Clinically significant reductions in morphine consumption need to take account of baseline risk: presentation of a novel meta-analysis methodology

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To illustrate the problem this causes in the interpretation of the meta-analysis of Fabritius and colleagues, we reanalysed their data from low risk of bias trials for 24 h morphine consumption on which their main conclusions are based. Their original estimate was a 5.81 mg morphine reduction in 24 h, which is indeed of questionable clinical significance. However, when performing meta-regression of baseline risk (control group consumption in milligrams), 86% of the between-study heterogeneity is explained by baseline risk ($P = 0.004$). The analysis shows that for surgeries where the average consumption is around 35 mg day$^{-1}$ then indeed, clinically significant reductions of 10 mg can be achieved. This issue also becomes important when comparing different analgesics/subgroups (see Table 3) as, again, morphine reductions from any agent will depend on the baseline risk of the included trials for each analgesic rather than the efficacy of the agent under study.

In view of the above, it was also interesting to read the editorial in the same issue from the PROSPECT group regarding procedure-specific evidence. We agree that there is certainly a role that type of surgery plays in the response to analgesics (and more specific to local anaesthetic techniques). However, when we analysed 344 randomised controlled trials of multimodal analgesics, type of surgery was not an independent predictor of morphine reductions when added to the model with baseline risk. Put simply, the evidence for better analgesic efficacy in certain types of surgery may be a product of differing baseline risk (some surgeries resulting in higher postoperative morphine consumption) rather than the type of surgery per se. Indeed, other factors that influence postoperative morphine consumption such as local patient factors and concurrent analgesic strategies also contribute to baseline risk and are controlled for with our models. Whilst we agree with many of the issues raised in the editorial, we would argue, as the title of the article suggests, there is a need for a re-evaluation, although this comes from a consideration of baseline risk, rather than just the type of surgery.

We welcome the updated evidence from Fabritius and colleagues and particularly the advantages alluded to previously. Indeed, the finding of increased serious adverse events...
with pregabalin requires serious re-evaluation for its use in multimodal analgesic protocols (which may also be subject to baseline risk and the issues highlighted above, for example in elderly populations). However, the statement that a 10 mg reduction was excluded does not consider the specific clinical contexts where these reductions may be achieved. This is of no fault of the authors based on established meta-analysis methodology. Despite this, we hope this letter has illustrated the limitations of current meta-analysis methods (both statistical and clinical) and advise future reviews take account of baseline risk to both reduce confounding from variable baseline risk (using meta-regression) and allow consumers to select the specific circumstances where clinically significant reductions may be achieved.

**Declaration of interest**

None declared.

**References**