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Possible redundant data in the network meta-analysis of pharmacological therapies for opioid-induced constipation

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**Possible redundant data in the network meta-analysis of pharmacological therapies for opioid-induced constipation.**

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**Letter to the editors:**

We read with great interest the recent systematic review and network meta-analysis by Sridharan and Sivaramakrishnan, (1) which synthesised data from 23 separate articles reporting randomised controlled trials (RCTs) of pharmacological therapies for opioid-induced constipation (OIC). After pooling and analysing the results from these articles, the authors concluded that subcutaneous methylnaltrexone performed better than other medications for OIC.

We have some concerns about the accuracy of the results in this study. From the accepted manuscript, in Table 1 "Key characteristics of the included studies", it appears that data from the same RCTs could have been entered into the meta-analysis more than once. The articles by Thomas *et al.*(2) and Chamberlain *et al.* (3) both report data from the same RCT investigating the efficacy of subcutaneous methylnaltrexone in 134 patients with OIC and advanced illness, conducted in the USA and Canada. Similarly, Iyer *et al.*(4) and Michna *et al.*(5) both report data from another trial investigating the efficacy of subcutaneous methylnaltrexone for OIC, recruiting 460 patients across multiple sites in the USA. All four of these articles appear in the included studies table, and may have been included as separate, unrelated, RCTs in the network meta-analysis.

If this is indeed the case, this would have serious implications for the results, and may well account for the fact that subcutaneous methylnaltrexone appeared significantly better than alternative pharmacological therapies for the treatment of OIC. It is impossible to know conclusively whether our suspicions are correct. The primary outcome of rescue-free bowel movement within 24

hours without laxation was drawn from 16 RCTs. The duplicate studies might not have been erroneously combined, but there are no references for each individual RCT that contributed data to each separate analysis. There is mention of "eight post-hoc studies or extension studies" being excluded in the PRISMA flow chart (Figure 1 of their article). However, neither of the studies by Chamberlain *et al.*(3) or Michna *et al.*(5) were identified as dual publications here by the authors, and thus excluded from the meta-analysis.

A systematic review and meta-analysis of RCTs is considered the highest level of evidence. (6) It is therefore important that data are synthesised accurately, and summarised in a reproducible way, as these studies are often used to guide clinical practice. It can be difficult for journal editors, peer reviewers and, not least, readers of these articles to confirm the accuracy of data included in them and therefore the veracity of the results, particularly when the authors' standard of reporting of the data included in the meta-analysis is suboptimal. We would welcome clarification from the authors about the individual RCTs included in their analyses, in order to ascertain whether the effect observed in favour of subcutaneous methylnaltrexone is genuine.

**Disclosures**

None of the authors have any conflicts of interest.

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