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LETTER TO THE EDITOR

Methodological concerns with network meta-analysis on drugs for attention deficit hyperactivity disorder

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We thank Padilha and colleagues for their network meta-analysis on efficacy and safety of drugs for attention deficit hyperactivity disorder in children and adolescents [1]. The network meta-analysis looks comprehensive and the results are interesting. We invite readers to consider the following potential limitations of the study.

The authors included head-to-head randomised clinical trials, with only 12 trials in the benefit analyses and 33 trials in the harm analyses [1]. By excluding placebo-controlled trials, they focus on a small and select sample out of the many available trials on drugs for attention deficit hyperactivity disorder in children and adolescents. The authors also stress the limited amount of comparisons themselves in their discussion section [1]. When we systematically reviewed methylphenidate alone, we found 185 randomised clinical trials on methylphenidate versus placebo or no intervention [2]. Head-to-head comparisons can be informative, but it would have been valuable if the authors had assessed placebo-controlled trials as well for a more complete treatment network. One recent network meta-analysis on pharmacological treatments for major depressive disorder did this [3].

The authors judged the methodological quality of the included trials to be good, and asserted that they were well designed, reported, and conducted. They used the Jadad scale, a risk of bias tool published 22 years ago, to assess quality [4]. The Cochrane Collaboration does not recommend this instrument because it lacks the crucial bias domain "allocation concealment" and there are issues with its scoring system [5]. Our Cochrane systematic review found 96.8% of the 185 included randomised clinical trials to be of high risk of bias [2]. We used the Cochrane Risk of Bias Tool, with vested interests as an added dimension [5]. One-factor analysis indicated that the dimensions in the Cochrane tool exhibit good fit indices for clinical trials on methylphenidate, although vested interest showed lower reliability than other bias domains [6]. Industry sponsorship can seriously alter effect estimates in clinical trials, and should therefore be addressed [7]. Another Cochrane review on amphetamines for attention deficit hyperactivity disorder judged the trials to be of low to very low evidence quality [8].

The authors did not adopt the commonly used Grading of Recommendation Assessment, Development and Evaluation (GRADE) system [9]. A previous network meta-analysis on pharmacological and non-pharmacological interventions for attention deficit hyperactivity disorder used the GRADE approach and concluded that the quality of evidence was low [10]. In addition, it looks as if Padilha and colleagues included cross-over trials without describing the method on how to pool these trials with parallel-group trials, or discussing the possible confounding issues with carry-over data, such as carry-over and period effects.

Network meta-analyses consist of both direct and indirect comparisons. The inclusion of indirect comparisons builds on the fundamental assumption that there is transitivity [11]. For the transitivity assumption to hold, the studies with different direct comparisons must be sufficiently similar in all respects apart from the treatments they compare. Padilha and colleagues did not assess the transitivity assumption in their network meta-analyses [1]. This is problematic, due to potentially divergent clinical and methodological study characteristics between the included direct comparisons [11]. We also expected the authors to assess the amount and impact of heterogeneity on their network meta-analytic estimates. If meaningful heterogeneity exists, the predictive interval is

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wide and includes effect sizes with very different practical implications [12].

When network meta-analyses include few trials, the risk of imprecise effect estimates increases [13]. Given the low number of included studies, especially for the studies measuring effect (with only two included studies), caution is advised when interpreting these results. Network meta-analyses are also prone to inflated type I errors. Del Re and colleagues used Monte Carlo simulations of trials with nil effect to replicate the findings from a network meta-analysis on antidepressants with 117 randomised clinical trials and found one or more false-positive results in 70% of the simulations [14]. We are not aware of any attempts to control for random errors in the network meta-analysis by Padilha and colleagues [1]. It would have been interesting to see parallel frequentist analyses taking risk of random errors into consideration [13].

Network meta-analyses can be valuable for assessing the benefits and harms of more than two interventions for the same condition, and researchers should embrace their merits and critically evaluate their shortcomings [13]. Padilha and colleagues presented novel data on head-to-head drug comparisons for attention deficit hyperactivity disorder in their network, and we thank them for this [1]. However, with the low quality reported in previous Cochrane reviews [2, 8], it is difficult to properly interpret the evidence put forward, let alone exert confidence in the head-to-head comparisons. High-quality randomised clinical trials in this field seem to be sorely lacking.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards The manuscript does not contain clinical studies or patient data.

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