

## Journal Watch

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Presented at CCI Journal Club, December 14, 2010

Meissner W, Leyendecker P, Mueller-Lissner S, Nadstawek J, Hopp M, Ruckes C, Wirz S, Fleischer W, Reimer K. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. *Eur J Pain* 2009; 13:56–64

*Abstract:* Background: Opioid-induced constipation can have a major negative impact on patients' quality of life. This randomised, double-blinded study evaluated the analgesic efficacy of prolonged-release (PR) oral oxycodone when co-administered with PR oral naloxone, and its impact on opioid-induced constipation in patients with severe chronic pain. Another objective was to identify the optimal dose ratio of oxycodone and naloxone.

Methods: A total of 202 patients with chronic pain (mainly non-cancer related, 2.5% of patients had cancer-related pain) under stable oral oxycodone therapy (40, 60 or 80 mg/day) were randomised to receive 10, 20, 40 mg/day naloxone or placebo. After a 4-week maintenance phase, patients received oxycodone only for 2 weeks. Pain intensity was evaluated using a numerical analogue scale and bowel function was assessed using the bowel function index.

Results: No loss of analgesic efficacy with naloxone was observed. Mean pain intensity scores on randomization were comparable for placebo, 10 mg, 20 mg and 40 mg naloxone dose, and remained unchanged during treatment. Bowel function improved with increasing naloxone dose. Naloxone 20 mg and 40 mg significantly improved bowel function at the end of the maintenance phase compared with placebo ( $p < 0.05$ ). Overall, the combination was well tolerated, with no unexpected adverse events. There was a trend towards an increased incidence of diarrhoea with higher doses of naloxone. The 2:1 oxycodone/naloxone ratio was identified as the most suitable for further development.

Conclusion: Co-administration of PR oral naloxone and PR oral oxycodone is associated with a significant improvement in bowel function compared with PR oral oxycodone alone, with no reduction in the analgesic efficacy of oxycodone.

*Strengths/uniqueness:* The trial appears to have been appropriately executed, although the methods used to ensure concealment of allocation and double-blinding could have been more adequately described. The finding that oral naloxone can influence bowel function in patients on opioids, without adversely affecting analgesia, seems to be valid.

*Weaknesses:* The clinical impact of naloxone on bowel function remains unclear. Firstly, in order to be eligible for randomization, patients did not have to experience refractory constipation – they just had to require laxatives in order to maintain bowel movements. The advantage of using naloxone versus more laxatives is undefined. Secondly, the primary outcome for constipation (Bowel Function Index) was entirely subjective.

Subjective assessment of constipation is notoriously unreliable. Although objective outcomes such as frequency of bowel movements and laxative use were also measured, the clinical significance of the observed differences is uncertain. Another concern is that, while the higher frequency of moderate and severe adverse events with increasing naloxone doses was mentioned, the adverse events themselves were incompletely described. In particular, there was no formal evaluation of opioid withdrawal symptoms.

*Implications for Palliative Care:* This combination sustained-release preparation of oxycodone and naloxone will become available in Canada in the near future. Currently, there are no published randomized controlled trials of this agent in patients with cancer pain, so its effects in this population are unknown. Also unknown at this time is the cost of this agent. Use of this agent would be limited to patients who achieve stable analgesia with oxycodone, at a maximum dose of 80 mg per day.