepressants are significantly more efficacious than placebo. They acknowledge a modest average effect size of $d=0.3$ but do not discuss its clinical relevance.

In applied statistics the null hypothesis is always false, because an absolute null-association between natural variables is impossible.² With the impressive sample size of $n=116'477$, even minor drug-placebo differences achieve statistical significance. Thus, statistical significance alone does not imply that antidepressants are clinically effective.

A mean efficacy of $d=0.3$ indicates that 88% of an antidepressant's action is overlapping with placebo effect and that 10 patients need antidepressant pharmacotherapy for 1 person to have an outcome superior to placebo. This effect size corresponds to less than 2 points difference on the Hamilton rating-scale for depression (HAMD), but per convention, differences less than 3 points are considered clinically insignificant.³ Research further suggests that at least 7 points (corresponding to approximately $d=0.9$) are necessary for a clinician to detect a minimal improvement with the HAMD.⁴

Finally, the pooled effect size of $d=0.3$ is most likely an overestimation of the true drug effect due to systematic method biases.⁵ Unblinding of outcome assessors considerably inflates the apparent drug-placebo difference on subjective symptom rating-scales such as the HAMD.⁶ Premature trial discontinuation is, therefore, considered the more objective outcome,⁷ but only 2 of 21 drugs were slightly superior to placebo with respect to dropout for any reason. Based on these arguments we conclude that, relative to placebo, antidepressants do not convey clinically relevant benefits.

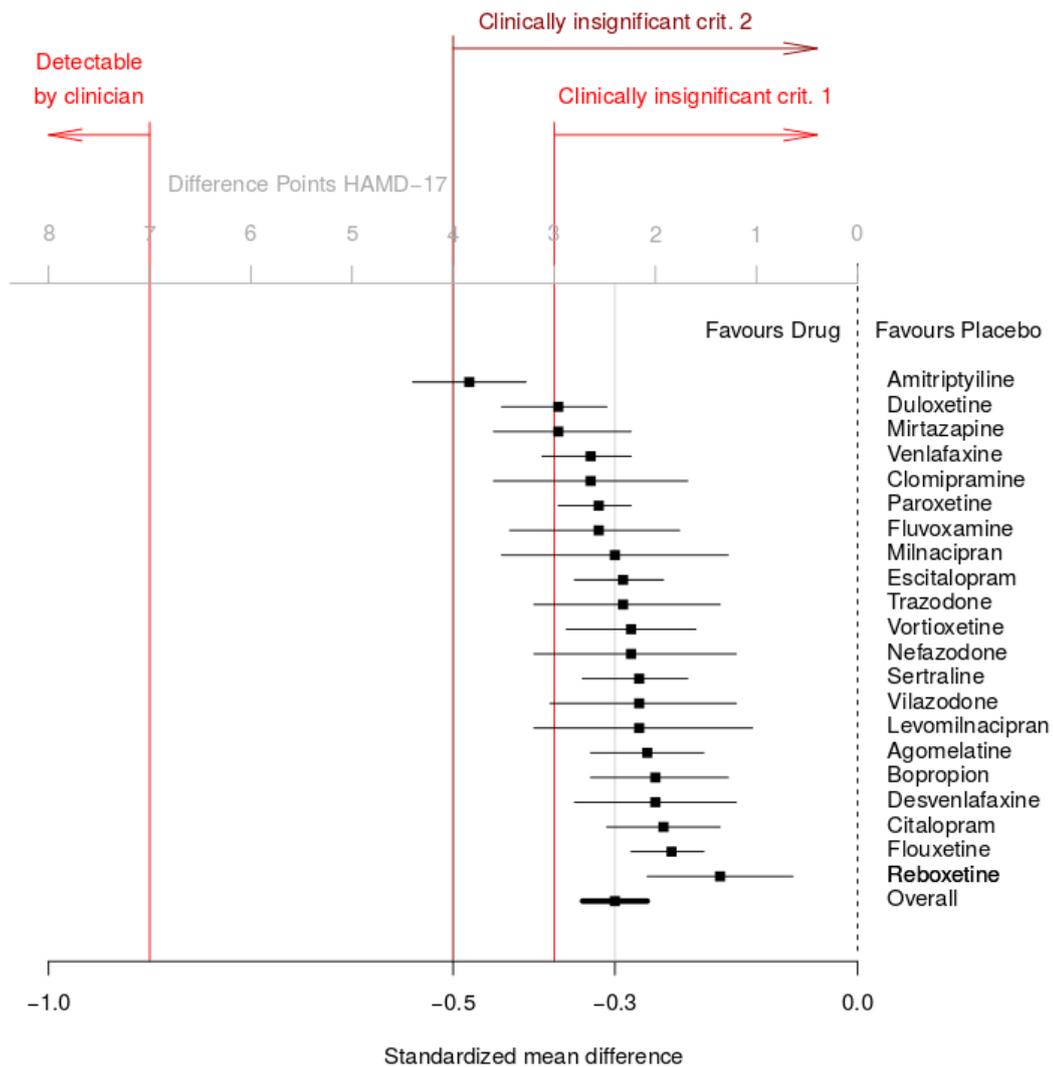


Fig. 1. Clinical significance of antidepressants, based on the results of Cipriani et al. (2018; additional online information, p. 150).

Black squares are the standardized mean differences d (drug vs. placebo) for each drug and the overall effect. Horizontal lines are the related 95% confidence intervals.

Corresponding mean point-differences on the HAMD-17 scale were calculated as suggested by Moncrieff and Kirsch (2015), assuming a standard deviation of the pooled differences of $SD=8.0$.

Two conventions for clinical insignificance were used. Criterion one was a difference of <3 points on the HAMD-17 scale ($d=0.375$), and criterion two was $d<0.5$.

Only point-differences >7 on the HAMD-17 scale were found to be detectable by clinicians. See text for related references.

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