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Smallwood, N;Barnes, H;McDonald, J;Manser, R

**Title:**

Author reply

**Date:**

2018-04-01

**Citation:**

Smallwood, N., Barnes, H., McDonald, J. & Manser, R. (2018). Author reply. *Internal Medicine Journal*, 48 (4), pp.486-487. <https://doi.org/10.1111/imj.13758>.

**Persistent Link:**

<https://hdl.handle.net/11343/283869>

**Opioids for the palliation of breathlessness: robust and rigorous analyses from latest  
Cochrane review**

**Short title:** Robust evidence from Cochrane review

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**This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.13758](https://doi.org/10.1111/imj.13758)**

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Word count: 604

References – 8

**Keywords**

Cochrane, opioids, review, meta-analyses, dyspnea, palliative

We thank Currow *et al* for their interest in the survey of Australian junior doctors regarding beliefs and attitudes to managing refractory breathlessness in patients with severe Chronic obstructive pulmonary disease undertaken by Smallwood *et al*<sup>1,2</sup>. However, as Currow *et al*'s letter<sup>2</sup> principally concerns the Cochrane review regarding the utility of opioids for refractory breathlessness undertaken by Barnes *et al*<sup>3</sup> and on which N Smallwood is a co-author, in this letter we would like to respond to Currow *et al*'s opinion that the Cochrane review contained methodological flaws. Their criticisms were published last year in the feedback section of our Cochrane review, as was our full response with evidence that their assertions were unfounded<sup>3</sup>. However, given the serious and ongoing nature of the criticisms now published in the IMJ, we think it is important to summarise our response here.

Firstly, there is not one "standard method" for incorporating crossover data into meta-analyses<sup>1</sup>, instead the Cochrane Handbook outlines several possible methods, including using the data as if it was a parallel study, which was the method first used in our Cochrane review<sup>3,4</sup>. We also conducted a sensitivity analysis with a meta-analysis using correlation coefficients and corrected standard errors (as an alternative method to include crossover data). The results of the original analysis and new sensitivity analysis were not dissimilar, thus were consistent with our previous conclusion<sup>3</sup>.

Secondly, Currow *et al* raise concerns regarding the use of a fixed effects versus a random effects model<sup>1</sup>. The *a priori* choice and rationale for a fixed effects model was outlined in advance in the protocol, which was peer reviewed prior to publication<sup>3</sup>. Both a fixed effects and random effects model were presented in the sensitivity analyses, and found no differences in effect<sup>3</sup>.

Thirdly, Currow *et al* suggested that we downgraded the quality of evidence based on concerns about study size alone <sup>1</sup>. We used GRADE methodology to rate the quality of the evidence and our decision to downgrade the quality of the evidence was based on the fact that more than 50% of included trials did not report on allocation concealment, blinding of participants or personnel, or blinding of outcome assessment <sup>3</sup>. This is potentially a serious limitation when the primary outcome (i.e. change in breathlessness) is entirely subjective. We acknowledge that study size *per se* does not influence the internal validity of trial results and that some of the trials included in the review were designed with sufficient statistical power. Additionally, the 'size bias' criterion was suggested by the Cochrane editorial team during the review process of our manuscript, as there is empiric evidence that study size may be a surrogate marker of trial quality when the reporting on aspects of trial quality is poor <sup>5</sup>.

As the additional sensitivity analyses do not change the original Cochrane review conclusions <sup>3</sup>, we strongly disagree with the repeated assertions made by Currow *et al* of flawed methodology <sup>1,3</sup>. There is some small, low quality evidence that shows a modest benefit from the use of parental or oral opioids to palliate breathlessness in the short term. Notably, long term studies and evidence suggesting an improvement in quality of life are lacking <sup>3</sup>. As such further studies are required, particularly given the risks of adverse events.

The Cochrane review process is recognized to be world class in providing robust systematic reviews and meta-analyses, which are essential for supporting evidence based practice for busy clinicians. A meta-analysis conducted without the context of this rigorous review process should be interpreted with caution and does not strengthen the evidence for the use of opioids for breathlessness.

## Acknowledgements

We thank Christopher Cates for his extensive input on the sensitivity analyses and comments on our previous response, Kerry Dwan, Toby Lasserson and the Cochrane Statistical Methods Group, and Julian Higgins for his report on the interpretation of this data.

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