Reply: A Network Meta-analysis of the Efficacy of Opioid Analgesics for the Management of Breakthrough Cancer Pain Episodes

To the Editor:

Zeppetella et al.\(^1\) conducted a network meta-analysis of 10 studies comparing six different fentanyl transmucosal formulations approved for breakthrough cancer pain (BTcP) medications and oral morphine. Their conclusion is that “although all BTcP medications provided pain relief within the time frames assessed, transmucosal fentanyl medications achieved a greater level of pain relief in a shorter time frame than placebo or oral morphine.” I would like to comment on the methodology of this network meta-analysis.

The publications included in the network meta-analysis review only covered the period until 2010. Three other randomized controlled studies published after this period were not included, although they were part of a Cochrane review by the same authors.\(^2\) These trials should have been included in this network meta-analysis.

The main outcome of interest in the network meta-analysis was the pain intensity difference (PID), measured at various time points after baseline. PID data were extracted from the publications “by one reviewer using a standard data extraction form and checked against the original publication by a second reviewer.” Data required for the network meta-analysis were the mean PID

References

1. Yano S, Kanematsu T, Miki T, et al. A report of two bronchioloalveolar carcinoma cases which were rapidly improved by treatment with the epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 (‘Iressa’). Cancer Sci 2003;94:453–458.


values at each time point for each treatment group, along with a measure of the precision of this mean. In most cases, these values had to be read off graphs as they were not explicitly reported in the publications. I have examined all the means and standard errors (SEs) extracted from the 10 publications. For the most part, it is hard to confirm the numbers accurately because all these studies are crossover in nature (all patients received both treatments). A more robust methodology would have been to extract the means and SEs of the within-patient treatment differences. The result of using the treatment means and SEs across patients is an overestimate of the SE of the treatment difference. It was not possible to extract the SE of the treatment difference in all cases, and it is important to recognize the effect of this on the confidence intervals.

Additionally, aspects of the statistical methods are not described in enough detail to allow others to reproduce the results. The following issues are unclear:

1. SE for missing time points: It is stated that “an average could be calculated using adjacent time points as proxy”; however, how the corresponding SE was calculated is not stated.

2. Missing SE data: How these values were treated in the network meta-analysis is not stated. In the study by Farrar et al., the only information provided is in a graph showing the SEs of the differences in PID between oral transmucosal fentanyl citrate and placebo. These SEs are more appropriate for the treatment comparisons but were not available for all the studies.

3. Fixed- and random-effects models: It is not clear how the prior distribution for the between-study variance for the random-effects model was chosen. I would question the appropriateness of random-effects models in this situation because there is only one pair of studies testing the same pair of treatments. This means that the between-study variance is hard to estimate and may be sensitive to the choice of prior distribution. I assume that the models used were fixed-effect models, although this is not made clear.

Based on these considerations, it may be concluded that this network meta-analysis is flawed.

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References


