COMMENTARY

Breakthrough pain is not a fixed fraction of constant cancer pain

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This journal recently published a paper by Currow et al., entitled “A randomised, double-blind, crossover, dose ranging study to determine the optimal dose of oral opioid to treat breakthrough pain for patients with advanced cancer already established on regular opioids” (Currow et al., 2020). Currow et al. demonstrated that for breakthrough pain (BTP) there were no differences between giving rescue opioid doses of 1/6, 1/8 or 1/12 of the scheduled daily opioid dose. This finding challenges the current WHO guideline routine advice for BTP of rescue opioid doses based upon the daily scheduled opioid dose (WHO, 2018). The study by Currow et al. was multicentric, most patients received all dose alternatives thereby excluding interindividual variability, they received the dose alternatives in random order and the study was double-blinded. Thus, the results are reliable.

The findings in this study are not surprising. The advice for a fixed oral rescue dose related to scheduled opioid dose is based upon expert opinions and not tested in studies. New drugs introduced later for BTP and subjected to more rigorous testing, such as transmucosal fentanyl, also showed no clear relationship between scheduled dose and effective rescue dose (Portenoy, Taylor, Messina, & Tremmel, 2006). Furthermore, from a clinical perspective the lack of a relationship between scheduled dose and rescue dose is as expected. BTP may be caused by other mechanisms than the constant pain; for example the constant pain may be visceral pain while the BTP can be lancinating neuropathic pain or movement elicited pain. The patient may therefore have a high baseline pain intensity/low BTP intensity, low baseline pain intensity/high BTP intensity and so forth (Figure 1). Moreover, BTP episodes in one patient may vary suggesting that the patient may benefit from self-administrating different opioid rescue doses for different BTP episodes.

![Different Combinations of Constant Pain and BTP](image)

**FIGURE 1** Different combination of constant pain and BTP. (a) High constant pain and high breakthrough (BTP) pain. (b) Low constant pain and high BTP pain. (c) Low constant pain and low repetitive BTP pain. Panel D: High constant pain and low BTP pain (Artwork by Julie Klepstad)

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different combinations intuitively suggest that the idea of a fixed relationship between scheduled and rescue doses is not to be expected, a view now also supported by Currow et al.

Another important implication from the study by Currow et al. is that oral opioid rescue medications do not work well. Only about one third had acceptable pain relief after 30 min and median time to pain relief was 120 min. One may speculate what parts of pain relief are due to respectively the effects from the oral rescue opioid or to that the BTP simply spontaneously subsides. It can be concluded that the effects from oral rescue opioids is limited and argued that upcoming guidelines perhaps should recommend the use of other routes.

The study by Currow et al. and others have important clinical implications. First, the results suggest that scheduled opioid dose of opioids for constant pain and rescue opioid doses for BTP should be titrated independently. Second, the results suggest that oral administration of opioids are not the ideal route for BTP. Both these points represent clinical advices that challenges many current guidelines for opioid therapy of cancer pain.

**AUTHOR CONTRIBUTION**
All authors contributed to the draft the commentary and take responsibility for the final content of the commentary.

**REFERENCES**
