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Reply to Wang et al.'s commentary on Xue et al.: The efficacy and safety of dual orexin receptor antagonists in primary insomnia: A systematic review and network meta-analysis

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We thank Wang et al. for their commentary [1] on our publication, "The efficacy and safety of dual orexin receptor antagonists in primary insomnia: A systematic review and network meta-analysis" [2]. Their comments focus mainly on two aspects: 1) the results of the surfaces under the curve ranking area (SUCRA) and 2) the certainty of evidence assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Here, we will respond accordingly to his comments.

First, Wang et al. point out that "The SUCRA score induce a ranking of efficacy or safety that mostly follows that of the point estimates." We really agree that the point estimates affect SCURA to a great extent and as we mentioned in Limitations that network meta-analysis calculated according to highly overlapping datasets and slight variations in methodology can produce contrasting and contradictory results. Therefore, not only SUCRA but also the effect size of pair-wise meta-analysis and network meta-analysis were taken into account in the conclusions. In addition, Wang et al. point out that "… conclusions using SUCRA to evaluate the efficacy and safety of drugs are inappropriate …" but in fact, our conclusion, dual orexin receptor antagonists (DORAs) are superior to placebo for primary insomnia, predominantly based on the point estimates of pair-wise meta-analysis and network meta-analysis. Wang et al. also consider the report of SUCRA about lemborexant and suvorexant may mislead readers. However, we have acknowledged that "no statistical differences were found between any two of the DORAs in terms of primary efficacy outcomes" in Abstract part and that "we still cannot draw a definitive conclusion that lemborexant is more worthy of clinical recommendation than suvorexant, because the results of our network meta-analysis showed that the differences between them were not statistically significant" in Discussion part of the original article. On the basis of the latest network meta-analysis guideline recommendations [3,4], we aimed to use SUCRA to compare with effect size of pair-wise meta-analysis and network meta-analysis to verify the consistency and reliability of the final results. In addition, a recent pivotal, well-designed network meta-analysis comparing effects of all pharmacological interventions for primary insomnia also confirmed the favorable profile of lemborexant, which is consistent with our results of SUCRA [5].

Second, Wang et al. strongly recommend using GRADE to assess the certainty of evidence and to rank the efficacy of five DORAs as many meta-analyses have done [6–8], which would have been

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ideal. We agree that the certainty of evidence should also be taken into consideration together with the ranking or point estimate. Although the risk of bias, inconsistency, indirectness, imprecision and etc., which downgrade the certainty of evidence, seem to be minimized in our article by developing inclusion/exclusion criteria, reporting risk of bias and characteristics of the included studies, performing sensitivity analysis and additional analysis (e.g., DORAs with specific dosage). The GRADE approach must help systematically describe the certainty of evidence in order to make more accurate evidence-based decisions but it is not the only way. In addition, we feel unnecessary to category the clinical importance of five DORAs and placebo by GRADE approach because no significant difference was found between any two of DORAs which means the second classification based on comparisons between pairs of interventions will not work [3,4].

Finally, we are grateful for the opportunity to discuss the concerns raised by Wang and colleagues. Despite the concerns raised, we maintain that DORA-based pharmacotherapy for primary insomnia is superior to that of a placebo in terms of both efficacy and safety measures and reiterate that there are only small differences in efficacy and safety between any two DORAs.

Declaration of competing interest

The authors declare that they have no competing interests.

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