Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review

CRD summary
The authors concluded that they found limited evidence to support diverse interventions for the management of opioid-related side-effects, as well as the general approach of opioid rotation, and that there is a need for higher quality research. These conclusions appear justified on the basis of the evidence reported in the review, though it is possible that relevant evidence may have been available that was not included in the review.

Authors' objectives
To assess the management of opioid side-effects in the context of cancer pain management or, in the event that no evidence was available for cancer pain, for chronic noncancer pain.

Searching
MEDLINE and the Cochrane Controlled Trials Register were searched for relevant studies reported in the English language. This was supplemented by screening reference lists for additional studies in any language. The search terms were reported, though the dates of the searches were not. Trials reported in foreign languages were included if they were identified via the reference list search.

Study selection
Study designs of evaluations included in the review
The authors stated that they included the best available evidence, be that from randomised controlled trials (RCTs) or observational studies.

Specific interventions included in the review
The authors did not explicitly state any inclusion criteria relating specifically to the interventions. It appears that studies were included if participants were receiving opioid therapy. Studies comparing two opioids in which side-effects were incidently assessed were excluded.

Participants included in the review
Studies of adults or children with cancer pain were included in the review. If no relevant evidence could be found in cancer pain, studies of participants with chronic noncancer pain were included. Studies of acute post-operative pain, or obstetrical pain were excluded. The participants in the included studies were primarily male. The mean age or age range were not reported.

Outcomes assessed in the review
The authors did not explicitly state any inclusion criteria relating to the outcomes. The included studies reported a range of outcomes relating to pain, sedation and possible side-effects of opioids (e.g. nausea, vomiting, delirium, myoclonus, pruritus, respiratory depression, constipation).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors stated that the quality of the included studies was assessed according to randomisation, blinding and description of drop-outs. These issues were occasionally mentioned in the text, but were not presented for every study. The authors did not state how quality was assessed, or how many reviewers performed the quality assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on pain scales, incidence of adverse events, cognitive function scales, opioid use and control of symptoms.

Methods of synthesis
How were the studies combined?
The studies were combined in a narrative. The synthesis was organised into eight sections: sedation, nausea and vomiting, delirium, myoclonus, pruritis, respiratory depression, constipation and opioid rotation.

How were differences between studies investigated?
Heterogeneity was not formally investigated, though some differences between the studies were discussed in the narrative synthesis.

Results of the review
Sixty-seven studies (n=3,991) were included in the review: 28 RCTs, 27 non-randomised trials and 12 case series/reports. Thirty-five studies were in patients with cancer pain. Other studies included patients with chronic pain, presumed substance abuse, HIV/AIDS, pre-surgical patients, or healthy volunteers.

Sedation (2 studies).
One study found no benefit of epidural versus oral opioid administration. The second reported moderate improvements in symptoms of sedation associated with the administration of donepezil.

Nausea and vomiting (7 RCTs and 3 case studies).
Methylnaltrexone reduce nausea and vomiting without reversing opioid analgesia. Co-administration of dopamine antagonists with opioids may help prevent nausea and vomiting. Ondansetron at doses of 8 to 16 mg demonstrated efficacy in controlling emesis. Cyclizine reduced the incidence of vomiting, with a less marked effect on nausea alone. Scopolamine patches behind the ear may benefit patients with worsened nausea while ambulatory.

Delirium (1 case series and 1 case report).
Both studies reported a reversal of delirium with treatment (rehydration, discontinuation of benzodiazepines and antihistamines, opioid rotation, addition of haloperidol or risperidone).

Myoclonus (12 case reports/series).
The majority of these related to morphine-induced myoclonus. Benzodiazepines (including diazepam, clonazepam and midazolam) have been successfully used for this indication. Alternatives included dantrolene, local anaesthetics and opioid rotation.

Pruritis (3 RCTs and 2 case reports).
Intravenous ondansetron and propofol were shown to be efficacious in the randomised studies. Intradermal co-administration of naloxone with morphine was not proven to reduce itching.

Respiratory depression (10 RCTs and 2 case studies).
Naloxone and nalmefene both reduced or reversed respiratory depression without compromising analgesia in RCTs. Case studies suggested that naloxone might be effective when administered intravenously or intralingually. Studies of psysostigmine to reverse respiratory depression had conflicting results. Other studies suggested that verapamil did not affect morphine-induced respiratory depression whereas ketoprofen reduced it, and ketamine reduced fentanyl-induced hypoventilation without preventing a decrease in blood oxygenation.
Constipation (17 studies).

Polyethylene glycol and senna might be as equally effective as lactulose, but more cost-effective. The Ayurvedic medication Misrakasneham might be as effective as senna and more acceptable to patients. Methylnaltrexone, naloxone and ADL 8-2698 demonstrated a dose-dependent reversal of constipation.

Opioid rotation (7 uncontrolled studies). One study showed that rotation from morphine to subcutaneous oxycodone improved mental state, nausea and vomiting. Studies generally suggested that multiple rotations might be required, various side-effects might be reduced, and that lower than putative equi-analgesic doses might be required once successful rotation has been accomplished.

Authors’ conclusions
The authors stated that they found evidence, generally limited, to support diverse interventions for the management of opioid-related side-effects as well as the general approach of opioid rotation.

CRD commentary
This review aimed to address a fairly broad research question, which was partially supported by inclusion criteria, though these were not reported clearly. The authors searched two electronic databases to identify relevant studies. The databases and search strategies used were appropriate but were limited to English language studies, which may mean that relevant studies were missed. The authors did not report the dates which the searches covered, so it is difficult to determine if recent studies were missed or simply published after completion of the review. The authors mentioned assessing study quality, but data pertaining to quality were rarely available for the individual studies; other basic study details were tabulated. It was unclear how many reviewers were involved in the selection, assessment or data extraction of the studies, thus there is the potential for errors and possible bias to exist within these processes.

The use of a narrative synthesis was appropriate given the methodological and clinical heterogeneity of the included studies. The authors’ conclusions regarding the need for higher quality research appear justified on the basis of the evidence reported in the review, though it is possible that relevant evidence may have been available that was not included in the review.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that well-designed trials in the specified populations are required to furnish clinicians with secure evidence on managing opioid side-effects successfully.

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