REVIEW

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

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Summary

Background and objective Numerous drugs have been used to prevent or to treat opioid-induced pruritus in the surgical setting. Their relative efficacy is not well understood.

Methods The methods employed involved the systematic search (MEDLINE, EMBASE, Cochrane library, bibliographies, without language restriction, up to June 2000) for full reports of randomized comparisons of any intervention which is thought to be anti-pruritic (active) compared with placebo or no treatment (control) in surgical (including labour) patients receiving opioids. The number of patients who had no pruritus were analysed using relative risk and number-needed-to-treat with 95% confidence interval.

Results Twenty-two trials (1477 patients) were analysed. Two trials (66 patients), both with low-dose propofol, were on treatment of established pruritus; propofol had no anti-pruritic effect compared with Intralipid. In prophylaxis trials, the average incidence of pruritus with control was 59% (range, 10% to 100%). Most mu-receptor antagonists were efficacious: intravenous naloxone 0.25–2.4 μg kg⁻¹ h⁻¹, relative risk 2.31 (95% confidence interval, 1.5 to 3.54), number-needed-to-treat to prevent pruritus compared with control 3.5; oral naltrexone 9 mg, relative risk 2.80 (1.35–5.80), number-needed-to-treat 1.7; naltrexone 6 mg was less effective and 3 mg did not work; different intravenous and epidural nalbuphine regimens, relative risk 1.71 (1.12–2.62), number-needed-to-treat 4.2. Intravenous nalmefene 0.5 or 1 mg was not anti-pruritic. Intravenous (but not epidural) droperidol 2.5 mg was efficacious, relative risk, 1.71 (1.28–2.29), number-needed-to-treat 4.9. There was a lack of evidence for any anti-pruritic efficacy with prophylactic propofol, epidural or intrathecal epinephrine, epidural clonidine, epidural prednisone, intravenous ondansetron, or intramuscular hydroxyzine.

Conclusion Naloxone, naltrexone, nalbuphine and droperidol are efficacious in the prevention of opioid-induced pruritus; minimal effective doses remain unknown. There is a lack of valid data on the efficacy of interventions for the treatment of established pruritus.

Keywords: pharmacology, naloxone, naltrexone, droperidol; pain, postoperative; complications, pruritus, vomiting; meta-analysis.

Introduction

Opioids are an integral part of the treatment of pain due to surgery and labour. Opioids, however, may induce adverse effects. In a cohort study on admissions of 4031 adults to medical and surgical units, morphine, demerol (pethidine) and oxycodone accounted for 18% of all adverse drug events [1]. Pruritus is a common adverse effect of opioids; it is thought to occur most frequently after epidural and intrathecal administration [2]. The mechanism of opioid-related pruritus is not fully understood. The role of histamine is unclear; pruritus may be induced by opioids which do not release histamine. The fact that mu-receptor antagonists (naloxone, nalbuphine) can reverse opioid-related pruritus suggests that there may be a mu-receptor mediated central mechanism [3].

Many different drugs with various potential mechanisms of action have been used to prevent or
to treat established pruritus. Their relative efficacy, optimal doses and likelihood for adverse effects are not well understood. Naloxone, for instance, although widely used to control opioid-related pruritus, may reverse the analgesic effect of opioids. The purpose of this study was 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.

Methods

Data search

We performed a systematic search for full reports of randomized comparisons of any intervention which is thought to be anti-pruritic (active) compared with placebo or ‘no treatment’ (control) in surgical patients (including labour) receiving an opioid. 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 considered. We searched in different electronic databases (MEDLINE from 1966, EMBASE from 1974, Cochrane library issue IV 1999) using the free text keywords pruritus, itching, anti-pruritic, opioid, postoperative, postsurgical, anaesthesia, anesthesia, randomized, randomised, controlled, human, and their combinations. We also checked reference lists of retrieved reports. We did not contact manufacturers or authors. The search was without language restriction, and included reports up to June 2000. We did not include data from letters, abstracts, case reports, experimental studies and review articles. Studies with group sizes <10 patients were excluded.

Critical appraisal and data extraction

Both authors read all included trials and scored them independently for methodological validity using the three-item, five-point Oxford scale which takes into account randomization, blinding and description of withdrawals [4]. In a trial with a ‘no treatment’ control, the method of blinding was a priori regarded as inadequate (i.e. 0 points for blinding in the Oxford scale). Both authors extracted data independently.

The primary end-point of efficacy was the number of patients who were completely free of pruritus with active and with control. Itching was considered as pruritus. Data on decreases in pruritus scores or visual analogue scales were not further analysed, as these data were inconsistently reported. Secondary efficacy end-points were the incidences of other opioid-induced adverse effects, for instance, nausea and vomiting. Data on adverse drug reactions were extracted when they were reported in a dichotomous form. Information on patients, clinical settings, doses and routes of administration of opioids and anti-pruritic drugs, and duration of observation periods were recorded. Discrepancies in validity scores and extracted data were resolved by discussion.

Quantitative analyses

Patients receiving no treatment were considered as placebo controls. In propofol trials, Intralipid was regarded as an inactive control. Statistical significance of any treatment effect was calculated as relative risk with 95% confidence interval [5]. For combined data, we used a fixed effect model throughout because we combined data only when they were clinically homogenous, and because heterogeneity tests lack sensitivity [6]. As an estimate of the clinical relevance of a treatment effect, the number-needed-to-treat was calculated [7] with 95% confidence interval [8]. A positive number-needed-to-treat indicated the number of patients who had to be exposed to an active intervention to show a particular end-point in one of them (for instance, prevention of pruritus) who would not have shown that end-point had they all received a control treatment. Upper and lower limits of the 95% confidence interval around the number-needed-to-treat, regardless of whether they were positive or negative, are reported [9]. When the 95% confidence interval of the relative risk excluded one, we assumed that the result was not statistically significant. In this case, we would expect the 95% confidence interval around the number-needed-to-treat to range from a positive limit to a negative limit, indicating that the confidence interval includes zero and thus infinity.

Results

Retrieved trials

We identified 70 reports addressing the issue of opioid-induced pruritus (Fig. 1) [10]. Twenty were
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score (random blinding withdrawals)</th>
<th>Surgical setting</th>
<th>Opioid (PCEA = patient controlled epidural analgesia; i.t. = intrathecal; epid = epidural)</th>
<th>Comparisons</th>
<th>Time of administration</th>
<th>Observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>[35] 2/1/0</td>
<td>Caesarean section</td>
<td>Morphine 4 mg epid</td>
<td>1. Naltrexone 6 mg oral (15) 2. Naltrexone 9 mg oral (15) 3. Placebo oral (15)</td>
<td>5 min after morphine</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>[36] 2/1/0</td>
<td>Caesarean section</td>
<td>Morphine 250 μg i.t.</td>
<td>1. Naltrexone 3 mg oral (10) 2. Naltrexone 6 mg oral (12) 3. Placebo oral (13)</td>
<td>60 min after morphine</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>[33] 2/1/0</td>
<td>Caesarean section</td>
<td>Morphine 250 μg i.t.</td>
<td>1. Propofol 10 mg 1-2 x (17) 2. Intralipid (12)</td>
<td>Treatment of pruritus</td>
<td>6 h</td>
<td></td>
</tr>
<tr>
<td>[37] 1/0/0</td>
<td>Labour</td>
<td>Sufentanil 10 μg kg⁻¹ i.t.</td>
<td>1. Epinephrine 200 μg i.t. (20) 2. No treatment (20)</td>
<td>With intrathecal sufentanil</td>
<td>3 h</td>
<td></td>
</tr>
<tr>
<td>[38] 1/1/0</td>
<td>Caesarean section</td>
<td>Morphine 200 μg + fentanyl 10 μg i.t.</td>
<td>1. Naloxone 48 μg h⁻¹ [0.6 μg kg⁻¹ h⁻¹] i.v. (20) 2. Nalmefene 0.25 μg kg⁻¹ i.v. x 2 (12 h) (20) 3. Nalmefene 0.5 μg kg⁻¹ i.v. x 2 (12 h) (20) 4. Placebo i.v. (20)</td>
<td>At the time of cord clamp and 12 h later (groups 2 and 3)</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>[39] 1/0/0</td>
<td>Caesarean section</td>
<td>Morphine 2 mg x 2 (18–24 h) epid</td>
<td>1. Prednisone 50 mg epidurally x 2 (18–24 h) (37) 2. No treatment (58)</td>
<td>End of surgery</td>
<td>18–24 h</td>
<td></td>
</tr>
<tr>
<td>[40] 2/2/0</td>
<td>Abdominal hysterectomy</td>
<td>Morphone-PCA</td>
<td>1. Naloxone 0.25 μg kg⁻¹ h⁻¹ i.v. (20) 2. Naloxone 1 μg kg⁻¹ h⁻¹ i.v. (20) 3. Saline i.v. (20)</td>
<td>Postanaesthetic Care Unit</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>[41] 1/1/1</td>
<td>Orthopaedic</td>
<td>Morphine 250 μg i.t.</td>
<td>1. Propofol 30 mg h⁻¹ i.v. for up to 20 h (40) 2. Intralipid (41)</td>
<td>End of surgery</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>[42] 1/0/1</td>
<td>Caesarean section</td>
<td>Morphone 2 mg epid</td>
<td>1. Droperidol 2.5 mg i.v. (54) 2. No treatment (53)</td>
<td>After delivery</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>Ref</td>
<td>Date</td>
<td>Procedure</td>
<td>Treatment Details</td>
<td>Time Notes</td>
<td></td>
<td></td>
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<tr>
<td>-----</td>
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<td>--------------------</td>
<td>-----------------------------------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
| [43] | 2/0/0 | Caesarean section | 1. Droperidol 2.5 mg i.v. (35)  
2. Droperidol 5 mg i.v. (35)  
3. No treatment (35)  
4. Droperidol 2.5 mg i.v. (35)  
5. Droperidol 5 mg i.v. (35)  
6. No treatment (35) | After delivery 24 h |
| [44] | 1/1/0 | Caesarean section | Morphine 5 mg epid  
1. Hydroxyzine 50 mg i.m. (20)  
2. Saline i.m. (20) | 10 min after epidural morphine 24 h |
| [45] | 1/1/0 | Any surgery       | Alfentanil 10 μg kg⁻¹ i.v.  
1. Ondansetron 4 mg iv (40)  
2. Saline i.v. (40) | 30 min before alfentanil 5 min |
| [46] | 1/1/0 | Caesarean section | Morphine 5 mg epid  
1. Nalbuphine 20 +10 +10 mg i.v. (28)  
2. Saline i.v. (32) | At skin closure, and at 6 h, and 12 h postoperatively 18 h |
| [47] | 1/2/0 | Hip replacement   | Morphine 4 mg epid  
1. Droperidol 2.5 mg epid (20)  
2. Saline epid (20) | On admission to recovery room 24 h |
| [48] | 1/1/1 | Caesarean section | Hydromorphone PCEA  
1. Nalbuphine 20 μg mL⁻¹ epid (19)  
2. Nalbuphine 40 μg mL⁻¹ epid (16)  
3. Nalbuphine 80 μg mL⁻¹ epid (20)  
4. Saline epid (20) | Postanaesthetic Care Unit 32 h |
| [49] | 2/0/1 | Major gynaecologic | Morphine 250μg i.t.  
1. Epinephrine 200 μg i.t. (25)  
2. No treatment (22)  
3. Saline (no morphine) (23) | With intrathecal morphine 24 h |
| [50] | 1/0/0 | Caesarean section | Morphine 5 mg epid  
1. Droperidol 2.5 mg epid (32)  
2. Droperidol 2.5 mg i.v. (32)  
3. No treatment (33) | With epidural morphine 24 h |
| [51] | 1/1/0 | Caesarean section | Morphine 4 mg epid  
1. Naloxone 400 μg i.v. + 1600 μg 12 h⁻¹ [2.4 μg kg⁻¹ h⁻¹] (15)  
2. Saline i.v. (15)  
3. Morphine i.m. + saline epid (15) | 1 h after epidural morphine 24 h |
| [52] | 1/1/0 | Arthroplasty      | Morphine 300 μg i.t  
1. Propofol 10 mg i.v. + 30 mg 24 h⁻¹ inf (20)  
2. Intralipid (20) | With intrathecal morphine 24 h |
not considered as they were not randomized trials, and six because they were not relevant for the purpose of this study. Of the remaining 44 reports, 22 were subsequently excluded. In 10, the number of patients who were completely free from pruritus after the administration of the study drugs was not reported [11–20]. Five had no placebo or ‘no treatment’ control group [21–25]. Three were not properly controlled [26–28]. In two, group sizes were <10 patients [29,30]. Finally, two were in children [31,32]; these were excluded as all other trials were in adults.

Of the 22 analysed trials, one was on treatment of established pruritus [33], and one on both, prevention and treatment (in two separate randomized designs) [34]. The others were on prevention only [35–54] (Table 1). Data on 1477 patients were analysed. Fourteen trials (1072 patients, 73% of all patients) were in obstetrics (labour or Caesarean section). Average trial size was 67 patients (range, 29–210). Median validity score was 2 (range, 1–4); three scored 4, six 3, nine 2, and four scored 1. In most trials, the observation period was 24 h (minimum 5 min [45], maximum 48 h [50]).

**Underlying risk**

In trials on prevention, analgesia was with epidural morphine in 10 trials [35,39,42–44,46,47,50,51,54], with intrathecal morphine in five [34,36,41,49,52], with intrathecal sufentanil in two [37,53], with a combination of intrathecal morphine and fentanyl in one trial

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**Table 1.** (Continued)

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Quality score (randomization bias; withdrawals)</th>
<th>Surgical setting</th>
<th>Opioid PCEA (oral, intravenous, epidural)</th>
<th>Exemplified regimen</th>
<th>Observation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>[53]</td>
<td>1/0/0</td>
<td>Abdominal hysterectomy</td>
<td>Morphone 200 μg i.t.</td>
<td>1. Propofol 10 mg i.v. (28) Prevention and treatment 8 h</td>
<td></td>
</tr>
<tr>
<td>[54]</td>
<td>2/1/1</td>
<td>Caesarean section</td>
<td>Sufentanil 4 μg i.t. + sufentanil PCEA</td>
<td>1. Ephedrine 2.5 μg mL⁻¹ epid (20) End of surgery 24 h</td>
<td></td>
</tr>
<tr>
<td>[34]</td>
<td>1/2/1</td>
<td>Caesarean section</td>
<td>Morphone 3 mg x 2 (12 h) epid</td>
<td>1. Nalbuphine 60 μg kg⁻¹ h⁻¹ i.v. (20) End of surgery 24 h</td>
<td></td>
</tr>
</tbody>
</table>

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**Fig. 1.** Control of opioid-induced pruritus. Flow chart of retrieved and analysed reports.
with i.v. morphine in one, with i.v. alfentanil in one, and with epidural hydromorphone in one. In placebo and ‘no treatment’ groups, the incidence of pruritus (i.e., the control event rate) was on average 58% with intrathecal morphine, 60% with epidural morphine, and 55% with all other opioids and routes of administration. There was graphically no evidence of a relationship between the dose of morphine and the incidence of pruritus with both intrathecal and epidural routes (Fig. 2). The incidence of pruritus in parturients was similar to those in the other settings.

Treatment of established pruritus

Two trials reported on treatment of established pruritus; both were with low-dose propofol [33,34]. In one [34], parturients received intrathecal morphine 200 μg, and were randomized to prophylactic propofol or Intralipid (control). Twenty-seven control patients developed pruritus, and were further randomized to treatment with propofol 10 mg or Intralipid. Within 8 h, one parturient in each group was completely free of pruritus (not significant). In the other trial [33], patients received 250 μg morphine intrathecally. Those who developed pruritus were treated either with propofol 10 mg once or twice, or Intralipid. The trial was terminated prematurely because the investigators noted that very few patients obtained any relief from their pruritus. Pruritus was relieved in 2 of 17 (11.8%) patients who received propofol compared with 1 of 12 (8.3%) of those receiving Intralipid (not significant). All failures were successfully treated with intravenous naloxone 40–80 μg. Three women receiving propofol felt dizzy compared with one who received Intralipid [33].

Prevention of pruritus

Data on prevention came from 21 trials. Opioid antagonists. There were four trials with i.v. naloxone 48 μg h⁻¹ [38], 0.25 and 1.0 μg kg⁻¹ h⁻¹ [40], 400 μg i.v. plus 1600 μg 12 h⁻¹ [51] and 2 μg kg⁻¹ h⁻¹ [54] (Table 1). To test for dose-responsiveness, we extrapolated fixed doses [38,51] to variable doses (i.e., μg kg⁻¹ h⁻¹) using patients’ average body weight as reported in the original trials. For the resulting dose range, 0.25–2.4 μg kg⁻¹ h⁻¹, there was graphically no evidence of dose-responsiveness (Fig. 3). Combined data suggested that naloxone was efficacious; compared with control, the number-needed-to-treat to prevent pruritus was 3.5 (Table 2a). With naxolene 0.6 μg kg⁻¹ h⁻¹, there was no significant difference in pain intensity compared with control [38]. With 1 μg kg⁻¹ h⁻¹, cumulative morphine consumption was increased compared with 0.25 μg kg⁻¹ h⁻¹, but there was no difference in the verbal pain rating scores [40]. With 2 μg kg⁻¹ h⁻¹, the number of patients requiring...
### Table 2. Prevention of opioid-induced pruritus. Efficacy data

<table>
<thead>
<tr>
<th>Active</th>
<th>Regimen</th>
<th>Incidence of pruritus</th>
<th>Number of patients without pruritus/total number of patients</th>
<th>Relative risk (95% confidence interval)</th>
<th>Number needed to treat</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Active</td>
<td>Control</td>
<td>Active</td>
<td>Control</td>
<td>(95% confidence interval)</td>
</tr>
<tr>
<td>A. mu-receptor antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>0.25 to 2.4 μg kg(^{-1}) h(^{-1}) i.v</td>
<td>46.2%</td>
<td>80.3%</td>
<td>52/97</td>
<td>24/98</td>
<td>2.31 (1.51 to 3.54)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>3 mg oral</td>
<td>70.0%</td>
<td>92.3%</td>
<td>3/10</td>
<td>1/13</td>
<td>3.90 (0.47 to 32.1)</td>
</tr>
<tr>
<td></td>
<td>6 mg oral</td>
<td>25.9%</td>
<td>78.6%</td>
<td>20/27</td>
<td>6/28</td>
<td>3.39 (1.69 to 6.80)</td>
</tr>
<tr>
<td></td>
<td>9 mg oral</td>
<td>6.7%</td>
<td>66.7%</td>
<td>14/15</td>
<td>5/15</td>
<td>2.80 (1.35 to 5.80)</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>0.5 or 1 mg i.v.</td>
<td>92.5%</td>
<td>95.0%</td>
<td>3/40</td>
<td>1/20</td>
<td>1.50 (0.17 to 13.5)</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>40 mg 12 h(^{-1}) or 60 μg kg(^{-1}) h(^{-1}) i.v. or 20-80 μg mL(^{-1}) epid</td>
<td>53.8%</td>
<td>77.3%</td>
<td>49/106</td>
<td>17/75</td>
<td>1.71 (1.12 to 2.62)</td>
</tr>
<tr>
<td>B. D(_2)-receptor antagonist</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Droperidol</td>
<td>2.5 mg i.v.</td>
<td>50.6%</td>
<td>71.2%</td>
<td>77/156</td>
<td>45/156</td>
<td>1.71 (1.28 to 2.29)</td>
</tr>
<tr>
<td></td>
<td>5 mg i.v.</td>
<td>60.0%</td>
<td>70.0%</td>
<td>28/70</td>
<td>21/70</td>
<td>1.33 (0.84 to 2.11)</td>
</tr>
<tr>
<td></td>
<td>2.5 mg epid</td>
<td>50.0%</td>
<td>64.2%</td>
<td>26/52</td>
<td>19/53</td>
<td>1.39 (0.90 to 2.15)</td>
</tr>
<tr>
<td></td>
<td>2.5 or 5 mg i.v or epid</td>
<td>47.1%</td>
<td>30.5%</td>
<td>131/278</td>
<td>75/246</td>
<td>1.58 (1.27 to 1.98)</td>
</tr>
<tr>
<td>C. Intravenous anaesthetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>10 mg or 10 mg + 30 mg 24 h(^{-1}) or 30 mg h(^{-1}) epid</td>
<td>41.6%</td>
<td>47.8%</td>
<td>52/89</td>
<td>47/90</td>
<td>1.12 (0.87 to 1.45)</td>
</tr>
<tr>
<td>D. Catecholamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1:400,000 epid or 200 μg i.t.</td>
<td>56.9%</td>
<td>59.7%</td>
<td>28/65</td>
<td>25/62</td>
<td>1.09 (0.72 to 1.64)</td>
</tr>
<tr>
<td>E. H(_1)-receptor antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>50 mg i.m.</td>
<td>25.0%</td>
<td>10.0%</td>
<td>15/20</td>
<td>18/20</td>
<td>0.83 (0.62 to 1.12)</td>
</tr>
<tr>
<td>F. Alpha(_2)-agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>3 μg mL(^{-1}) epid</td>
<td>25.0%</td>
<td>15.0%</td>
<td>15/20</td>
<td>17/20</td>
<td>0.88 (0.65 to 1.21)</td>
</tr>
<tr>
<td>G. Corticosteroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>50 mg epid</td>
<td>8.1%</td>
<td>13.8%</td>
<td>34/37</td>
<td>50/58</td>
<td>1.07 (0.93 to 1.23)</td>
</tr>
<tr>
<td>H. 5-HT(_3) receptor antagonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>4 mg i.v.</td>
<td>30.0%</td>
<td>42.5%</td>
<td>28/40</td>
<td>23/40</td>
<td>1.22 (0.87 to 1.70)</td>
</tr>
</tbody>
</table>

epid = epidural, i.m. = intramuscular, i.t. = intrathecal, i.v. = intravenous.
rescue analgesia was significantly increased compared with control [54], and with 2.4 $\mu$g kg$^{-1}$ h$^{-1}$, there was less pain relief compared with control [51].

Oral naltrexone 3, 6 and 9 mg was tested in two trials [35,36]. There was evidence of dose-responsiveness (Table 2a). Naltrexone 3 mg was not different from control. The 6 and 9 mg doses, however, were significantly more efficacious than control; numbers-needed-to-treat were below 2. With both 6 mg and 9 mg, the average duration of analgesia was shortened compared with control; with 9 mg, more patients reported unsatisfactory analgesia compared with 6 mg. Intravenous nalmefene 0.25 or 0.5 $\mu$g kg$^{-1}$, tested in one trial [38], was not anti-pruritic (Table 2a).

Five different regimens of i.v. nalbuphine were tested in three trials: 60 $\mu$g kg$^{-1}$ h$^{-1}$ [54], 40 mg [46], and 20, 40 and 80 $\mu$g mL$^{-1}$ epidurally [48]. With this variety of regimens it was impossible to test for dose-responsiveness. Combined data suggested anti-pruritic efficacy with nalbuphine; the number-needed-to-treat to prevent pruritus compared with control was 4.2 (Table 2a). With 40 mg i.v., there was no difference in pain scores compared with control, but one patient who received nalbuphine required oxygen therapy [46]. With 20–80 $\mu$g mL$^{-1}$ epidurally, less patients reported moderate or severe pain compared with control (33% to 47% with nalbuphine vs. 56% with control), but more were drowsy (23% to 39% with nalbuphine vs. 15% with control) [48].

When all trials on opioid antagonists which reported emesis data were combined, the anti-nausea effect was significant [average incidence of nausea with all opioid antagonists 44.4% vs. 54.4% with control, relative risk 1.30 (1.03 to 1.63)]. There was no effect on vomiting [34.7% with opioid antagonists vs. 37.7% with control, relative risk 1.07 (0.89–1.29)].

**Dropenidol** Intravenous droperidol 2.5 or 5 mg was tested in three trials [42,43,50], and epidural droperidol 2.5 mg in two [47,50]. Intravenous droperidol 2.5 mg was efficacious, whereas both i.v. 5 mg and epidural 2.5 mg were not significantly different from control (Table 2b). When all droperidol data were combined, the number-needed-to-treat to prevent pruritus compared with control was 6. Droperidol significantly prevented nausea and vomiting [15% with droperidol vs. 24.8% with control, relative risk 1.15 (1.25 to 10.3)], but induced somnolence [11.9% vs. 2.6%, relative risk 4.57 (1.77 to 10.8)].

**Other interventions** Three different low-dose propofol regimens were tested in three trials (Table 1c). With 30 mg h$^{-1}$ [41], there was more pruritus compared with Intralipid; 10 mg [34] was no different from Intralipid; and with 10 mg bolus plus 30 mg 24-h$^{-1}$ [52], there was significantly less pruritus compared with Intralipid. To test for dose-responsiveness was not possible. When all data were pooled, there was no significant difference in anti-pruritic efficacy with propofol compared with Intralipid; the number-needed-to-treat to prevent pruritus was 16. With the 30 mg h$^{-1}$ infusion, one of 40 patients receiving propofol needed naloxone for respiratory depression, and eight of 40 needed dose reduction due to oversedation [41].

Intrathecal or epidural epinephrine, tested in two trials [37,49], had no significant effect on pruritus (Table 2d). Epidural clonidine 3 $\mu$g mL$^{-1}$ [53], intramuscular hydroxyzine 50 mg [44] and epidural prednisone 50 mg [39] were tested in one trial each; none was significantly different from control (Table 2e–g). Prophylactic i.v. ondansetron 4 mg [45], was also tested in only one valid trial (Table 2h). During the administration of i.v. alfentanil, there was significantly less ‘perinasal scratching’ [42.5% with ondansetron vs. 70% with saline (0.9% NaCl)]. However, 5 min after the administration of i.v. alfentanil, when patients were asked about the presence of itching, there was no significant difference (30% vs. 42.5%).

**Discussion**

We retrieved 70 reports addressing the issue of the pharmacological control of opioid-induced pruritus. This suggests that many investigators perceive pruritus as an important issue that is worthwhile studying. However, there were several problems with these reports. Numerous potentially relevant randomized trials had to be excluded as they were invalid for the purpose of this analysis. Many trialists reported on self-invented and non-validated measurements of anti-pruritic efficacy. The decrease of 4 points on a 10-point visual analogue pruritus scale may indeed suggest efficacy. However, such an end-point is likely to be chosen arbitrarily, or post hoc. These data cannot be put into a wider context; they cannot be compared or combined with data from other trials. Our dichotomous hurdle of complete absence of pruritus after
the application of the study drugs may be unnecessar-
ily high. An active intervention which does not com-
pletely prevent pruritus may alleviate symptoms to a
great extent. Such an intervention may be, of course,
useful. However, in order to extract homogeneous
data and to minimize the risk of observational bias
due to different definitions of end-points, we decided
to concentrate on complete absence of pruritus. Data
from 11 randomized trials could thus not be used for
the purpose of this analysis. The quality of the ana-
lysed trials, according to the validated Oxford scale
[54] was often unsatisfactory. More than half scored 1
or 2, and none scored 5. Poor quality trials are likely to
report biased estimates of efficacy [55]. This effect
cannot be ruled out here, although it was impossible
to test this hypothesis because of the large variety of
different drugs and regimens tested. There was also
the problem of active controlled trials without a pla-
cebo or ‘no treatment’ control. It has been shown
in other settings that head-to-head comparisons
are unlikely to further our understanding on the effi-
cacy of interventions unless there is a gold standard
treatment against which all other active treatments
may be compared [56]. This also applies to anti-pruritic
drugs.

The message that can be derived from this large
body of data is of limited value only to clinical practice.
Most trials were on prevention of pruritus. It may be
interesting from a pharmacological point of view to
know that very different molecules (for instance,
antagonists of the mu or the dopamine receptors)
may possess some anti-pruritic properties. The clinical
relevance of this, however, is doubtful. It is unlikely
that anaesthetists will change practice based on these
data, and give, for instance, prophylactic droperidol or
naloxone to their patients in an attempt to prevent
pruritus. Only a very limited number of valid data on
the treatment of established pruritus could be found.
Thus, we still do not know what treatment a patient
should receive who is complaining about opioid-
related pruritus.

What then is the clinical message? Antagonists of
the mu receptor are effective anti-pruritic drugs. Intra-
venous naloxone was most frequently tested. Of four
patients receiving prophylactic naloxone, one will not
have pruritus who would have had pruritus had they
all received a placebo or no treatment. The failure to
show dose-responsiveness most likely indicated that
the doses tested in these trials were too high. Pain
outcomes suggested that the dose of naloxone
should probably not exceed 2 μg·kg⁻¹·h⁻¹. Naltrexone
did show dose-responsiveness; the lowest dose
tested, 3mg orally, did not work, and higher doses,
6mg and 9mg, showed significant anti-pruritic effi-
cacy. Nine milligrams seemed to be too high a dose,
as pain scores were increased. Nalbuphine, an ago-
nist/antagonist at the mu-receptor, was also effica-
cious, although the variety of regimens tested
makes it difficult to provide clear treatment recom-
endations. There was some evidence for less
pain intensity but increased drowsiness with nalbu-
phine. Nalmefene, a pure opioid antagonist, tested
in one trial with 40 treated patients only, did not
show any efficacy. Finally, opioid-related nausea
(but not vomiting) was decreased with mu-receptor
antagonists. An alternative for prophylaxis may be i.v.
(but not epidural) droperidol. The optimal dose
remains unknown (the dose-response with 2.5 and
5mg i.v. was inverse), and there is less efficacy too
compared with the mu antagonists (number-needed-
to-treat about 6). Again not unexpectedly, patients
are less likely to suffer from nausea or vomiting,
but, with these relatively high doses tested, they
are more likely to be somnolent [57]. None of the
other tested drugs, epinephrine, propofol, clonidine,
hydroxyzine or prednisone, showed any worthwhile
benefit. This may be partly due to the limited num-
ber of tested patients. Ondansetron showed some
efficacy on perinasal scratching but not on pruritus
(itching). If the absolute risk difference of pruritus was
about right (i.e. 30% with ondansetron vs. 42.5% with
placebo), then the hypothetical number-needed-to-
treat to prevent pruritus with prophylactic ondans-
estron compared with placebo was about 8 (i.e. the
reciprocal of 12.5%). The clinical relevance of this
result is not obvious, and the fact the authors termi-
nated the study 5 min after the administration of alfentanil
does not make it easier to put the result into a
clinical context.

A further message relates to the risk of pruritus with
opioids. In placebo and ‘no treatment’, controlled
randomized trials, we may assume that there is some
relationship between the control event rate (i.e. the
incidence of pruritus in patients receiving a placebo or
‘no treatment’) and the true underlying risk for prur-
itus. In these trials, on average 60% of patients

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receiving an opioid without an anti-pruritic drug had some pruritus. Thus, we may assume that these trials represent a high-risk population for opioid-induced pruritus. With epidural and intrathecal morphine, there was no evidence that the dose, in the range of doses tested in these trials, made any difference. Other opioids represented the same range of risk although the data were limited (Fig. 2). Knowing that pruritus due to opioid analgesia happens frequently, independent on the opioid used, the route of administration, and the dose, begs the question as to whether this adverse effect is clinically important. Pruritus never becomes chronic and it does not kill. An expert panel of anaesthesiologists ranked opioid-induced pruritus almost last in a hierarchy of the clinical relevance of different anaesthesia outcomes [58]. Even postoperative nausea, pain, or shivering ranked much higher. We do not know how patients themselves would rank the importance of pruritus.

Research agenda

A large variety of different drugs have been tested in these trials. Often, it was unclear if the trials were designed to provide a new and clinically useful treatment against pruritus, or if the authors primary interest was to study the origin of opioid-induced pruritus. As with other systematically searched trials, there was not much evidence for any scientific basis for most of these studies [59]. This systematic review reveals more what we do not know than what we know about the control of opioid-induced pruritus. Almost 1500 patients have been randomized in the 22 analysed trials, and hundreds in the trials which had to be excluded from our analyses. Many questions, however, remain unanswered. More data are needed on the treatment of established pruritus, on the efficacy of these drugs in children, on dose-responsiveness, and on optimal doses (i.e. minimal effective doses with an acceptable risk of adverse effects). Valid trials are needed, properly randomized, and double-blind, with a reasonable number of patients, and an adequate length of follow-up (ideally, 24 h). End-points should be standardized, and should include the number of patients who are completely free of pruritus after administration of the study drugs. In the absence of a gold-standard treatment, trials should be placebo controlled.

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