Reply to Mercadante *et al* on breakthrough cancer pain.

Running title: Opioids for breakthrough cancer pain

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Mercadante *et al* are to be commended for adding to the science of breakthrough cancer pain in this large, recently published cohort study. [1] The authors described differences in the characteristics of pain and subsequent analgesia with the use of breakthrough medications in 3,892 people with cancer pain on regular low (<60mg oral morphine equivalent daily (OME)) and high (≥60mg OME) dose opioids.

The characteristics of breakthrough cancer pain vary from person to person, and across populations. [2] The clinical response to breakthrough cancer pain (incident pain, spontaneous pain or both), once a regular dose of an opioid has been established, has been to prescribe a proportion of the regular dose of (mostly) the same opioid. Despite the ubiquitous nature of breakthrough cancer pain, the evidence remains poor for many key questions for its ideal management: [3]

- What should the proportion of the regular opioid dose be, accounting for any differences in formulation or route of administration?

- What should the lockout period / dose interval before an additional dose of breakthrough opioid can be given? and

- Should there be a limit on the number of doses that a patient can self-administer in any 24 hour period?

A recent multi-site, randomised, double-blind study complements the findings of the study by Mercadante *et al*. [4] The study was undertaken to address a long-standing question in the evidence in the clinical literature about the ideal dose of opioid for breakthrough cancer pain. [3] In this study, three different dose proportions (1/6, 1/8, 1/12 of the fourth hourly dose) were studied for each person who was established on a regular dose of opioid (morphine or oxycodone) for cancer pain. The findings that the time to analgesia and harms were similar for all three proportions suggest that, from first principles, the lowest effective proportion (1/12) should be used, thus refining current recommendations. [5]

Standardising dose proportions in future cohort studies will optimise the ability to compare across differing clinical practices, and further progress our understanding of this widespread cause of suffering. In the interim, using the lowest dose to achieve the desired clinical effect while minimising harms from opioids for pain should direct current practice, given that fewer than one in two people identify benefit when using breakthrough opioids. [2]

References

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