

## The best treatment for young people with depression? - Network meta-analysis may lead to questionable results and conclusions

In their network meta-analysis (NMA) of treatments for children and adolescents with depression, Zhou and colleagues suggested fluoxetine with or without CBT to be the best choice.<sup>1</sup> This conclusion, however, seems to be questionable due to methodological problems of their MA. In NMA, valid conclusions from indirect comparisons can only be drawn if the assumptions of transitivity and consistency hold.<sup>2,3</sup> As a first limitation, the Zhou et al. could only statistically control for known confounders affecting transitivity<sup>1</sup>, as contrasted to controlling all confounders by randomization, leading to observational evidence only. They found some global and local inconsistencies in efficacy outcomes and for some comparisons relatively low or high values in the transitivity assessment.<sup>1</sup> Thus, some effect sizes may be biased.<sup>3</sup> Related to this, the power of this NMA for indirect comparisons and for testing consistency is not clear: For most treatments only 1-2 direct comparisons with another specific condition were included.<sup>1supplement</sup> Power may be particularly low in comparisons including few studies with small samples, especially if heterogeneity is large<sup>3,4</sup>, which seems to be the case for several comparisons including fluoxetine with or without CBT vs. pill or psychological placebo.<sup>1supplement</sup> For these reasons, the authors' solely reliance on p-values in testing consistency is questionable.<sup>1supplement</sup> Inconsistencies may not have been detected (type II error).<sup>4</sup> Regarding type I error, Zhou and colleagues do not seem to have adjusted for multiple testing although they carried out hundreds of tests of significance (Figure 3).<sup>1</sup> Some significant results may be false positives. Furthermore, treatment ranking in NMA may be affected by differences that are not clinically important<sup>3</sup>: for Zhou and colleagues, this applies to for example, fluoxetine+CBT vs. CBT+placebo ranking second and third (0.73 vs. 0.64).<sup>1</sup> As most head-to-head comparisons of active treatments, the difference between these two treatments was not significant.<sup>1Figure3</sup> Furthermore, it was below the clinically meaningful

threshold defined by the authors ( $0.09 < 0.20$ ).<sup>1supplement</sup> This result questions the gain of adding fluoxetine to CBT (0.09). Furthermore, rankings need to take benefits and harms into account<sup>3</sup>, but drop-outs due to adverse events could not be examined.<sup>1</sup> For suicidality CBT+pill placebo ranks first, fluoxetine+CBT 12<sup>th</sup>, and fluoxetine 17<sup>th</sup>.<sup>1supplement</sup> The authors did not take these important results into account when ranking treatments. As another limitation, they do not seem to have included follow-up effects beyond the end of treatment, although psychotherapy (in adults) was shown to have more stable long-term effects than pharmacotherapy.<sup>5</sup> For risk of bias, there were major concerns for most comparisons.<sup>1supplement</sup>

In sum, Zhou et al. rated 100% of the comparisons for efficacy as being of low or very low confidence, reflecting the NMA's limitations (acceptability: 95%, suicidality: 93%).<sup>1+supplement</sup> Low level evidence of such a high degree does not allow for any valid conclusion.

A more appropriate conclusion would have been that no conclusions from NMA can currently be drawn with confidence regarding the treatment of young people with depression. This NMA could result in far-reaching consequences concerning the treatment of pediatric depression but inappropriately so. We thank the authors for their enormous work and high degree of transparency.

### **Competing interests**

FL, CS, and PL have developed and evaluated psychodynamic treatments for adults with depression. SR and AA have no conflicts to declare.

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