Efficacy of pharmacological therapies for the treatment of opioid-induced constipation:

systematic review and meta-analysis

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CRD summary
This review found that μ-opioid receptor antagonists were safe and effective for the treatment of opioid-induced constipation. There was some concern over uncertain trial quality but the results appear to be reliable. The conclusion on safety may be overstated given the evidence.

Authors' objectives
To investigate the evidence for the benefits of pharmacological therapies for opiate-induced constipation.

Searching
MEDLINE, EMBASE and Cochrane CENTRAL were searched to December 2012 without language restrictions. Search terms were presented. Conference proceedings and reference lists of identified papers were searched.

Study selection
Randomised controlled trials (RCTs) in adults (at least 90% of participants aged over 16) who received opioid or opiate drugs were eligible. Trials had to be placebo controlled or compare two different treatments. Opiate-induced constipation had to be diagnosed by clinical symptoms, a physician's opinion or specified diagnostic criteria. The primary outcome was efficacy of therapy; adverse events were considered.

Treatments used included μ-opioid receptor antagonists (methylnaltrexone, naloxone, oxycodone, alvimopan) and other types of treatment (prucalopride, lubiprostone). Treatment duration ranged from two days to 12 weeks. Most trials were conducted in patients with chronic non-malignant pain. Between 45.5% and 68.3% of the participants were women. Most trials were conducted in USA or were multinational. Most recruited patients who were in secondary or tertiary care. Definitions of opiate-induced constipation and criteria used to define response to therapy varied across trials.

Two reviewers assessed studies for inclusion, with disagreements resolved by consensus.

Assessment of study quality
Two investigators independently assessed study quality using the Cochrane risk of bias tool.

Data extraction
Two reviewers extracted data from studies. Data sufficient to calculate treatment efficacy in terms of the relative risk and its 95% confidence interval were extracted. An intention-to-treat approach was used, with drop-outs assumed to be treatment failures. Attempts to contact trial authors for missing details were made when necessary.

Methods of synthesis
Trials were pooled using random-effects meta-analysis. Heterogeneity was assessed using $I^2$ and Cochran's Q statistics ($I^2>50\%$ was taken to indicate significant heterogeneity).

Subgroup analyses were performed for type of therapy used, dose, risk of bias, definition of constipation, therapy duration and definition of response to therapy. Publication bias was assessed using funnel plots and Egger's test.

Results of the review
Seventeen trials (5,174 participants, range nine to 803) were included. Six trials were reported to be at a low risk of bias overall; other studies were limited by lack of reporting of randomisation sequence generation and allocation concealment methods or by lack of an intention-to-treat analysis.

In 14 trials of μ-opioid receptor antagonists treatment was found to be more effective than placebo (RR 0.69, 95% CI 0.63 to 0.76; $I^2=51\%$). Among the specific treatments, methylnaltrexone (RR 0.67, 95% CI 0.54 to 0.84; $I^2=72\%$; six
trials), naloxone (RR 0.64, 95% CI 0.56 to 0.72; I²=0; four trials) and alvimopan (RR 0.71, 95% CI 0.65 to 0.78; I²=11%; four trials) were all found to be more effective than placebo. Data were limited for other treatments.

The μ-opioid receptor antagonists increased adverse events by 11% compared to placebo (RR 1.11, 95% CI 1.04 to 1.20; 10 trials). Increases in risk were statistically significant for diarrhoea (RR 1.61, 95% CI 1.21 to 2.13; 11 trials) and abdominal pain (RR 1.63, 95% CI 1.06 to 2.51; 11 trials) but were not statistically significant for other adverse events. For each specific treatment a general trend towards increased incidence of adverse events was reported but these results were not statistically significant. There was no statistically significant difference between treatment and placebo for reversal of analgesia.

There was some evidence of possible publication bias.

**Authors’ conclusions**
μ-opioid receptor antagonists were safe and effective for the treatment of opioid-induced constipation. More evidence was needed for prucalopride and lubiprostone.

**CRD commentary**
This review addressed a relevant review question with appropriate inclusion criteria. The search was suitable and included efforts to identify unpublished trials. Appropriate action was taken to avoid reviewer error and bias. Study quality was assessed and only half of the included trials were judged to be at low risk of bias overall. Accounting for risk of bias did not appear to modify the results in analyses where this was considered. Trials were synthesised in meta-analyses. Some evidence of possible publication bias was found. The authors recognised the possibility of bias due to uncertain trial quality; despite this the results are likely to be reliable.

The authors’ conclusions on efficacy reflect the results appropriately but the conclusion that treatment is safe may be overstated given the evidence.

**Implications of the review for practice and research**

**Practice:** The authors concluded that μ-opioid receptor antagonists were highly effective, even in patients with failed treatment with laxatives.

**Research:** The authors suggested that more trials on prucalopride and lubiprostone were needed.

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