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Pathophysiology and Management of Opioid-Induced Pruritus

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Abstract

Pruritus occurs frequently following opioid use, particularly after neuraxial administration. Although not life threatening, pruritus is discomforting and may decrease patient satisfaction. Even though the mechanism of opioid-induced pruritus is not yet fully understood, there is increasing evidence of the important role played by μ opioid receptors. Animal experiments pointing to the role of the μ opioid receptor and the efficacy of μ opioid receptor antagonists for opioid adverse effect prophylaxis and treatment have been replicated in several studies. Serotonin and dopamine D_2 receptors, prostaglandins and spinal inhibitory pathways may also be involved in the genesis of pruritus.

Several pharmacological agents have been used both for the treatment of established pruritus and in its prevention. Of these, μ opioid receptor antagonists have been most consistent in terms of attenuating opioid-induced pruritus but present problems in dose and administration. Other drugs, including mixed opioid

receptor agonist-antagonists, serotonin 5-HT_3 receptor antagonists, propofol, NSAIDs and D_2 receptor antagonists, have also been demonstrated to be useful.

This review summarises the current understanding of the mechanisms causing opioid-induced pruritus and the pharmacological therapies available to prevent and/or manage this disorder.

Opioids are universally used in the management of moderate to severe pain. However, the adverse effects associated with opioid use may be distressing to patients and result in increased length of hospital stay, treatment costs and use of personnel resources. Pruritus is one of the common adverse events noted after opioid use, particularly when opioids are administered into the intrathecal or epidural space.[1-4] The incidence of pruritus is reported to be 10–50% following intravenous administration of opioids[5,6] and 20–100% following neuraxial administration.[1,7-9]

This article reviews the current understanding of the pathophysiology of opioid-induced pruritus (OIP), and the available literature on options for medical management and prophylaxis. The literature source for this review was obtained via a PubMed search for reports (1970–2006) evaluating the cause and/or treatment of OIP. Keywords used in the search included 'pruritus', 'opioids', 'postoperative', 'analgesia', 'itching', 'treatment', 'pathophysiology', 'mechanisms' and the different combinations. The reference lists of retrieved reports were also checked.

1. Pathophysiology

Itch is an unpleasant sensation that elicits the desire or reflex to scratch.[10] Itch, like all other cutaneous sensations, is thought to be an extracutaneous event related to CNS activities.[11] The itch felt is a neuronal projection of a centrally formed sensation into defined regions causing localised pruritus or into large areas of the body surface causing generalised pruritus. The afferents for mediating the itch sensation are probably a group of C-fibres with thin axons and excessive terminal branching.[12]

The mechanism of OIP remains unclear.[4,13,14] Experiments in animals[15-17] and the clinical response to μ opioid receptor antagonists in humans[5,18-23] suggest a central μ opioid receptor-mediated mechanism as the primary cause for OIP. It has also been shown[16] that activation of κ and δ opioid receptors does not cause pruritus. As shown in table I, more than one mechanism may be involved in the development of OIP.[4] These mechanisms are discussed in sections 1.1–1.6.

1.1 μ Opioid Receptor

There is now increasing evidence that OIP is primarily mediated through central μ opioid receptors. Ko et al.[16] have very nicely used pharmacological methods in a primate model to identify receptors that are primarily involved in causing pruritus. They administered μ opioid receptor agonists, namely, fentanyl, alfentanil and remifentanil, intravenously in monkeys. The resulting pruritus (scratching) was effectively reversed with a peripherally administered μ opioid receptor antagonist (naltrexone), but not significantly blocked by a peripherally-administered, quaternary form of naltrexone (this form does not effectively cross the blood-brain barrier). These investigators also administered morphine intravenously and intrathecally to induce pruritus in the second part of their study. The pruritus induced by morphine was significantly amelio-

Table I. Possible pathophysiological mechanisms contributing to opioid-induced pruritus

μ Opioid receptors
brain
spinal cord
Dopamine D_2 receptors
Serotonin 5-HT_3 receptors
Prostaglandin system
Other
GABA receptors
Glycine receptors

rated by naltrexone, but not by its quaternary form or by diphenhydramine. Furthermore, these investigators suggested that, with use of this approach, scratching in monkeys can be used to identify specific receptors involved in pruritus and facilitate development of drugs targeting those receptors. Thomas et al.[24] reached similar conclusions from their experiments that also demonstrated that the medullary dorsal horn is a site where morphine acts on μ opioid receptors to cause itching.

In a mouse model, Kuraishi et al.[17] demonstrated that intracisternal and intrathecal injections, but not intradermal injections, of morphine and other opioids increased scratching of the face and trunk. This finding supported the conclusion that opioids induce scratching through central μ opioid receptors in the mouse. Scott and Fischer[8] suggested that a preponderance of opioid receptors in the spinal nucleus of the trigeminal nerve could explain the high incidence of itching in the distribution of the trigeminal nerve, particularly the ophthalmic division.

In a review, Szarvas et al.[4] suggested that neuraxially administered fentanyl, unlike morphine, may not cause pruritus through μ opioid receptors in the brain. They reviewed articles by Chaney[25] and Asokumar et al.,[26] which suggested that the rapidity with which the lipophilic fentanyl is absorbed into the spinal cord and causes pruritus precludes any involvement of μ opioid receptors in the brain. Thus, an effect on the spinal cord as proposed by Ballantyne et al.[27] may also be involved in the aetiology of pruritus.

1.2 Dopamine D_2 Receptors

Studies by Horta et al.[7,28] and Horta and Vianna[29] demonstrating the efficacy of D_2 receptor antagonists, such as droperidol and alizapride, in reducing morphine-induced pruritus suggested that central D_2 receptors may also contribute to OIP or interact with μ opioid receptors to cause pruritus.

1.3 Serotonin 5-HT_3 Receptors

There is a dense concentration of serotonin receptors in areas of high μ opioid receptor density such as the trigeminal nerve nucleus and the dorsal part of the spinal cord.[30] This suggests the involvement of serotonin 5-HT_3 receptors in the development of pruritus.[4] Also, several trials have shown that a 5-HT_3 receptor antagonist, such as ondansetron, decreases the incidence and severity of pruritus.[9,19,30-32]

1.4 Prostaglandins

Release of prostaglandin (PG)E_1 and PGE_2 have also been associated with OIP.[4] Tenoxicam and diclofenac have been shown to have anti-pruritic effects in patients receiving neuraxial opioids.[33,34] However, Lee et al.[35] found no reduction of pruritus with use of celecoxib following intrathecal morphine administration. Also, Romsing et al.[36] and Marret et al.[37] concluded that cyclo-oxygenase-2 inhibitors did not provide any significant reduction in opioid-related adverse effects.

1.5 Histamine Release

The role of histamine release in the pathogenesis of OIP is very minimal. Systemically administered opioids, particularly morphine, may lead to histamine release from mast cells, which may play a very small role in causing pruritus. The manifestation of histamine release with intravenous morphine may be seen as a wheal formation in the same extremity containing the intravenous cannula through which the morphine is administered. Hermens et al.[38] used *in vitro* techniques to demonstrate that morphine-induced histamine release does not involve opioid receptors. Histamine release does not occur following administration of neuraxial opioids and is therefore unlikely to be a component of neuraxial OIP.[16,39,40]

1.6 Other Mechanisms

Antagonism of GABA and glycine receptors in the CNS has also been suggested as a possible mechanism of OIP.[41] Itching was seen in cats when intrathecal strychnine, a glycine receptor antagonist, was administered, suggesting that antagonism of glycine receptors may be one of the mechanisms of OIP.[4] Yaksh et al.[42] also suggested that non-

opioid receptors may be involved in the development of pruritus.

2. Management

A wide variety of drugs with different mechanisms of action have been used to prevent or treat established OIP.[13] Kjellberg and Tramer[13] have questioned the significance of pruritus and quoted a study in which an expert panel of anaesthesiologists ranked OIP very low in a hierarchy of adverse anaesthesia outcomes ranked according to clinical relevance.[43] However, one should note that drugs effective against pruritus may also decrease the incidence of nausea and vomiting. One should also study patients' views of the distress caused by OIP, especially when interventions resulting in a high incidence of pruritus are undertaken.

2.1 Treatment of Established Opioid-Induced Pruritus

Compared with studies evaluating the role of drugs for prevention of OIP, there are very few studies (table II) that have evaluated treatment of established OIP.

A sub-hypnotic dose of propofol (10mg) was evaluated in adult subjects undergoing gynaecological, orthopaedic, thoracic or gastrointestinal surgery for the treatment of pruritus induced by intrathecal morphine in a prospective, randomised, double-blind, placebo-controlled study.[44] The propofol group had a significantly higher success rate compared with placebo (84% vs 16%, respectively; $p < 0.05$). In another study, Naganuma et al.,[45] investigated the role of propofol 10–20mg in 20 patients who underwent obstetric and gynaecological surgery, and received intrathecal morphine. Propofol was effective in six of seven subjects who developed pruritus. They concluded that low-dose propofol is effective in intrathecal morphine-induced pruritus, although it may transiently cause hypnosis in post-operative patients. However, other studies[47,48] did not show any improvement in pruritus with the use of sub-hypnotic doses of propofol. These studies were conducted in patients undergoing caesarean section, and Szarvas et al.[4] in their review suggested that the lack of efficacy of propofol in treating pruritus in this group of patients could be due to other mechanisms operating in the peripartum period.

Table II. Summary of trials and reports evaluating the treatment of established opioid-induced pruritus

Drug	Effective	Ineffective
Propofol	Borgeat et al.[44] Naganuma et al.[45] Charuluxananan et al.[46]	Beilin et al.[47] Warwick et al.[48]
Nalbuphine	Charuluxananan et al.[46] Somrat et al.[49] Cohen et al.[50] Alhashemi et al.[51] Henderson and Cohen[52] Penning et al.[53]	Nakatsuka et al.[54]
Ondansetron	Borgeat and Stirnemann[30] Charuluxananan et al.[31] Arai et al.[55] Henry et al.[56] Larijani et al.[57]	
Rifampicin	Mercadante et al.[58]	

In a prospective double-blind study,[46] propofol 20mg was compared with nalbuphine 3mg in the treatment of pruritus induced by intrathecal morphine following caesarean delivery. Treatment was significantly more successful in the nalbuphine group than in the propofol group (83% vs 61%, respectively; $p < 0.001$). There was no significant difference in other adverse effects between groups. In another prospective randomised study,[49] different doses of intravenous nalbuphine (2, 3 or 4mg) were evaluated in the treatment of intrathecal morphine-induced pruritus following caesarean section. Successful treatment with nalbuphine 2, 3 and 4mg was observed in 86.7, 96.7 and 100%, respectively, of patients ($p = 0.12$). Adverse effects were similar in all groups, except that the 4mg group had significantly higher pain scores compared with the other groups. In another double-blind study, Cohen et al.[50] compared nalbuphine 5mg with naloxone 0.2mg for the treatment of adverse effects due to epidural morphine administered for post-caesarean section analgesia. In that study, pruritus was significantly better controlled by nalbuphine than by naloxone, perhaps because of the very short half-life

of naloxone. Other studies[51-53] have also demonstrated the usefulness of nalbuphine in treating OIP.

In a paediatric study, Nakatsuka et al.[54] evaluated the effectiveness of intravenous nalbuphine 50 μg/kg (maximum 5 mg/dose) for the treatment of pruritus in children >7 years of age who received intravenous morphine patient-controlled analgesia (PCA), continuous intravenous infusion of morphine or epidural morphine for postoperative analgesia. These investigators used a pruritus score based on a colour analogue scale modified from one used for self evaluation of pain that had not been validated for pruritis.[59] They treated children with a pruritus score of ≥5 out of 10 and considered a reduction of 50% in the pruritus score as significant. The study was placebo (saline)-controlled and randomised. The investigators concluded that nalbuphine 50 μg/kg/dose was ineffective in the management of postoperative OIP in children.

Ondansetron has also been found to be useful in the management of OIP. In a prospective, randomised, double-blind, placebo-controlled trial, Borgeat and Stirnemann[30] found ondansetron 8mg to be effective in the management of OIP in patients who received intrathecal morphine for postoperative analgesia for orthopaedic procedures. In another placebo-controlled randomised trial of patients who received intrathecal morphine for post-caesarean section analgesia, Charuluxananan et al.[31] concluded that ondansetron 4mg relieved intrathecal morphine-induced pruritus after caesarean delivery, particularly in patients with both nausea/vomiting in addition to pruritus. Other studies and case reports[55-57] have also shown the effectiveness of ondansetron in managing OIP.

A case report has also described the successful use of rifampicin in the management of morphine-induced pruritus in the setting of palliative care.[58] Rifampicin was first found to be effective for the relief of pruritus due to cholestasis; its mechanism of action in that setting is thought to be related to inhibition of bile acid uptake by hepatocytes.[60]

2.2 Prevention of Opioid-Induced Pruritus

Several classes of drugs (see table III) have been evaluated for the prevention of OIP.

2.2.1 μ Opioid Receptor Antagonists

Several studies have evaluated the effectiveness of naloxone, nalmefene and naltrexone in the prevention of morphine-induced pruritus. In a detailed review, Kjellberg and Tramer[13] concluded that ant-

Table III. Summary of trials and reports evaluating the prevention of opioid-induced pruritus

Drug	Effective	Ineffective
Naloxone	Gan et al.[5] Cepeda et al.[18] Maxwell et al.[22] Wang et al.[61] Okutomi et al.[23]	Cepeda et al.[62] Sartain et al.[63]
Nalmefene	Joshi et al.[64]	Connelly et al.[65] Pellegrini et al.[66]
Naltrexone	Abboud et al.[2]	
Nalbuphine	Charuluxananan et al.[19] Wang et al.[61] Ben-David et al.[67] Kendrick et al.[68]	Morgan et al.[69]
Butorphanol	Gunter et al.[20] Bailey et al.[70] Lawhorn and Brown[71] Lawhorn et al.[72] Abboud et al.[73]	
Ondansetron	Yeh et al.[9] Charuluxananan et al.[19] Iatrou et al.[32] Gurkan and Toker[74] Pirat et al.[75] Tzeng et al.[76]	Korhonen et al.[77] Sarvela et al.[78] Wells et al.[79] Yazigi et al.[80]
Dopamine D_2 receptor agonists (droperidol and alizapride)	Horta et al.[7] Horta et al.[28] Horta and Vianna[29] Horta et al.[81]	
Propofol	Horta et al.[28] Torn et al.[82] Saiah et al.[83] Kostopanagiotou et al.[84]	Warwick et al.[48]
Histamine H_1 receptor antagonists (antihistamines)	Juneja et al.[85]	Horta et al.[28]
NSAIDs	Colbert et al.[33] Colbert et al.[34]	
Prednisone	Etchin et al.[86]	

agonists of the μ opioid receptor are effective antipruritic drugs. They determined that prophylactic naloxone infusion decreases the incidence of OIP by 25%. They also concluded that the naloxone dose should not exceed 2 μg/kg/h as higher doses could result in reversal of analgesia. Naloxone administered by continuous intravenous infusion at doses of 0.25–2 μg/kg/h has been found to decrease the incidence of OIP in other studies.[5,22,61] Two of these studies[5,22] evaluated the use of naloxone at a rate of 0.25 μg/kg/h in patients who received morphine intravenously via PCA. Both studies found that naloxone significantly decreased the incidence of morphine-induced adverse effects, including pruritus, without affecting analgesia. In addition, the study by Gan et al.[5] demonstrated an opioid-sparing effect in adult patients. Maxwell et al.[22] studied children and recommended consideration of use of a concomitant low-dose naloxone infusion when initiating intravenous morphine via PCA. In the third study,[61] Wang et al. used a higher dose naloxone infusion (2 μg/kg/h) and compared this with a nalbuphine infusion of 60 μg/kg/h in patients who received epidural morphine following abdominal hysterectomy. These investigators found that both infusions decreased the incidence of opioid-related adverse effects but, unlike naloxone, nalbuphine did not attenuate the analgesic effect of epidural morphine. Okutomi et al.[23] tested the addition of naloxone to a bupivacaine/fentanyl infusion for combined spinal-epidural labour analgesia in a double-blind randomised trial. They reported a significantly decreased incidence of pruritus in the naloxone group with no significant effects on the fetus.

Nalmefene was found to decrease the need for anti-emetic and anti-pruritic medications in a prospective, randomised, placebo-controlled trial of a group of adult patients undergoing lower abdominal surgery who received intravenous morphine for postoperative analgesia.[64] The nalmefene doses used in this study were 15μg and 25μg. There was no difference in analgesia between the nalmefene and the saline group. The need to treat adverse effects was similar in the two nalmefene groups. Oral naltrexone at doses of 6mg or 9mg was also found to be more effective than placebo following intrathecal morphine administration.[2]

However, some studies have shown μ opioid receptor antagonists to be ineffective in managing OIP. In a double-blind placebo-controlled study, Connelly et al.[65] evaluated the role of naloxone infusion (48 μg/h) and nalmefene (0.5 μg/kg; two doses, 12 hours apart) in patients who received intrathecal morphine for post-caesarean section analgesia. They found no significant difference between groups with respect to occurrence of or need for treatment of pruritus. In another study, Pellegrini et al.[66] did not find a reduction in the incidence of pruritus with prophylactically administered intravenous nalmefene 0.25 μg/kg/dose following use of intrathecal morphine for post-caesarean section analgesia. In addition, patients receiving nalmefene required supplemental analgesia at a significantly earlier time than those receiving placebo.

It has been suggested that the lack of benefit seen in studies in which a mixture of morphine and naloxone was administered via a PCA pump[62,63] could have been due to (i) the fact that naloxone was administered only intermittently in small doses and did not persist at the receptor because of its extremely short half-life; or (ii) the possibility that the naloxone/morphine combination might not have been compatible in solution together over a prolonged time period.[22]

2.2.2 Mixed Opioid Receptor Agonist-Antagonists

Nalbuphine, both as a bolus and an infusion, has been found to be useful in decreasing the incidence of opioid-induced pruritus when administered prophylactically.[19,61,67,68] Charuluxananan et al.,[19] in a prospective, randomised, double-blind study, compared nalbuphine 4mg with ondansetron (4mg or 8mg) and saline placebo. Nalbuphine and ondansetron were more effective than placebo in preventing pruritus. Also, there was no difference in analgesia or sedation scores between the groups. However, Morgan et al.[69] found no benefit for nalbuphine prophylaxis in obstetric patients.

Butorphanol, administered epidurally by continuous infusion in combination with bupivacaine and morphine, was found to be associated with less

pruritus than that seen with epidural bupivacaine and morphine alone in a randomised study of children.[20] Other studies[70-73] have also shown a decreased incidence of pruritus when butorphanol was administered with morphine epidurally. In one of these studies,[73] when epidural butorphanol was compared with epidural morphine in patients undergoing caesarean section, a lower incidence of pruritus was observed in the butorphanol group. One of the potential adverse effects of drugs in this class is an increase in sedation, with butorphanol being more sedating than nalbuphine. Sedation is thought to be a κ opioid receptor effect and butorphanol is a more potent κ opioid receptor agonist.[87] There is experimental evidence suggesting that activation of κ opioid receptors attenuated morphine-induced itching without interfering with nociception in monkeys.[88]

2.2.3 Serotonin 5-HT_3 Receptor Antagonists

Studies have demonstrated that ondansetron prophylaxis decreases the incidence of OIP.[9,19,32,74-76] In a randomised placebo-controlled study, Pirat et al.[75] evaluated the efficacy of prophylactic ondansetron (ondansetron 4mg intravenously or 8mg orally-disintegrating tablets) in young male patients who received intrathecal morphine. They found a significantly decreased incidence of OIP with ondansetron administered both by the oral and intravenous routes compared with placebo. However, other studies have found ondansetron to be ineffective.[77-80] In one of these studies,[80] ondansetron decreased the incidence of nausea and vomiting but not of pruritus following intrathecal sufentanil administration.

2.2.4 Dopamine D_2 Receptor Agonists

D_2 receptor agonists have been found to provide effective prophylaxis against OIP. Horta et al.[81] and Horta and Vianna[29] have demonstrated the effectiveness of pre-emptively administered intravenous droperidol and alizapride, respectively, for reducing the incidence and severity of pruritus following neuraxial opioid administration. In another randomised study, Horta et al.[28] compared the effectiveness of prophylactic droperidol 1.25mg, propofol 20mg, alizapride 100mg and promethazine 50mg with that of a saline control. These drugs were administered immediately following caesarean section delivery. The investigators concluded that droperidol, propofol and alizapride, in decreasing order of effectiveness, reduced the incidence and severity of pruritus caused by intrathecal morphine. Horta et al.[7] have also demonstrated the effectiveness of epidurally administered droperidol for preventing pruritus evoked by epidural morphine administration.

2.2.5 Propofol

Prophylactic intravenous propofol has been shown to decrease the incidence of pruritus following intrathecal[28,82,83] and epidural[84] administration of morphine. Torn et al.[82] administered propofol as an infusion (30 mg/24h) following a 10mg bolus, while Horta et al.[28] administered only a single dose of propofol 20mg. In these two studies, only sub-hypnotic doses of propofol were used. Conversely, Kostopanagiotou et al.[84] used propofol intraoperatively only as an anaesthetic. The mechanism by which propofol may reduce OIP probably involves decreased posterior horn transmission in the spinal cord.[82] However, some investigators have found propofol (sub-hypnotic dose) to be ineffective at preventing OIP.[48]

2.2.6 Histamine H_1 Receptor Antagonists (Antihistamines)

Juneja et al.[85] evaluated hydroxyzine 50mg administered intramuscularly following administration of epidural morphine in a placebo-controlled trial and concluded that hydroxyzine was effective at attenuating the incidence of severe OIP. However, Horta et al.[28] found promethazine 50mg to be ineffective at preventing OIP. Although histamine H_1 receptor antagonists (antihistamines) may occasionally help treat OIP, this action is probably not dependent on the inhibition of histamine receptors. The sedative properties of antihistamines may be helpful by providing much needed sleep by interrupting the itch-scratch cycle without relieving the itch sensation.[4]

2.2.7 Other Drugs

Prednisone administered epidurally[86] and NSAIDs, such as intravenous tenoxicam[33] and rectal diclofenac,[34] have shown some efficacy in the prevention of pruritus induced by neuraxially administered opioids.

3. Conclusion

Pruritus is a recognised complication of opioid use and is more common when opioids are administered neuraxially. It is particularly common when opioids are administered intrathecally in the peripartum period. Most studies of prevention of OIP and its treatment in established cases have therefore been conducted in the obstetric population. As pointed out by Szarvas et al.,[4] the varied efficacy of anti-pruritic agents in this population could be a result of the contribution of hormonal changes to the pathogenesis of pruritus.

OIP is usually self-limiting and not life threatening.[13] Current evidence is still insufficient to clearly mandate prophylactic administration of drugs to prevent OIP. However, in situations associated with high risk of pruritus and in patients who have had a bad experience of pruritus in the past, a role for prophylactic treatment probably exists. There is also increasing evidence to suggest that drugs that decrease the incidence of OIP may also decrease the incidence of other opioid-induced adverse effects, such as nausea and vomiting, and may thus significantly improve the postoperative satisfaction of patients.

Although several mechanisms may be involved in the pathogenesis of OIP, there is compelling evidence to suggest that the μ opioid receptor mechanism is the dominant pathway for OIP. This has been fairly well documented in animal experiments and also in clinical trials, which are now demonstrating efficacy of μ opioid receptor antagonists in doses that do not reduce analgesia. There may also be a role for other classes of drugs such as 5-HT_3 receptor antagonists, D_2 receptor antagonists and propofol. Basic science research has also demonstrated the effect of κ opioid receptor agonists in relieving pruritus. This may lead to development of drugs that may be used in humans.

There is increasing evidence for the efficacy of opioid receptor antagonists for OIP prophylaxis. A continuous infusion of naloxone at doses of 0.25–1 μg/kg/h run 'piggy-backed' with maintenance intravenous infusion is recommended.[5,22] However, this treatment requires the use of an infusion pump and the upper threshold at which such an infusion may begin to antagonise analgesia is unknown. Mixed opioid receptor agonist-antagonists and 5-HT_3 receptor antagonists are other useful options. More clinical studies evaluating the dose-responsiveness of drugs with standardised endpoints as suggested by Kjellberg and Tramer[13] are required. Data analysis should also include potential cost-savings from pruritus prevention. Further studies also need to be conducted in the paediatric population to facilitate the development of appropriate dosing guidelines in younger patients.

Treatment of established pruritus is clearly a problem requiring further study. There is a paucity of studies in the management of established OIP and further placebo-controlled studies are necessary to offer better recommendations. Mixed opioid receptor agonist-antagonists appear to be the most commonly used drugs for treating established pruritus. There is also a need for additional research to study the impact of pruritus on the postoperative experience and satisfaction of patients.

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