Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials

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Authors' objectives
To identify all pharmacological therapies that have been used to control opioid-related pruritus in the surgical setting (including labour), and to establish their relative efficacy.

Searching
MEDLINE (from 1966 to June 2000), EMBASE (from 1974 to June 2000) and the Cochrane Library (Issue 4, 1999) were searched using the keywords 'pruritus', 'itching', 'antipruritic', 'opioid', 'postoperative', 'postsurgical', 'anaesthesia', 'anesthesia', 'randomized', 'randomised', 'controlled' and 'human', either alone or in combination. In addition, the reference lists of retrieved articles were checked for additional studies. No language restrictions were imposed. The reviewers did not contact the authors and manufacturers. Data from abstracts were not included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included in the review. Any studies in which the sample size was less than 10 were excluded.

Specific interventions included in the review
Studies of any intervention that is thought to be anti-pruritic (active) compared with placebo or 'no treatment' (control) in surgical (including labour) patients receiving opioids were included. Comparisons of an active drug with another active drug, but without a placebo or 'no treatment' arm (i.e. head-to-head comparisons), were not included.

In the trials on the prevention of pruritus, analgesia was with epidural (e.p.) morphine (10 trials), intrathecal (i.t.) morphine (5 trials), i.t. sufentanil (2 trials), a combination of i.t. morphine and fentanyl (1 trial), intravenous (i.v.) morphine (1 trial), i.v. alfentanil (1 trial) or e.p. hydromorphone (1 trial). The anti-pruritic interventions administered in these trials were: droperidol, epinephrine, hydroxyzine, nalbuphine, naloxone, naltrexone, ondansetron, prednisone and propofol; details of the doses and routes of administration were provided.

Two trials examined treatment for established pruritus using propofol (10 mg).

Participants included in the review
Only adults undergoing surgical procedures were included in the review. The main types of surgery were Caesarean section, labour, abdominal, hysterectomy, orthopaedic, hip replacement, major gynaecologic and arthroplasty.

Outcomes assessed in the review
The primary end point assessed was the number of patients who were completely free from pruritus or itching. The authors also examined the incidences of other opioid-induced adverse effects.

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
Validity was assessed using the 3-item, 5-point Oxford scale, which takes into account randomisation, blinding and description of withdrawals (see Other Publications of Related Interest). In a trial with a 'no treatment' control, the method of blinding was a priori regarded as inadequate. Both authors read all of the included trials and scored them independently for methodological validity. Any discrepancies were resolved by discussion.
**Data extraction**
Both authors extracted the data independently and resolved any discrepancies by discussion. Data were extracted on patient information, clinical setting, doses and routes of administration of opioids and anti-pruritic drugs, and the duration of the observation periods. Data on adverse drug reactions were also extracted when it was in a dichotomous form. The statistical significance of any treatment effect was calculated as a relative risk (RR) with a 95% confidence interval (CI).

**Methods of synthesis**

**How were the studies combined?**
To calculate summary RRs and 95% CIs the data were combined using a fixed-effect model. As an estimate of the clinical relevance of a treatment effect, the number-needed-to-treat (NNT) was also calculated with a 95% CI.

**How were differences between studies investigated?**
The authors stated that the data were combined only when they were clinically homogeneous and that heterogeneity tests lacked sensitivity, thereby implying that they did not test for statistical heterogeneity.

**Results of the review**

Twenty-two RCTs (n=1,477) were included.

**Prevention of pruritus.**

The results from the 4 trials with i.v. naloxone suggested that it was efficacious in comparison with the control (RR 2.31, 95% CI: 1.51, 3.54); the NNT was 3.5. Oral naltrexone (3, 6 and 9 mg) was tested in 2 trials and there was evidence of dose responsiveness. Naltrexone 3 mg was no different from the control, while doses of 6 and 9 mg were significantly more efficacious than the control; the RRs were 3.39 (95% CI: 1.69, 6.80) and 2.80 (95% CI: 1.35, 5.80), respectively, and both NNTs were below 2.

Intravenous nalmefene (1 trial) was not anti-pruritic (RR 1.50, 95% CI: 0.17, 13.5). Five different regimens of nalbuphine i.v. were tested in 3 trials. The combined data suggested anti-pruritic efficacy (RR 1.71, 95% CI: 1.12, 2.62); the NNT was 4.2.

Intravenous droperidol (2.5 or 5 mg) was tested in 3 trials and e.p. droperidol (2.5 mg) in 2 trials. Intravenous droperidol 2.5 mg was efficacious (RR 1.71, 95% CI: 1.28, 2.29), whereas both i.v. 5 mg and e.p. 2.5 mg were not significantly different from the control. When all the droperidol data were combined, the NNT to prevent pruritus (compared to the control) was 6.

Three different low-dose propofol regimens were tested in 3 trials. At 30 mg/hour i.v., there was more pruritus compared with Intralipid; 10 mg was no different from Intralipid; and with a 10 mg bolus plus 30 mg/day, there was significantly less pruritus compared with Intralipid. It was not possible to test for dose-responsiveness. When all the data were pooled, there was no significant difference in anti-pruritic efficacy with propofol compared with Intralipid (RR 1.12, 95% CI: 0.87, 1.45); the NNT was 16.

Intrathecal or e.p. epinephrine (2 trials) had no significant effect on pruritus (RR 1.09, 95% CI: 0.72, 1.64; the NNT was 36. Epidural clonidine, intramuscular hydroxyzine and e.p. prednisone were tested in one trial each; the results indicated that none of them were significantly different from the control. Prophylactic i.v. ondansetron was also tested (1 trial) and the results indicated no significant difference between the intervention and control.

**Treatment of established pruritus.**

Two trials, both with a low dose of propofol, reported on the treatment of established pruritus. The results of the first trial indicated no significant differences between the intervention group and the placebo-controlled group. The second trial was terminated prematurely, as very few patients obtained any relief from their pruritus.
Authors' conclusions
Naloxone, naltrexone, nalbuphine and droperidol are efficacious in the prevention of opioid-induced pruritus. However, the minimal effective doses remain unknown. Overall, there was a lack of valid data on the efficacy of interventions for the treatment of established pruritus.

CRD commentary
The authors addressed a well-defined review question in terms of the types of interventions, study designs, participants and outcome measures that were to be assessed in the review. The literature search was adequate, but it only searched for published studies; this means that some unpublished data may have been missed. The authors did not state how the studies were selected for inclusion in the review, or how many reviewers selected the papers. Consequently, selection bias may have been introduced into the review process. The authors reported the method for assessing the validity of the included studies, allowing the reader to assess how the quality of the individual studies may have influenced the results obtained. They also provided adequate details on the characteristics of the individual studies. The statistical analysis appears to have been appropriate, but no attempt was made to explore the results for statistical heterogeneity. This could influence the results as a fixed-effect model was used, and it is difficult to assess whether it was appropriate to pool the results of the primary studies. However, the authors did state that they only pooled data where clinically homogeneous.

Overall, the review process may have been subject to a number of biases. Whilst the authors' conclusions appeared consistent with the results obtained, they should be treated with a degree of caution.

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

Research: The authors stated that valid RCTs with an adequate length of follow-up (approximately 24 hours) are needed. The end points need to be standardised, and should include the number of patients who are completely free from pruritus after administration of the study intervention.

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Other publications of related interest

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AccessionNumber
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.