Considering the methodological limitations in the evidence base of antidepressants for depression: A reanalysis of a network meta-analysis

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S1 Appendix

Risk of bias

Blinding of the participants

Cipriani et al.[1] classified three [2-4] out of the 522 trials as being at low risk of bias in the "blinding of participants" domain:

Brunoni et al.[2] tested the blinding, by asking the participants who completed the trial to guess their allocation. They reported that 39 (75%) of 52 participants on placebo, and 29 (58%) of 50 participants on sertraline were able to correctly guess their allocation. Brunoni et al. suggested that the results were "driven by clinical improvement… rather than blinding failure" [2]. We disagree and would categorise this trial at high risk of blinding bias of the participants.

Edwards et al.[3] did not describe how and when they tested the blinding, and two of the included participants were not asked. They reported that 12 (60%) of 20 participants on placebo and 12 (63%) of 19 participants on paroxetine were able to correctly guess their treatment allocation. Edwards et al. concluded that their results "confirmed the blindness of the study", but we would categorise the trial to be at unclear risk of bias.

Schatzberg et al.[4] did not test the blinding, and it is unclear why this trial was rated at low risk of bias, rather than the "stated but not tested" categorisation.

Other bias domain

While Cipriani et al.[1] categorised each arm individually according to sponsorship, we considered sponsorship on the study level: trials with any sponsored arm (as categorised by Cipriani et al.[1]) were categorised as "sponsored"; of the remaining trials, those with any arms categorised as "unclear" we labelled "unclear" and the remaining trials were categorised "not-sponsored".

Summary risk of bias assessments

Criteria for assessments

To categorise the 522 trials included by Cipriani et al.[1], we followed the Cochrane Handbook's criteria for an overall risk of bias assessment.[5] Each domain in the risk of bias tool likely affects all five included outcomes assessed by Cipriani et al., and we therefore considered all bias domains as "key domains", according to table 1.

Table 1. Criteria for overall risk of bias assessment.

Low risk of bias	All key domains classified as low risk of bias
Unclear risk of bias	One or more key domains classified as unclear risk of bias, and no domains classified as high risk of bias.
High risk of bias	One or more key domains classified as high risk of bias

We collapsed the three blinding domains in our Excel dataset and used the following criteria for our categorisation: All placebo-controlled trials were classified as unclear risk of bias in the main analysis and as high risk of bias in the sensitivity analysis. Trials that only contained head-to-head antidepressant arms, and no placebo arm, were rated as low risk of bias if the three blinding domains were rated as 'low' or 'stated but not tested' by Cipriani et al.[1]. We rated the collapsed blinding domain as unclear risk of bias, if one or more of the blinding domains were rated as unclear by Cipriani et al. Trials with missing data for any of the five included outcomes were categorised as high risk of bias. For the remaining bias domains, we adopted the categorisations by Cipriani et al.[1]. Our results are compared with Cipriani et al.'s in table 2.

Table 2. Comparison of the overall risk of bias assessments.

Cipriani et al. overall assessment		**Our overall assessments**			
		Cochrane categorisation	Sensitivity analysis using the Cipriani et al. categorisation	Our assessment	Sensitivity analysis of the blinding domains
Low risk	46 trials (9%)	Low	1 trial (0.2%)	0 trials (0%)	0 trials (0%)
"Moderate" risk	380 trials (73%)	Unclear	383 trials (73%)	261 trials (50%)	108 (21%)
High risk	96 trials (18%)	High	138 trials (26%)	261 trials (50%)	414 (79%)

References

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