

Skapinakis P\*, Caldwell DM, Hollingworth W, Welton NJ, Fineberg N, Salkovskis P, Churchill R, Lewis G. Network meta-analyses and treatment recommendations for obsessive-compulsive disorder - Authors' reply. *Lancet Psychiatry* 2016 Oct; 3(10): 921-922. doi:10.1016/S2215-0366(16)30282-6.

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We agree with Tan Shian Ming that concomitant use of medications in psychotherapy trials is a problem for interpreting the treatment effects of psychotherapy in OCD. Concurrent medications used in these trials are not just antidepressant but specifically anti-obsessive drugs. In our network meta-analysis, based on the existing study data, we cannot be sure to what extent we are evaluating outcomes on psychotherapy as monotherapy or psychotherapy combined with medication.

Tan Shian Ming's second point is that the transitivity assumption of our network meta-analysis may not hold because the proportion of patients with concomitant use of medications differed among psychotherapy trials. We were very careful in assessing the methodological assumptions of the network meta-analysis, including the transitivity assumption and assessment of statistical inconsistency between direct and indirect evidence.<sup>1</sup> For the transitivity assumption, we considered several potential effect modifiers, such as baseline symptom severity, age, length of trial follow-up, proportion of participants with depression, and year of publication, but there was no evidence that the assumption of transitivity did not hold across the trials and comparisons.<sup>1</sup> Proportion of patients with concomitant use of medications in psychotherapy trials was not considered at the protocol stage as this was not reported in

previous meta-analyses in the field. Only two studies reported that they excluded such patients and for a third it was unclear. In our second sensitivity analysis (“incomplete outcome assessment”), we excluded these three studies and the results were not different from the main analysis. Therefore, we think it is unlikely that this aspect of the study threatens the (internal) validity of our results. Finally, we are aware of the several techniques used in variants of cognitive behavioral treatment for OCD; all trials in our review used techniques specific to OCD but the more detailed assessment of these specific interventions was beyond the scope of the current review. Future research focusing only in psychotherapy trials may be more suitable for such comparisons.

Michael Wheaton and colleagues argue that our data “do not clearly demonstrate superiority of combination treatment”. We agree and reported that “psychotherapeutic interventions had a greater effect than did medications”. Interpretation of these results, however, should take into account both internal and external validity (generalisability)<sup>2</sup>. Regarding internal validity Wheaton and colleagues note that “direct comparisons offer a higher level of evidence”. However, in cases where there are both direct and indirect evidence, ignoring the indirect part will result in reduced precision and less confidence<sup>3</sup>. Leucht and colleagues<sup>3</sup> argue that network meta-analyses should be now considered as the highest level of evidence. Regarding external validity, since most psychotherapeutic studies did not exclude patients on medications, it is not appropriate to generalise findings to patients not taking such medications. Even though patients were symptomatic at trial recruitment, there is no information on the pre-randomization / pre-medication period, including the severity and course of both the obsessive-compulsive symptoms and comorbid depression. Abramowitz et al.<sup>4</sup> have shown that the relationship between depressive symptoms and response to psychotherapy in OCD is non-linear. In their pragmatic cohort of OCD patients, treatment response for behavioural therapy differed according to depression severity, being 100% in the non-depressed patients versus 0% in the severely depressed.<sup>4</sup> These patients are usually excluded from RCTs, but it is likely that prior treatment with antidepressants reduced the levels of depression and thus contributed to the subsequent good effect of psychotherapies in such trials.

Patients included in the reviewed RCTs had long-standing and severe OCD. This is typical in treated samples: in a long-term follow-up study (10-20 years), half the cohort still had symptoms that would make them eligible for inclusion in a new trial, while 70% were receiving medication at follow-up and 50% had received behavioural or cognitive-behavioural therapy at some point in their lives.<sup>5</sup> First-line treatment decisions will require trials with treatment-naïve patients or patients with shorter duration of illness, but given the available evidence, we believe that our interpretation better reflects what happens in everyday clinical practice.

We declare no competing interests

## References

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