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Li X & Zhang C. Comparative efficacy of nine antidepressants in treating Chinese patients with poststroke depression

Kok, Rob M.; Veraart, Jolien K. E.

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Correspondence

Li X & Zhang C. Comparative efficacy of nine antidepressants in treating Chinese patients with post-stroke depression: A network meta-analysis. Journal of affective disorders. 2020; 266: 540–548.

Dear Editors,

We have read with great interest the article entitled “Comparative efficacy of nine antidepressants in treating Chinese patients with post-stroke depression: A network meta-analysis” by Li & Zhang (2020). This article has included more RCTs of post-stroke depression than other meta-analysis that have been published so far, and is therefore a very welcome addition to the published articles. The authors concluded that escitalopram was associated with a quicker relief of depression, but that mirtazapine was probably the best option when it comes to the efficacy of 8-week duration. They also concluded that amitriptyline and doxepin were nearly the worst choice regardless of treatment duration.

We have several concerning points about this article. First of all, all 51 included RCTs have been published in Chinese journals and the articles cannot be found with the usual English-language databases or websites (PubMed, Google Scholar). Even abstracts in English are not available for checking essential data. This means that one crucial part of science, controlling the validity of published data, is not possible.

The authors state that they included studies with “symptoms of depression diagnosed according to ICD-10, DSM-IV or the Chinese Classification of Mental Disorders”. This is quite unclear, are only patients with a depressive disorder included, or also patients with depressive symptoms not fulfilling diagnostic criteria for a mood disorder? According to the table ‘Characteristics of included trials’, some studies did not use an official classification but only a Hamilton Depression Rating Scale (HAMD) cut-off score, even though the HAMD was designed as a scale for measuring depression severity and should not be used as a diagnostic instrument (Hamilton, 1967). The inclusion of studies that used very low doses of antidepressants, for example venlafaxine 5 mg or amitriptyline 25 mg, adds to the serious doubt what the authors have studied, depressive disorders, depressive symptoms, or both. Another inclusion criterion was the use of one of nine antidepressants that the authors have selected, but there is not any justification why other antidepressants were excluded.

In the results section, the authors suggest that after two weeks, citalopram had a greater decrease in HAMD score than other antidepressants, and that after 4 weeks escitalopram had the largest reduction in HAMD score, without mentioning that these differences are not statistically significant.

In the discussion section, the authors state that their NMA aimed to rank the effectiveness of nine commonly prescribed antidepressants in patients with post-stroke depression. We are afraid that the authors are not aware of the discussion about the misleading suggestions of ranking orders in NMAs (Chaimani et al., 2017). The authors acknowledge that rank orders vary significantly at 4 weeks, but not that they also vary significantly at 8 weeks and at endpoint, thus illustrating the very limited meaning of rank orders. Doxepin for example, is the last out of nine antidepressants in rank order after 4 weeks, and second in rank order after 8 weeks.

Another important point of concern is that statements in the discussion are not supported by data. For example, the authors state that escitalopram was superior to sertraline and citalopram with faster relief from depressive symptoms. However, according to the results after 2 weeks in Table 1, these differences are not statistically significant. In fact, escitalopram is statistically significantly better than amitriptyline, duloxetine and paroxetine after 2 weeks but this is not mentioned by the authors. After 4 weeks, the authors conclude that sertraline showed superior advantages to escitalopram, which is in contrast with the results presented in Table 2 suggesting no statistically significant difference. After 8 weeks, the authors conclude that mirtazapine is superior to venlafaxine and duloxetine, ignoring that Table 3 suggests that mirtazapine is significantly better than all antidepressants except sertraline and doxepin. However, Fig. 3 with forest plots of the NMA results show that after 8 weeks, mirtazapine is ranked highest and doxepin as second with completely overlapping 95% CI, meaning that either Table 3 of Fig. 3 should be wrong.

The authors claim that this (non-existing) superiority is the result of the bias of allowing sertraline to be flexibly dosed (50–200 mg/day) compared to the fixed dose of escitalopram. How can they be so sure and why is this explanation not mentioned to explain other differences? Using very low dosages of both tricyclic antidepressant (five studies allowed only 25 mg of amitriptyline or doxepin) is not mentioned by the authors as explanation for the disappointing results with these antidepressants.

This may be very important, because the validity of NMAs depends on the transitivity assumption that patients and treatment are similar in different comparisons. The dose of antidepressant of the studies are published as supplementary material and varies from 5 to 225 for venlafaxine and from 25 to 300 mg for amitriptyline, thus casting serious doubts about the transitivity assumption. The authors do mention as limitation that there was no restriction of drug doses, but we suggest that a sensitivity analysis with studies using only dosages that are commonly used to treat depressive disorders is essential to be able to interpret the results.

One very important limitation acknowledged by the authors is that the majority of the studies published no overall discontinuation rate or discontinuation due to side effect. These data are essential for intention-to-treat analyses and the authors did not state whether this is what they have done. If this NMA is the result of an unknown mix of studies with intention-to-treat and completers analyses, then the results are not valid at all. Studies who do not present data of drop-outs and intention-to-treat analyses should have been excluded from the NMA.

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Author statement

Both authors have approved the final version.

Contributors

Dr. Kok wrote the first draft of this paper. Dr. Veraart approved the final version.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jad.2020.09.078](https://doi.org/10.1016/j.jad.2020.09.078).

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Rob M. Kok^{a,*}, Jolien K.E. Veraart^{a,b}

^a *Parnassia Psychiatric Institute, Mangostraat 1, 2552, KS, Den Haag, the Netherlands*

^b *University of Groningen, University Medical Center Groningen, Department of Psychiatry, Groningen, the Netherlands*

E-mail address: r.kok@parnassia.nl (R.M. Kok).

* Corresponding author.