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Evaluation of Therapies for Peripheral and Neuraxial Opioid-induced Pruritus based on Molecular and Cellular Discoveries

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ABSTRACT

Opioids are a mainstay of treatment for pain worldwide. Pruritus, a common side effect of opioids, is a patient dissatisfier that limits their use in many clinical settings. Both parenteral and neuraxial administration of opioids frequently evoke pruritus. The ability of opioids to suppress pain while causing itch continues to perplex clinicians and researchers alike. Several mechanisms have been proposed to explain how opioids can give rise to pruritus, but specific knowledge gaps perpetuate debate. This review summarizes the clinical burden of opioid-induced pruritus and emphasizes recent discoveries of peripheral and central mechanisms for opioid-induced pruritus, particularly with respect to scientific and conceptual advances in spinal cord circuitry and mast cell biology. The mechanisms and effectiveness of existing medications used for clinical management of pruritus will be evaluated, and we will highlight the emerging preclinical utility of selective κ-opioid receptor agonists, such as nalfurafine, for the management of opioid-induced pruritus.

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Opioids have been used to control pain for millennia. Today, they are used for numerous types of pain, including acute, chronic, preoperative, perioperative, and postoperative, and cancer pain.[1] One route of opioid administration that is frequently used is the neuraxial (epidural and intrathecal) route of administration. Neuraxial opioids are frequently administered for abdominal and lower extremity surgeries.[2–6] Although neuraxial analgesia is associated with improved postoperative outcomes such decreased length of hospital stay[7–9] and extended dosing for acute pain control,[3,5,9] it is also associated with many side effects, particularly pruritus.[10–13] Oral and parenteral opioid analgesia are other routes used in ambulatory and inpatient settings whenever neuraxial administration is not possible. In contrast to the neuraxial route of opioid administration, the oral and parenteral routes are less frequently associated with pruritus.[14,15]

The purpose of this review is to assess the incidence of opioid-induced pruritus among different routes of opioid medication and to summarize the most recent advances in treatments. New treatments stem from new knowledge in the mechanistic underpinnings of opioid-induced pruritus due to novel insights in spinal cord circuitry and mast cell biology. Based on these mechanisms, we weigh the appropriateness of existing therapies for opioid-induced pruritus.

Epidemiology and Burden of Opioid-induced Pruritus

Although neuraxial opioids are frequently used in acute perioperative pain, they also have side effects. These side effects include pruritus,[10–13] nausea (25%), sedation (17%), urinary retention (19%), and, very rarely, respiratory depression (3%).[9,16,17] Although pruritus is occasionally observed with parenteral opioid use,[18,19] it is an extremely common side effect of neuraxial opioids, with an incidence ranging from 30 to 85%, depending on the dose and lipophilicity of the opioid administered.[12,20,21] Dose-response relationships between spinal morphine, analgesic duration, and pruritus have indicated that escalating doses of morphine improve analgesia but are correlated with higher incidences and severity of pruritus.[22,23] This relationship suggests that the duration of analgesia of neuraxial morphine can be improved with increased doses but xst be weighed against increasing side effects.

Because of the widespread use of neuraxial opioids in the childbirth setting, opioid-induced pruritus is most frequently observed among obstetric patients[16,24–26] (table 1), where it has an incidence of up to 85%,[20] and is primarily dose-dependent.[22,23] Pruritus is also frequently reported among orthopedic patients receiving neuraxial opioids (30 to 70%)[37,38] for Enhanced Recovery after Surgery. The incidence of pruritus in patients receiving neuraxial morphine is more common among female patients (60 to 85%),[16,24–26] which mirrors the incidence and burden of chronic pain that also disproportionately affects women.[32] Differences in estrous cycle, which could affect the sensitivity of the μ-opioid receptor to opioid drugs,[39] have been proposed to underlie these differences, yet the extent to which nonbiologic factors could also contribute to disparities in experiences of pruritus warrants further investigation.

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Table 1. Incidence of Parenteral and Neuraxial Opioid-induced Pruritus

Route	Opioid	Incidence of Pruritus, %	Onset	Mechanism
Parenteral	Morphine (0.05 mg · kg^{-1} · h^{-1} IV)	< 10[14,27]	Apparent with chronic use[14,15]	Peripheral (histamine-dependent)[33–35]
Neuraxial	Morphine (1.5 to 5 mg epidural; 50 to 200 μg IT)	60 to 85[10,11,13,19,31]	Hours to days[31,32]	Central/spinal[12,28,36]
Neuraxial	Lipid-soluble (fentanyl and sufentanil; 20 to 100 μg epidural; 10 to 20 μg IT)	60 to 90[29,30]	Rapid (within minutes to 4 h)[25,30]	Central/spinal[12,28,36]

The route of administration, incidence, onset, and proposed mechanism of action are listed.
IT, intrathecally; IV, intravenously.

Although it is less common than neuraxial opioid–induced pruritus, parenteral opioid–induced pruritus has been observed in 10 to 50% of patients, particularly in the setting of patient-controlled analgesia (PCA)[15,27,40,41] and among patients receiving IV morphine for vasoocclusive crisis in sickle cell disease.[42] Thus, in contrast to neuraxial opioid–induced pruritus, which is observed after a single dose of opioids, parenteral opioid–induced pruritus is mostly observed after extended dosing.[15,27,40,41] Among pediatric patients on PCA, pruritus was the most common reason for switching medications to another opioid class: for example, from morphine to a semisynthetic opioid such as hydromorphone.[27] In these settings, the development of pruritus may be associated with central sensitization to opioids that may occur independently of tolerance to opioid-induced analgesia.[43] Proposed mechanisms include sensitization of itch-responsive circuits within the spinal dorsal horn after chronic use.[43] In particular, central, but not peripheral, μ-opioid receptors have recently been implicated in modulation of dermatitis and lymphoma-induced chronic itch.[44] Further research is necessary to elucidate the contribution of these central pathways to chronic opioid-induced pruritus. Thus, although pruritus is most common after neuraxial opioid administration, it also poses a troublesome side effect for a small number of patients, such as those on PCA for postoperative pain management.

Polymorphisms of *OPRM1* on Opioid-induced Analgesia and Pruritus

Sequencing of the human μ-opioid receptor (*OPRM1*) gene, which encodes for the μ-opioid receptor, indicates that certain polymorphisms may be associated with protection against the side effect of pruritus.[28,46] For example, genetic association studies have focused on the A118G polymorphism of *OPRM1*.[28,46] The recessive G allele in this polymorphism is associated with lower incidences of pruritus among obstetric patients receiving epidural (4.8%) and spinal (0 to 50%) morphine.[28,46] This variant is further associated with reduced sensitivity to the analgesic effects of opioids,[47] suggesting that the A118G polymorphism may give rise to a μ-opioid receptor that is generally less responsive to opioid medications. However, given the heterogeneity among clinical populations receiving opioid analgesia and their self-reported experiences for both pain and itch, many of these studies are underpowered to provide definitive conclusions about these polymorphism relationships.[48,49] In mice, distinct splice variants of the u-opioid receptor isoform consisting of exons 1-3 and 8-9 (*MOR1D*) and exons 1-4 (*MOR1*), have been shown to differentially modulate morphine-induced itch and morphine-induced analgesia, respectively.[50] However, the contributions of these splice variants have not been characterized in humans. Additional large population genetic association studies are necessary to further assess the clinical significance and utility of identifying genetic variations on acute postoperative pain management and risk for opioid-related side effects.

Differences in Opioid Medications and Pruritus

Opioid-induced pruritus is observed after the use of intrathecally administered hydrophilic opioids (such as morphine) and lipophilic opioids (such as fentanyl and sufentanil).[29,51] The high incidence of pruritus after morphine (60 to 85%)[10,11,13,19,30] and lipophilic opioids (60 to 90%)[29,51] suggests a common μ-sensitive pathway modulates pruritus in response to these medications (table 1). However, a key difference between these two classes of opioid drugs is the onset and duration of pruritus; pruritus occurs within hours and lasts up to several days in patients receiving epidural and spinal morphine.[30,31] With lipid-soluble opioids, the onset of pruritus can occur as rapidly as within minutes of administration and persists up to several hours.[25,29] These differences in onset and duration reflect the pharmacokinetics of these intrathecally administered opioid medications. Microdialysis studies in pigs[32] (using equimolar doses of morphine, fentanyl, and sufentanil) have revealed that spinal exposure to morphine was greater than lipophilic opioids because of morphine's low spinal cord distribution volume and slow clearance into the plasma. Fentanyl and sufentanil, in contrast, have been found to rapidly clear into the plasma and epidural fat, respectively, reducing their spinal bioavailability.[32] In a clinical study examining the clearance of opioid medications from the cerebrospinal fluid (CSF), volunteers received an intrathecal injection of both morphine and fentanyl (50 μg each). The ratio of morphine to fentanyl in the

CSF was found to increase over time (reaching 4:1 within 2 h).[52] The solubility of morphine compared to lipid-soluble opioids, such as fentanyl, clearly affect the bioavailability and thus onset and duration of opioid analgesia and its side effects. Furthermore, the bioavailability of neuraxial morphine supports its suitability for acute postoperative pain, such as for Enhanced Recovery after Surgery[53] and in obstetric settings[54]; however, its long elimination time must be considered against its delayed adverse effects, such as pruritus.

The Role of Mast Cells in Opioid-induced Pruritus

It has been proposed that release of histamine underlies opioid-induced pruritus,[55] although the route of administration might lead to differential impact of mast cells on pruritus (fig. 1). Intramuscular and subcutaneous morphine have been shown to evoke pruritus and vasodilation at the injection site.[56] One study that performed *in vivo* microdialysis in human skin found that intradermal injections of morphine led to dose-dependent increases in local histamine and itch sensations.[57] Similarly, examination of blood samples from patients with parenteral exposure to opioids has also revealed an elevation in histamine levels.[33–35] Last, *in vitro* studies in both human and rodent models have confirmed that opioids, such as morphine, act directly on mast cells to drive degranulation and histamine release.[58–60]

Only recently, however, has it become clear how opioids could directly activate mast cells. Morphine was recently found to induce mast cell degranulation through activation of mas-related G protein-coupled receptor X2 (MRGPRX2), a primate-exclusive G protein–coupled receptor, rather than canonical opioid receptors (such as the μ-opioid receptor).[58] Binding of opioids to MRGPRX2 leads to increases in intracellular calcium in mast cells.[58] This is thought to occur through the phospholipase Cβ pathway, which results in the release of mediators, such as histamine.[61] MRGPRX2 is implicated in itch and pain,[62] and the restricted expression of MRGPRX2 on mast cells, which can be activated in the absence of atopy,[61] such as by direct binding of opioids,[58] establishes a mechanism for how opioids can directly act on mast cells to give rise to pruritus (fig. 2). The expression of MRGPRX2 on mast cells may also underlie anaphylaxis after opioid administration, which comprised 2.6% of all cases of anaphylaxis caused by anesthetics.[63] For these reasons, MRGPRX2 should be considered a target for IgE-independent allergic reactions to perioperative drugs such as morphine administered subcutaneously and intravenously.

However, for neuraxial opioids, the evidence that a mast cell–dependent mechanism underlies pruritus is less compelling. In humans, the neuraxial administration of fentanyl, a lipophilic and synthetic opioid, evokes pruritus, even though fentanyl does not cause mast cell degranulation and histamine release as morphine does.[60,64–66] Furthermore, clinical plasma concentrations of morphine are orders of magnitude smaller than CSF concentrations after neuraxial morphine administration (less than 0.01%),[67,68] and the concentration of morphine detected in the plasma is likely insufficient to cause mast cell degranulation, as suggested by *in vitro* studies (fig. 2).[58–60] Mast cell–mediated pruritus after the local injection of opioids, as seen after intradermal injections of morphine, is restricted to the site of injection[57] and does not explain how neuraxial opioids, frequently administered into lumbar segments, evoke pruritus in other dermatomes, including those innervating facial regions.[10,11,13] Last, genetically modified mice lacking mast cells scratch at levels similar to controls in response to intrathecal morphine.[36] Therefore, a mast cell-dependent mechanism does not explain the prevalence and spread of neuraxial opioid–induced pruritus. Taken together, although there is evidence that histamine

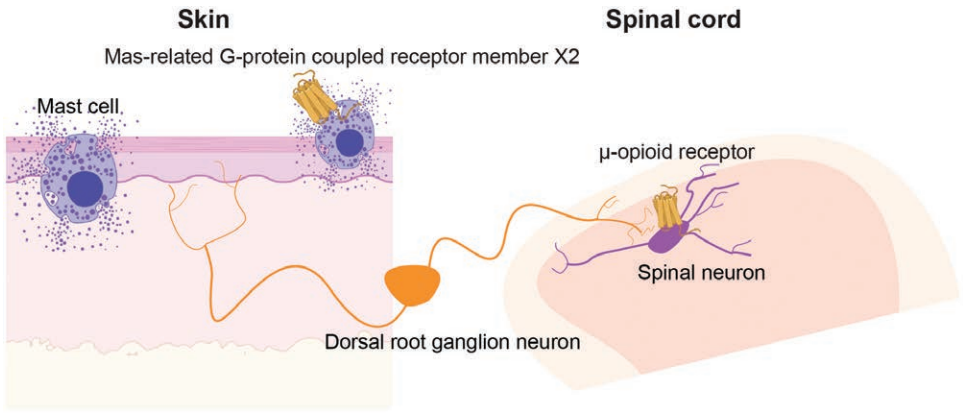

Fig. 1. Proposed mechanisms of opioid-induced pruritus. This review summarizes mechanisms by which opioids could drive pruritus in the skin, dorsal root ganglia, and spinal cord dorsal horn. In the skin, systemic opioids can cause mast cell degranulation through activation of mas-related G protein–coupled receptor X2 (MRGPRX2) on mast cells. Neuraxial opioids are proposed to drive itch through spinal neurons containing the μ-opioid receptor in the spinal cord dorsal horn.

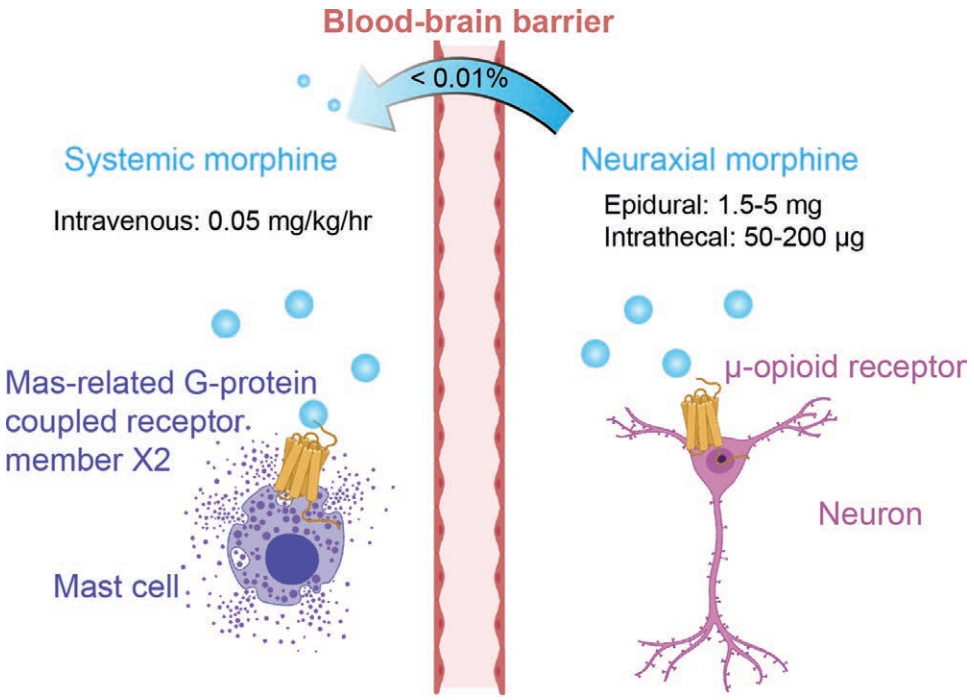

Fig. 2. Systemic and neuraxial opioid–induced pruritus are separately modulated. Systemic (oral, subcutaneous, and parenteral) morphine may drive pruritus through the engagement of mas-related G protein–coupled receptor X2 (MRGPRX2) on mast cells. Neuraxial (epidural and intrathecal) opioid-induced pruritus, on the other hand, is likely driven by spinal neurons containing the μ-opioid receptor, because less than 0.01% of the peak concentration detected in the cerebrospinal fluid is detected in the plasma after neuraxial opioid administration.

release may cause itch from peripheral (subcutaneous, oral, and intravenous) opioids, this process is unlikely to contribute to neuraxial opioid–induced pruritus.

Central Mechanisms of Opioid-induced Pruritus

With neuraxial morphine-induced itch, it has been proposed that the nervous system could be responsible for mediating the sensation of itch[12,69] (fig. 2). The analgesic benefits of opioids are mediated through the nervous system[70,71]; therefore, it is proposed that pruritus, another sensory symptom, may also be mediated through neurons. Although both intrathecal and epidural opioids cause pruritus,[10,11] pruritus occurs more commonly with the intrathecal route of administration; a review of 11 trials by Simmons *et al.*[72] found the average relative risk of developing pruritus in combined spinal analgesia relative to epidural analgesia to be 1.80 (95% CI, 1.22 to 2.65).[72] This supports the possibility that pruritus occurs because of a direct effect of the opioid within the neuraxis.

Further evidence for a neuronal mechanism for pruritus is the observation that opioid lipophilicity is associated with the onset and severity of pruritus among patients. For example, lipophilic opioids, such as fentanyl, which more readily cross the blood–brain barrier, are associated with a more rapid onset and shorter duration of pruritus than hydrophobic opioids such as morphine,[12,21,25,73] consistent with a neuronal mechanism of action. These clinical observations further support the idea that two separate mechanisms underlie opioid-induced pruritus arising from different routes of administration (fig. 2): systemic opioids activate mast cells to drive itch through histamine release, whereas neuraxial opioids act on CNS pathways to cause itch.

Opioid-induced Pruritus Mediated by Primary Afferents

Primary sensory neurons respond directly to itch-inducing agents. For example, a class of transient receptor potential cation channel subfamily V member 1 (TRPV1)-containing C-fibers that innervate the skin expresses the histamine receptor, which can be activated by histamine.[74,75] Upon activation with histamine, these neurons transmit pruriceptive information to the superficial layers of the spinal cord, and this information ascends through the spinothalamic tracts to target the primary sensory and cingulate cortices.[76] Thus, if opioid-induced pruritus causes the release of histamine, then peripheral opioid-induced itch may occur through this pathway (fig. 1). Consistent with this view, intradermal injection of the μ-opioid receptor agonist D-Ala2, N-MePhe4, Gly-ol]-enkephalin (DAMGO) elicits itch in mice that is abrogated with the ablation of TRPV1-expressing fibers.[56] Another channel expressed

by primary afferents is transient receptor potential cation channel, subfamily A, member 1 (TRPA1), which has also been implicated in acute and chronic itch.[77,78] However, the contribution of TRPA1 to peripheral opioid-induced itch is unlikely because TRPA1-deficient mice exhibit normal histamine-evoked itch.[77,78] These findings suggest that for subcutaneous, oral, and intravenous opioids, itch likely occurs through TRPV1, and not TRPA1, sensory neurons after the release of histamine from mast cells.[33–35] However, given the weak association between neuraxial opioids and histamine release,[60,64–66] histamine receptor–expressing sensory neurons are not likely to be involved in neuraxial opioid–induced pruritus.

Presently, neuraxial opioids are not believed to act directly on μ-opioid receptor expressing sensory neurons to elicit itch. Conditional deletion of the μ-opioid receptor from TRPV1 and somatostatin neurons, which have been implicated in itch signaling, did not affect intrathecal morphine–induced itch in mice.[45] In support of this view, other studies have suggested that rather than direct modulation of these peripheral sensory neurons, neuraxial opioids may influence pruriceptive processing centrally. One study, performed in rats, identified that neuraxial morphine augmented the activity in trigeminothalamic tract neurons in response to itch stimuli.[79] Trigeminothalamic tract neurons are analogous to spinothalamic tract neurons in the spinal cord but relay information pertaining to the head and neck regions rather than the body. It was found that intrathecal morphine caused these neurons to increase their ongoing activity to pruritogens applied to the skin.[79] Intrathecal morphine also enhanced responses to innocuous mechanical stimuli, suggesting that opioids may also cause sensitization to touch-evoked itch.[79] Another study in mice also examined the role of TRPV1 antagonists and neuraxial morphine-induced itch.[80] In this study, it was observed that the intrathecal delivery of a TRPV1 antagonist reduced morphine-induced itch in mice. Together, these studies suggest that neuraxial morphine can evoke sensitization of central pathways, leading to an enhancement of responsiveness within these circuits to peripheral stimulation.

Opioid Pharmacology as a Key to Understanding Spinal Circuitry

It is curious that opioids suppress pain but evoke itch. Conversely, intense pain can also suppress itch.[81,82] Previously, it was believed that itch occurs because of a reduction in pain signaling.[44] However, detailed pharmacologic investigations have largely ruled out this theory.[50,83] Several studies have shown that μ-opioid agonists, such as morphine, elicit itch, but δ- and κ-opioid receptor agonists, which also produce analgesia,[84] do not cause scratching behavior.[69,83,85] Instead, selective κ-opioid receptor agonists have been shown to suppress itch in preclinical models[86–88] and have been approved to treat chronic pruritus in Japan.[89] Notably, μ and κ-opioid receptors often exert opposing effects in several regions of the central nervous system; whereas μ-opioid receptor agonists produce analgesia, euphoria, and itch, κ-opioid receptor agonists are antipruritic and dysphoric.[90,91] Clearly, a simple model whereby a suppression of pain is sufficient to evoke itch does not explain these observations. The differential roles of these opioid receptors and their agonism in the context of itch underscores that opioid-induced pruritus is a complex and active process.

Spinal Disinhibition Causes Neuraxial Opioid–induced Itch in Preclinical Models

The mechanisms of opioid-induced itch at the level of the dorsal horn have only recently begun to be examined. One study in mice suggested that neuraxial morphine causes itch through activation of gastrin-releasing peptide receptor neurons in the dorsal horn,[50] an excitatory population that is involved in mediating itch (fig. 3).[92,93] This study suggested that neuraxial morphine triggers heterodimerization of the μ-opioid receptor with gastrin-releasing peptide receptor.[50] After heterodimerization, the authors proposed that itch occurs after the activation of excitatory downstream pathways involving phospholipase Cβ3 and an increase in intracellular calcium.[50] However, recent sequencing[94,95] and neurochemical studies[36,45] cast doubt on this conclusion. Opioids typically signal through Gαi-coupled G protein–coupled receptors, resulting in potassium efflux and hyperpolarization, which inhibits neuronal activity.[96,97] Thus, the conclusion that neuraxial opioid–induced itch occurs through dimerization of the μ-opioid receptor and gastrin-releasing peptide receptor is controversial.[69]

Alternatively, molecularly defined inhibitory neurons have been implicated in the modulation of itch. For example, inhibitory neurons containing dynorphin and neuropeptide Y have been shown to be important for the inhibition of chemical[88,98,99] and mechanical itch,[100,101] respectively. When either dynorphin neurons or neuropeptide Y neurons are lost during development, mice show spontaneous scratching behavior suggesting that these populations are involved in the tonic inhibition of itch.[88,98–101] In a recent study, selective removal of the μ-opioid receptor from inhibitory neurons (neurons that produce γ-amino butyric acid [GABA]) abolished opioid-induced itch in a mouse model.[45] A second study focused on a subset of inhibitory neurons containing dynorphin, the endogenous peptide for the κ-opioid receptor.[36] In this study, the expression of the μ-opioid receptor was found to be required for morphine-induced itch.[36] κ-opioid signaling alleviated morphine-induced itch in both mice and nonhuman primates.[36] Therefore, emerging evidence highlights that opioids could cause itch through inhibition of inhibitory neurons; rather than through heterodimerization between the μ-opioid receptor and gastrin-releasing

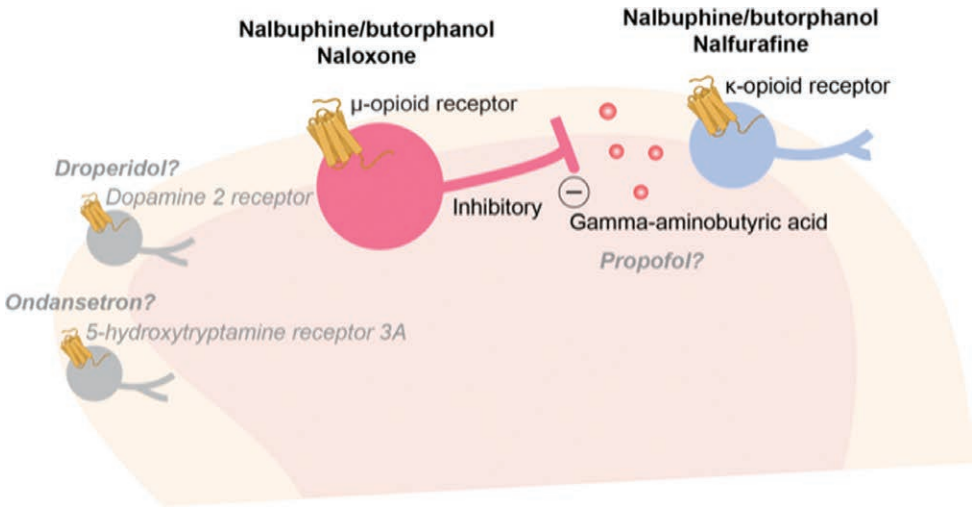

Fig. 3. Mechanisms of action of proposed therapies for neuraxial opioid–induced pruritus. Antagonists (naloxone) of the μ-opioid receptor are proposed to act on μ-opioid receptor–expressing inhibitory neurons to relieve pruritus. Propofol may potentiate the inhibitory action of these inhibitory neurons to suppress itch. Mixed antagonist–agonists (nalbuphine and butorphanol) inhibit itch through antagonism of the μ-opioid receptor and agonism of the κ-opioid receptor. Dopamine and serotonin receptor antagonists (droperidol and ondansetron, respectively) are thought to exert their action on spinal neurons, although this has not been tested directly. GABA, γ-aminobutyric acid.

peptide receptor, there is now compelling evidence that opioids cause itch through a mechanism of neuronal disinhibition (fig. 3).

These two recent studies, from two independent groups, highlight the role of inhibitory neurons in the spinal cord as the crucial mediators of opioid-induced itch. To date, they provide the most compelling evidence for how a spinal mechanism is responsible for neuraxial opioid–induced itch.

Treatments for Opioid-induced Pruritus

Given the dose-dependent nature of opioid-induced pruritus, clinicians have managed to control unwanted side effects by tightly titrating the dose needed to optimize analgesia.[102] Multimodal analgesia has also been shown to be effective at both managing pain and reducing opioid side effects through synergy between multiple agents.[103] For example, the combination of local anesthetics, such as bupivacaine, with opioid analgesics reduces the severity of pruritus in the immediate postoperative period.[51,73] However, despite efforts to reduce the dose of opioids administered and to apply a multimodal approach to neuraxial analgesia, pruritus as a side effect persists for some people. Common and modern treatment options for these patients are described below (table 2).

Histamine Receptor Antagonists

The role of antihistamines in neuraxial opioid–induced pruritus is contested. Antihistamines reduce diaphoresis and wheal-and-flare responses to parenteral opioids,[34] and many providers continue to use antihistamines to manage pruritus induced by opioids. Nevertheless, the appropriateness of this practice in the setting of neuraxial opioid–induced pruritus is questionable.[124] Several studies indicate that histamine receptor antagonists, such as diphenhydramine and promethazine, reduce itch in obstetric patients who receive neuraxial opioids.[104,124–127] However, antihistamines have also been shown to cause sedation,[19,105,106] and it has been observed that the sedating effects of antihistamines have caused patients to verbally deny itch but continue to scratch or that patients report itchiness in between periods of sleep.[10,104,106] Thus, it is possible that the apparent reduction in itch with antihistamine treatment seen in some studies may, in fact, be secondary to drowsiness.[128]

Comparisons between the effectiveness of mixed κ agonist–μ antagonist and antihistamines for the management of neuraxial opioid–induced pruritus have revealed major limitations of antihistamine treatment for this form of pruritus.[104,125,126,129–131] In spite of these limitations, they continue to be prescribed for both peripheral and central opioid-induced pruritus.[12,127] Given new evidence that spinal neurons mediate neuraxial opioid–induced pruritus,[45,36,69] antihistamines likely have no role in the treatment of neuraxial opioid–induced pruritus, but they may have a key role in the treatment of subcutaneous, oral, and intravenous morphine–induced pruritus.

Table 2. Frequently Prescribed Treatments for Opioid-induced Pruritus

Class	Example (Recommended Dose and Route)	Site of Action	Recommended Appropriate Clinical Use	Notes
Histamine receptor antagonist	Diphenhydramine (25 mg IV)	Peripheral	Parenteral morphine	Sedation is a common and problematic side effect[19,105,106]
μ-Antagonist	Naloxone (0.25 to 2 μg · kg^{-1} · h^{-1} IV)	Central	Parenteral and neuraxial opioids	Limited by reduction in analgesia[108]
Mixed μ-antagonist, κ-agonist	Nalbuphine (1 to 5 mg IV), butorphanol (0.2 to 2 mg IV)	Central	Neuraxial opioids	Highly effective antipruritic, without major reductions in analgesia but can cause drowsiness[19,107,109]
5-Hydroxytryptamine receptor 3A antagonist	Ondansetron (4 mg IV)	Central	Neuraxial opioids	Does not decrease the incidence of pruritus, but prophylactic treatment may reduce severity[20,110–114] 15and reduce postoperative nausea and vomiting
Selective κ-agonist (preclinical)	Nalfurafine (in primates: 0.1 to 1 μg/kg IV; 0.3 μg IT; in mice: 40 ng IT)	Central	Neuraxial opioids	Clinically approved for pruritus of systemic disease in Japan[89]; effectively treats morphine-induced itch in preclinical models without affecting analgesia[36]
Dopamine receptor antagonist	Droperidol (1.25 mg IV)	Central	Neuraxial opioids	Data limited but has been observed to reduce incidence of pruritus[104,122,123]
GABA analog	Gabapentin (1,200 mg *per os*)	Central	Neuraxial opioids	Effective for pruritus in systemic disease,[119] but effectiveness is unclear for opioid-induced pruritus[120,121]
Potentiation of $GABA_AR$	Propofol (10 to 30 mg IV)	Central	Neuraxial opioids	Controversial; reduces incidence of pruritus in patients undergoing some elective surgeries[116,117] but not cesarean delivery[118]

Examples and sites of action are listed.
GABA, γ-aminobutyric acid; $GABA_AR$, γ-aminobutyric acid type A; IT, intrathecally; IV, intravenously.

μ-Opioid Receptor Antagonists

To date, the most effective treatments for opioid-induced pruritus have included pharmacologic agents that antagonize the μ-opioid receptor, which pose disadvantages in that they can reverse analgesia.[107,132] Clinically, μ-opioid receptor antagonists have also been shown to be effective for the management of parenteral opioid–induced pruritus.[129] For patients on parenteral opioid therapy, such as patients with sickle cell disease, the coadministration of the opioid analgesic and its antagonist helps to mitigate pruritus,[42] particularly when small doses are infused (*e.g.*, naloxone 0.25 to 2 μg · kg^{-1} · h^{-1} intravenous push).[133,134] Naloxone is also effective at reducing wheal-and-flare responses caused by morphine.[135] These findings highlight the utility of μ-opioid receptor antagonists in the management of peripherally mediated and histamine-dependent opioid induced pruritus.

μ-Opioid receptor antagonists are also effective for the treatment of pruritus induced by neuraxial opioid administration.[12,13] Naloxone and naltrexone are direct opioid receptor antagonists often used to reduce both the frequency and the severity of pruritus evoked by neuraxial opioid analgesia.[132] Unfortunately, these antagonists, at doses that are clinically effective at reversing pruritus, may also reverse the analgesic effects of opioids[41] (*e.g.*, complete reversal for opioid-induced respiratory depression at doses of naloxone 0.1 mg/kg intravenous push).[108] In nonhuman primates, the one-time administration of a selective μ-opioid receptor antagonist, such as nalmefene, produced a 10-fold rightward shift in both morphine-induced scratching and analgesia.[83] Furthermore, the mean pK_B (an estimate of antagonist affinity) of nalmefene was found to be similar for both scratching and thermal nociception endpoints,[83] indicative of a circumscribed window for the management of itch without affecting analgesia by μ-opioid receptor antagonism, making these agents suboptimal for the treatment of pruritus in obstetric patients. Thus, optimal doses of μ antagonists, such as naloxone or naltrexone, to relieve clinical pruritus often come with a risk-benefit discussion with patients about their preferential priorities on pain control *versus* itch.

Alternatively, mixed opioid receptor agonists, such as nalbuphine (1 to 5 mg IV)[136] and butorphanol (0.2 to 2 mg IV)[137] are also clinically effective therapies for neuraxial opioid–induced pruritus.[19,107,138] They are frequently used due to their improved ability to manage pruritus without reducing analgesia compared to selective μ-opioid receptor antagonists.[107] Nalbuphine is a mixed antagonist of the μ-opioid receptor and agonist of the κ-opioid receptor, and because of its partial antagonism of the μ-opioid receptor, reversal of analgesia remains a concern.[109] Another potential limitation of nalbuphine is its sedating side effect,[19,133] although this is only observed when a high dose (10 mg/70 kg) is used,[139] which is beyond the range used to manage pruritus clinically.[24] In contrast, butorphanol is a partial agonist of both the μ- and κ-opioid receptors. Similar to nalfurafine, butorphanol has also been reported as an effective treatment of opioid-induced pruritus, particularly among pediatric patients.[140,141] Thus, nalfurafine and butorphanol may pose

therapeutic advantages over selective μ-antagonists because of their agonism of the κ-opioid receptor and the ability to directly modulate spinal itch circuits.

Notably, both opioid antagonists and mixed agonist–antagonists are effective for other clinical instances of pruritus, including those associated with systemic disease or of dermatologic origin. Nalbuphine, for example, is effective at managing pruritus among patients with end stage renal disease[142,143] and contact dermatitis.[144] These observations suggest that different forms of pruritus (spanning from systemic disease to drug-induced) converge on a common itch pathway that depend on central opioid signaling, likely centered upon the involvement of endogenous endorphin and dynorphin tone. Like many drugs frequently used in clinical anesthesia practice, the use of nalbuphine for the clinical management of opioid-induced pruritus is off-label.[145] Given the effectiveness of nalbuphine for the prevention and severity of pruritus,[19] a new drug indication of nalbuphine for opioid-induced pruritus could facilitate its widespread use within clinical practice.

Selective κ-Opioid Receptor Agonists

The dynorphin–κ-opioid receptor system has been heavily implicated in itch. Pharmacologic and genetic manipulations of spinal dynorphin-expressing neurons in freely behaving animals have uncovered that spinal dynorphin is required for the inhibition of itch.[88,99] In rodent and nonhuman primate models, selective κ-opioid receptor agonists, such as nalfurafine, have been shown to be important for the inhibition of several forms of chemical, immunologic, and drug-induced (including opioid-induced) itch.[87,146,147] Clinically, nalfurafine (2.5 or 5.0 μg *per os*)[148] has been shown to be effective for the treatment of uremic and cholestatic pruritus in Japan.[89]

Emerging evidence in preclinical models, involving both mice and nonhuman primates, indicate that the intrathecal and systemic administration of κ-opioid receptor agonists can reduce morphine-induced itch without reducing morphine-induced analgesia.[36,87,149] In preclinical models, nalfurafine has been found to restore dynorphin signaling disrupted by neuraxial μ-opioid receptor agonists, such as morphine.[36] These preclinical findings indicate that selective κ-opioid receptor agonists should be further considered for opioid-induced pruritus in the future.

Presently, however, nalfurafine does not have approval by the European Medicines Agency (Amsterdam, The Netherlands) or Food and Drug Administration (Silver Spring, Maryland) for clinical use in Europe and the United States, respectively.[150] One concern has been its sedating effects, which has been observed after long-term use in dogs,[151] but this has not been a consistent finding in other animal models and in patients.[87,148,152] In European trials, nalfurafine (5 μg *per os*) did not significantly reduce the severity of uremic pruritus compared to placebo over 8 weeks.[151] However, one key difference between the studies conducted in Europe[151] and Japan[153] was the duration of the trial (weeks compared to days, respectively), and notably, in the European trials, both the nalfurafine-treated and placebo groups exhibited significant reductions in self-reported visual analogue scale intensities of pruritus over the course of the study.[151] Given the incidence of opioid-induced pruritus in the postoperative setting, the effectiveness of nalfurafine may be more evident in acute settings, although further clinical trials in perioperative and acute care settings is necessary.

Serotonin Receptor Antagonists

5-Hydroxytryptamine receptor antagonists are frequently used to treat postoperative nausea and vomiting. Both of these side effects are observed in postoperative patients who receive neuraxial morphine.[154,155] Several studies have revealed that prophylaxis with a 5-hydroxytryptamine receptor antagonist (such as ondansetron, ranging from 4 to 8 mg IV) does not significantly reduce the incidence of pruritus.[20,110–114,154] A systematic review by Bonnet *et al.*[115] of 15 randomized controlled trials suggests that 5-hydroxytryptamine receptor antagonists may reduce the intensity of opioid-induced pruritus but also concluded that the trials included in the systematic review, such as small studies that favor the publication of positive findings, may have suffered from publication bias. Thus, there is still a lack of consensus on the clinical effectiveness of 5-hydroxytryptamine receptor antagonists in opioid-induced pruritus.[115,156]

The mechanism by which 5-hydroxytryptamine receptor antagonists such as ondansetron alleviate itch is not clear. 5-Hydroxytryptamine receptor immunoreactivity has been observed in the spinal dorsal horn,[157] and the endogenous source of serotonin is thought to originate from descending fibers arising within the brainstem.[158] Depletion of supraspinal serotonin has been shown to alleviate pruritogen-induced itch in rodents,[159] which may partially explain how antagonism of 5-hydroxytryptamine receptor reduces opioid-induced itch. However, spinal neurons expressing 5-hydroxytryptamine receptor and the μ-opioid receptor have been found to comprise nonoverlapping populations,[95] making it unlikely that agents such as ondansetron could directly reduce the activity of neurons responsible for opioid-induced itch. In rhesus monkeys, ondansetron has also been found to be ineffective at reducing morphine-induced itch, even at high doses that caused extrapyramidal effects.[69] Given these conflicting reports between human and animal models and the lack of a cellular basis for how serotonin and opioid signaling could converge, 5-hydroxytryptamine receptor antagonists are currently not considered front-line therapies for opioid-induced pruritus and likely have a limited role in prophylaxis against opioid-induced pruritus.

Propofol

The effectiveness of subhypnotic doses of propofol (10 to 30 mg IV) for the treatment of opioid-induced pruritus

remains controversial. In one double-blind trial, propofol (10 mg IV) was observed to reduce morphine-induced pruritus compared to placebo (85% compared to 16%, respectively).[160] The patients in this study had received either epidural or spinal morphine for a variety of surgical procedures including gynecologic, gastrointestinal, thoracic, and orthopedic surgery.[160] Another study also reported that propofol (10 mg IV) protected against pruritus after intrathecal morphine for arthroplasty surgery.[116] However, Warwick *et al.*[117] did not confirm these findings in a double-blind study of obstetric patients; propofol (10 to 20 mg IV) had no effect on the onset or severity of pruritus after intrathecal morphine. Age and sex differences among these studies may account for the variable effectiveness of the similar doses of propofol used to mitigate neuraxial morphine-induced pruritus. These studies further underscore that pruritus disproportionately occurs in younger and female obstetric patients,[16,24–26] who may be less responsive to the antipruritic effects of propofol. Another possibility for the observed differences across studies is that the dose of propofol used may not have been adequate to achieve clinical effect. Thus, although propofol has been observed to reduces incidence of pruritus in patients receiving morphine for a variety of elective surgeries,[116.160] its benefit in the treatment of opioid-induced pruritus within the obstetric population remains questionable.[117]

Recent work in rodents have revealed that neurons producing GABA are required for neuraxial opioid–induced itch,[36,45] and the administration of propofol, through potentiation of GABA receptors, may enhance the ability of these neurons to dampen excitatory spinal circuits[92] involved in itch transmission. Additional dose-response studies are necessary to identify the appropriate dose of propofol for management of pruritus without sedation.

Gabapentin

Gabapentin has been shown to be effective for several forms of pruritus in systemic disease, including uremic pruritus, pruritus in multiple sclerosis, and pruritus of unknown origin.[118,119,161] Its use in the treatment of neuraxial opioid–induced pruritus is less clear. Preoperative gabapentin (1,200 mg *per os*) has been found to significantly delay the onset and reduce the incidence and severity of intrathecal morphine–induced pruritus in patients undergoing orthopedic surgery[162] and prolong the onset of pruritus in patients receiving spinal morphine for unilateral hernia repair.[120] However, a lower dose (600 mg) was not found to significantly decrease the incidence of pruritus compared to placebo and was associated with urinary retention.[163] Further pharmacologic studies in preclinical and clinical models are necessary to characterize the mechanism of action of gabapentin within the nervous system. However, recent efforts have noted the safety concerns associated with gabapentin in the perioperative setting; the risks of adverse effects and lack of significant analgesic effect on postoperative pain suggest that the use of gabapentin for opioid-induced pruritus should also be avoided.[121,164]

Dopamine D2 Receptor Antagonists

Droperidol (1.25 mg IV), a short-acting, potent dopamine receptor antagonist, has been shown in several studies to be effective at reducing the incidence and severity of neuraxial opioid–induced pruritus and has previously been used for postoperative nausea and vomiting.[104,122,165] However, dopamine receptor antagonists have been reported to be effective only when small doses of opioids are administered. Sedation has been shown to increase with escalating doses of droperidol (2.5 to 5 mg IV), which may confound its antipruritic effects.[122] Given the broad influences of supraspinal dopamine signaling on the functions of spinal and dorsal root ganglion neurons, the antipruritic effects observed may be nonspecific.[123] Emerging evidence indicates that low doses of droperidol may be safely used; however, clinical use of droperidol in a perioperative setting is limited by an Food and Drug Administration black box warning because of its risk for sudden cardiac death.[166] The warning will likely preclude any clinical adoption of droperidol to treat opioid-induced pruritus.

Emerging Treatments for Opioid-induced Pruritus and Future Directions

All existing treatment options for opioid-induced pruritus have undesirable side-effect profiles. Furthermore, many of these treatments are used empirically and off-label. Because of the limitations of currently available treatments, some patients or providers may elect to forgo analgesia or opt for suboptimal analgesia that excludes neuraxial opioids, but these practices can lead to unnecessary pain and suffering.[167] Recent success in preclinical models suggests that nalfurafine, a selective κ-opioid receptor agonist, may be used to manage opioid-induced pruritus without limiting opioid-induced analgesia,[36] but further basic, translational, and clinical research is required before recommendations for clinical use in opioid-induced pruritus can be made. Optimization of opioid analgesia and development of improved therapies for opioid-induced pruritus have the potential to significantly improve the clinical standards of care for patients who receive opioids for the management of perioperative pain and experience pruritus as an unwanted side effect.

Conclusions

Pruritus after neuraxial opioids remains a highly common and dissatisfying side effect. Advancements in the understanding of mast cell biology and neuronal itch circuitry have provided clues as to how opioids can induce analgesia and evoke pruritus. Existing evidence suggests that parenteral opioids cause pruritus through histamine release, whereas neuraxial opioid–induced pruritus occurs through a mechanism of

neuronal disinhibition in the spinal cord dorsal horn. The differential modulation of peripheral and neuraxial opioid–induced pruritus by mast cells and neurons, respectively, further highlight the complexity of the side effects of opioid use. Emerging evidence suggests that pruritus arises because of the dysregulation of opioid-sensitive pathways involving μ- and κ-opioid receptor signaling, which parallels other forms of chronic, systemic, and drug-induced pruritus. Ultimately, a richer understanding of the genetic, molecular, and cellular underpinnings of opioid-induced pruritus may provide a basis upon which to develop improved therapies that can manage pain but do not cause itch.

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Competing Interests

The authors declare no competing interests.

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References

1. Dowell D, Haegerich TM, Chou R: CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. MMWR Recomm Rep 2016; 65:1–49
2. Sarma VJ, Boström UV: Intrathecal morphine for the relief of post-hysterectomy pain: A double-blind, dose-response study. Acta Anaesthesiol Scand 1993; 37:223–7
3. Fassoulaki A, Gatzou V, Petropoulos G, Siafaka I: Spread of subarachnoid block, intraoperative local anaesthetic requirements and postoperative analgesic requirements in caesarean section and total abdominal hysterectomy. Br J Anaesth 2004; 93:678–82
4. Dualé C, Frey C, Bolandard F, Barrière A, Schoeffler P: Epidural *versus* intrathecal morphine for postoperative analgesia after caesarean section. Br J Anaesth 2003; 91:690–4
5. Chadwick HS, Ready LB: Intrathecal and epidural morphine sulfate for post-cesarean analgesia: A clinical comparison. Anesthesiology 1988; 68:925–9
6. Grant CRK, Checketts MR: Analgesia for primary hip and knee arthroplasty: The role of regional anaesthesia. Cont Educ Anaesth Crit Care Pain 2008; 8:56–61
7. de Leon-Casasola OA, Karabella D, Lema MJ: Bowel function recovery after radical hysterectomies: Thoracic epidural bupivacaine-morphine versus intravenous patient-controlled analgesia with morphine: A pilot study. J Clin Anesth 1996; 8:87–92
8. Jørgensen H, Wetterslev J, Møiniche S, Dahl JB: Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev 2000:CD001893
9. Chestnut DH: Efficacy and safety of epidural opioids for postoperative analgesia. Anesthesiology 2005; 102:221–3
10. Ballantyne JC, Loach AB, Carr DB: Itching after epidural and spinal opiates. Pain 1988; 33:149–60
11. Szarvas S, Harmon D, Murphy D: Neuraxial opioid–induced pruritus: A review. J Clin Anesth 2003; 15:234–9
12. Kumar K, Singh SI: Neuraxial opioid–induced pruritus: An update. J Anaesthesiol Clin Pharmacol 2013; 29:303–7
13. Ganesh A, Maxwell LG: Pathophysiology and management of opioid-induced pruritus. Drugs 2007; 67:2323–33
14. Werawatganon T, Charuluxanun S: Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database Syst Rev 2005:CD004088
15. Hong D, Flood P, Diaz G: The side effects of morphine and hydromorphone patient-controlled analgesia. Anesth Analg 2008; 107:1384–9
16. Yurashevich M, Habib AS: Monitoring, prevention and treatment of side effects of long-acting neuraxial opioids for post-cesarean analgesia. Int J Obstet Anesth 2019; 39:117–28
17. Mugabure Bujedo B: A clinical approach to neuraxial morphine for the treatment of postoperative pain. Pain Res Treat 2012; 2012:612145
18. Tarcatu D, Tamasdan C, Moryl N, Obbens E: Are we still scratching the surface?: A case of intractable pruritus following systemic opioid analgesia. J Opioid Manag 2007; 3:167–70
19. Jannuzzi RG: Nalbuphine for treatment of opioid-induced pruritus: A systematic review of literature. Clin J Pain 2016; 32:87–93
20. Yeh HM, Chen LK, Lin CJ, Chan WH, Chen YP, Lin CS, Sun WZ, Wang MJ, Tsai SK: Prophylactic intravenous ondansetron reduces the incidence of intrathecal

morphine–induced pruritus in patients undergoing cesarean delivery. Anesth Analg 2000; 91:172–5
21. Shah MK, Sia AT, Chong JL: The effect of the addition of ropivacaine or bupivacaine upon pruritus induced by intrathecal fentanyl in labour. Anaesthesia 2000; 55:1008–13
22. Jiang CJ, Liu CC, Wu TJ, Sun WZ, Lin SY, Huang FY, Chao CC: Mini-dose intrathecal morphine for post-cesarean section analgesia. Ma Zui Xue Za Zhi 1991; 29:683–9
23. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B: The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: A meta-analysis. Anesth Analg 2016; 123:154–64
24. Tubog TD, Harenberg JL, Buszta K, Hestand JD: Prophylactic nalbuphine to prevent neuraxial opioid–induced pruritus: A systematic review and meta-analysis of randomized controlled trials. J Perianesth Nurs 2019; 34:491–501.e8
25. Wells J, Paech MJ, Evans SF: Intrathecal fentanyl-induced pruritus during labour: The effect of prophylactic ondansetron. Int J Obstet Anesth 2004; 13:35–9
26. Charuluxananan S, Somboonviboon W, Kyokong O, Nimcharoendee K: Ondansetron for treatment of intrathecal morphine–induced pruritus after cesarean delivery. Reg Anesth Pain Med 2000; 25:535–9
27. DiGiusto M, Bhalla T, Martin D, Foerschler D, Jones MJ, Tobias JD: Patient-controlled analgesia in the pediatric population: Morphine *versus* hydromorphone. J Pain Res 2014; 7:471–5
28. Tsai FF, Fan SZ, Yang YM, Chien KL, Su YN, Chen LK: Human opioid μ-receptor A118G polymorphism may protect against central pruritus by epidural morphine for post-cesarean analgesia. Acta Anaesthesiol Scand 2010; 54:1265–9
29. Gulhas N, Erdil FA, Sagir O, Gedik E, Togal T, Begec Z, Ersoy MO: Lornoxicam and ondansetron for the prevention of intrathecal fentanyl-induced pruritus. J Anesth 2007; 21:159–63
30. Waxler B, Dadabhoy ZP, Stojiljkovic L, Rabito SF: Primer of postoperative pruritus for anesthesiologists. Anesthesiology 2005; 103:168–78
31. Slappendel R, Weber EW, Benraad B, van Limbeek J, Dirksen R: Itching after intrathecal morphine: Incidence and treatment. Eur J Anaesthesiol 2000; 17:616–21
32. Ummenhofer WC, Arends RH, Shen DD, Bernards CM: Comparative spinal distribution and clearance kinetics of intrathecally administered morphine, fentanyl, alfentanil, and sufentanil. Anesthesiology 2000; 92:739–53
33. Ennis M, Schneider C, Nehring E, Lorenz W: Histamine release induced by opioid analgesics: A comparative study using porcine mast cells. Agents Actions 1991; 33:20–2
34. Philbin DM, Moss J, Rosow CE, Akins CW, Rosenberger JL: Histamine release with intravenous narcotics: Protective effects of H1 and H2-receptor antagonists. Klin Wochenschr 1982; 60:1056–9
35. Baldo BA, Pham NH: Histamine-releasing and allergenic properties of opioid analgesic drugs: Resolving the two. Anaesth Intensive Care 2012; 40:216–35
36. Nguyen E, Lim G, Ding H, Hachisuka J, Ko M-C, Ross SE: Morphine acts on spinal dynorphin neurons to cause itch through disinhibition. Sci Transl Med 2021; 13:eabc3774
37. Kaye AD, Urman RD, Cornett EM, Hart BM, Chami A, Gayle JA, Fox CJ: Enhanced recovery pathways in orthopedic surgery. J Anaesthesiol Clin Pharmacol 2019; 35(suppl 1):35–9
38. Szarvas S, Chellapuri RS, Harmon DC, Owens J, Murphy D, Shorten GD: A comparison of dexamethasone, ondansetron, and dexamethasone plus ondansetron as prophylactic antiemetic and antipruritic therapy in patients receiving intrathecal morphine for major orthopedic surgery. Anesth Analg 2003; 97:259–63
39. LaBella FS, Kim RS, Templeton J: Opiate receptor binding activity of 17-α-estrogenic steroids. Life Sci 1978; 23:1797–804
40. Woodhouse A, Hobbes AFT, Mather LE, Gibson M: A comparison of morphine, pethidine and fentanyl in the postsurgical patient-controlled analgesia environment. Pain 1996; 64:115–21
41. Gan TJ, Ginsberg B, Glass PS, Fortney J, Jhaveri R, Perno R: Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. Anesthesiology 1997; 87:1075–81
42. Koch J, Manworren R, Clark L, Quinn CT, Buchanan GR, Rogers ZR: Pilot study of continuous co-infusion of morphine and naloxone in children with sickle cell pain crisis. Am J Hematol 2008; 83:728–31
43. Schmelz M, Paus R: Opioids and the skin: "Itchy" perspectives beyond analgesia and abuse. J Invest Dermatol 2007; 127:1287–9
44. Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M: The neurobiology of itch. Nat Rev Neurosci 2006; 7:535–47
45. Wang Z, Jiang C, Yao H, Chen O, Rahman S, Gu Y, Zhao J, Huh Y, Ji RR: Central opioid receptors mediate morphine-induced itch and chronic itch via disinhibition. Brain 2021; 144:665–81
46. Pettini E, Micaglio M, Bitossi U, De Gaudio AR, Degl'Innocenti DR, Tofani L, Limatola V, Adembri C, Di Filippo A: Influence of OPRM1 polymorphism on postoperative pain after intrathecal morphine administration in Italian patients undergoing elective cesarean section. Clin J Pain 2018; 34:178–81
47. Sia AT, Lim Y, Lim EC, Goh RW, Law HY, Landau R, Teo YY, Tan EC: A118G single nucleotide polymorphism of human μ-opioid receptor gene influences pain perception and patient-controlled intravenous morphine consumption after intrathecal morphine

for postcesarean analgesia. Anesthesiology 2008; 109:520–6
48. Wong CA, McCarthy RJ, Blouin J, Landau R: Observational study of the effect of μ-opioid receptor genetic polymorphism on intrathecal opioid labor analgesia and post-cesarean delivery analgesia. Int J Obstet Anesth 2010; 19:246–53
49. Kung CC, Chen SS, Yang HJ, Lai CJ, Chen LK: Pharmacogenetic study of pruritus induced by epidural morphine for post cesarean section analgesia. Taiwan J Obstet Gynecol 2018; 57:89–94
50. Liu XY, Liu ZC, Sun YG, Ross M, Kim S, Tsai FF, Li QF, Jeffry J, Kim JY, Loh HH, Chen ZF: Unidirectional cross-activation of GRPR by MOR1D uncouples itch and analgesia induced by opioids. Cell 2011; 147:447–58
51. Mulroy MF, Larkin KL, Siddiqui A: Intrathecal fentanyl-induced pruritus is more severe in combination with procaine than with lidocaine or bupivacaine. Reg Anesth Pain Med 2001; 26:252–6
52. Eisenach JC, Hood DD, Curry R, Shafer SL: Cephalad movement of morphine and fentanyl in humans after intrathecal injection. Anesthesiology 2003; 99:166–73
53. Tang J, Churilov L, Tan CO, Hu R, Pearce B, Cosic L, Christophi C, Weinberg L: Intrathecal morphine is associated with reduction in postoperative opioid requirements and improvement in postoperative analgesia in patients undergoing open liver resection. BMC Anesthesiol 2020; 20:207
54. Sutton CD, Carvalho B: Optimal pain management after cesarean delivery. Anesthesiol Clin 2017; 35:107–24
55. Galloway KS, Yaster M: Pain and symptom control in terminally ill children. Pediatr Clin North Am 2000; 47:711–46
56. Melo H, Basso L, Iftinca M, MacNaughton WK, Hollenberg MD, McKay DM, Altier C: Itch induced by peripheral μ opioid receptors is dependent on TRPV1-expressing neurons and alleviated by channel activation. Sci Rep 2018; 8:15551
57. Blunk JA, Schmelz M, Zeck S, Skov P, Likar R, Koppert W: Opioid-induced mast cell activation and vascular responses is not mediated by μ-opioid receptors: An *in vivo* microdialysis study in human skin. Anesth Analg 2004; 98:364–70
58. Lansu K, Karpiak J, Liu J, Huang XP, McCorvy JD, Kroeze WK, Che T, Nagase H, Carroll FI, Jin J, Shoichet BK, Roth BL: *In silico* design of novel probes for the atypical opioid receptor MRGPRX2. Nat Chem Biol 2017; 13:529–36
59. Grosman N: Histamine release from isolated rat mast cells: Effect of morphine and related drugs and their interaction with compound 48/80. Agents Actions 1981; 11:196–203
60. Hermens JM, Ebertz JM, Hanifin JM, Hirshman CA: Comparison of histamine release in human skin mast cells induced by morphine, fentanyl, and oxymorphone. Anesthesiology 1985; 62:124–9
61. Porebski G, Kwiecien K, Pawica M, Kwitniewski M: Mas-related G protein–coupled receptor-X2 (MRGPRX2) in drug hypersensitivity reactions. Front Immunol 2018; 9:3027
62. Meixiong J, Anderson M, Limjunyawong N, Sabbagh MF, Hu E, Mack MR, Oetjen LK, Wang F, Kim BS, Dong X: Activation of mast-cell-expressed mas-related G-protein-coupled receptors drives non-histaminergic itch. Immunity 2019; 50:1163–71.e5
63. Laxenaire MC, Moneret-Vautrin DA, Widmer S, Mouton C, Guéant JL, Bonnet MC, Bricard H, Facon A, Lesage F, Valfrey J: [Anesthetics responsible for anaphylactic shock. A French multicenter study.] Ann Fr Anesth Reanim 1990; 9:501–6
64. Rosow CE, Moss J, Philbin DM, Savarese JJ: Histamine release during morphine and fentanyl anesthesia. Anesthesiology 1982; 56:93–6
65. Warner MA, Hosking MP, Gray JR, Squillace DL, Yunginger JW, Orszulak TA: Narcotic-induced histamine release: A comparison of morphine, oxymorphone, and fentanyl infusions. J Cardiothorac Vasc Anesth 1991; 5:481–4
66. Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ: Histamine release by four narcotics: A double-blind study in humans. Anesth Analg 1987; 66:723–30
67. Sjöström S, Tamsen A, Persson MP, Hartvig P: Pharmacokinetics of intrathecal morphine and meperidine in humans. Anesthesiology 1987; 67:889–95
68. Bernards CM, Shen DD, Sterling ES, Adkins JE, Risler L, Phillips B, Ummenhofer W: Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids: Part 1. Differences among opioids. Anesthesiology 2003; 99:455–65
69. Ko MC: Neuraxial opioid–induced itch and its pharmacological antagonism. Handb Exp Pharmacol 2015; 226:315–35
70. Pathan H, Williams J: Basic opioid pharmacology: An update. Br J Pain 2012; 6:11–6
71. Pan Z, Hirakawa N, Fields HL: A cellular mechanism for the bidirectional pain-modulating actions of orphanin FQ/nociceptin. Neuron 2000; 26:515–22
72. Simmons SW, Taghizadeh N, Dennis AT, Hughes D, Cyna AM: Combined spinal-epidural *versus* epidural analgesia in labour. Cochrane Database Syst Rev 2012; 10:CD003401
73. Asokumar B, Newman LM, McCarthy RJ, Ivankovich AD, Tuman KJ: Intrathecal bupivacaine reduces pruritus and prolongs duration of fentanyl analgesia during labor: A prospective, randomized controlled trial. Anesth Analg 1998; 87:1309–15

74. Shim WS, Oh U: Histamine-induced itch and its relationship with pain. Mol Pain 2008; 4:29
75. Davidson S, Giesler GJ: The multiple pathways for itch and their interactions with pain. Trends Neurosci 2010; 33:550–8
76. Schmelz M, Schmidt R, Bickel A, Handwerker HO, Torebjörk HE: Specific C-receptors for itch in human skin. J Neurosci 1997; 17:8003–8
77. Wilson SR, Nelson AM, Batia L, Morita T, Estandian D, Owens DM, Lumpkin EA, Bautista DM: The ion channel TRPA1 is required for chronic itch. J Neurosci 2013; 33:9283–94
78. Wilson SR, Gerhold KA, Bifolck-Fisher A, Liu Q, Patel KN, Dong X, Bautista DM: TRPA1 is required for histamine-independent, Mas-related G protein–coupled receptor-mediated itch. Nat Neurosci 2011; 14:595–602
79. Moser HR, Giesler GJ Jr: Itch and analgesia resulting from intrathecal application of morphine: Contrasting effects on different populations of trigeminothalamic tract neurons. J Neurosci 2013; 33:6093–101
80. Sakakibara S, Imamachi N, Sakakihara M, Katsube Y, Hattori M, Saito Y: Effects of an intrathecal TRPV1 antagonist, SB366791, on morphine-induced itch, body temperature, and antinociception in mice. J Pain Res 2019; 12:2629–36
81. Liu T, Ji RR: New insights into the mechanisms of itch: Are pain and itch controlled by distinct mechanisms? Pflugers Arch 2013; 465:1671–85
82. Graham DT, Goodell H, Wolff HG: Neural mechanisms involved in itch, itchy skin, and tickle sensations. J Clin Invest 1951; 30:37–49
83. Ko MC, Naughton NN: An experimental itch model in monkeys: Characterization of intrathecal morphine–induced scratching and antinociception. Anesthesiology 2000; 92:795–805
84. Woolf CJ: μ and δ opioid receptors diverge. Cell 2009; 137:987–8
85. Ko MC, Lee H, Song MS, Sobczyk-Kojiro K, Mosberg HI, Kishioka S, Woods JH, Naughton NN: Activation of κ-opioid receptors inhibits pruritus evoked by subcutaneous or intrathecal administration of morphine in monkeys. J Pharmacol Exp Ther 2003; 305:173–9
86. Kamei J, Nagase H: Norbinaltorphimine, a selective κ-opioid receptor antagonist, induces an itch-associated response in mice. Eur J Pharmacol 2001; 418:141–5
87. Ko MC, Husbands SM: Effects of atypical κ-opioid receptor agonists on intrathecal morphine–induced itch and analgesia in primates. J Pharmacol Exp Ther 2009; 328:193–200
88. Kardon AP, Polgár E, Hachisuka J, Snyder LM, Cameron D, Savage S, Cai X, Karnup S, Fan CR, Hemenway GM, Bernard CS, Schwartz ES, Nagase H, Schwarzer C, Watanabe M, Furuta T, Kaneko T, Koerber HR, Todd AJ, Ross SE: Dynorphin acts as a neuromodulator to inhibit itch in the dorsal horn of the spinal cord. Neuron 2014; 82:573–86
89. Cowan A, Kehner GB, Inan S: Targeting itch with ligands selective for κ opioid receptors. Handb Exp Pharmacol 2015; 226:291–314
90. Pfeiffer A, Brantl V, Herz A, Emrich HM: Psychotomimesis mediated by κ opiate receptors. Science 1986; 233:774–6
91. Pan ZZ: μ-Opposing actions of the κ-opioid receptor. Trends Pharmacol Sci 1998; 19:94–8
92. Sun YG, Chen ZF: A gastrin-releasing peptide receptor mediates the itch sensation in the spinal cord. Nature 2007; 448:700–3
93. Pagani M, Albisetti GW, Sivakumar N, Wildner H, Santello M, Johannssen HC, Zeilhofer HU: How gastrin-releasing peptide opens the spinal gate for itch. Neuron 2019; 103:102–117.e5
94. Sathyamurthy A, Johnson KR, Matson KJE, Dobrott CI, Li L, Ryba AR, Bergman TB, Kelly MC, Kelley MW, Levine AJ: Massively parallel single nucleus transcriptional profiling defines spinal cord neurons and their activity during behavior. Cell Rep 2018; 22:2216–25
95. Häring M, Zeisel A, Hochgerner H, Rinwa P, Jakobsson JET, Lönnerberg P, La Manno G, Sharma N, Borgius L, Kiehn O, Lagerström MC, Linnarsson S, Ernfors P: Neuronal atlas of the dorsal horn defines its architecture and links sensory input to transcriptional cell types. Nat Neurosci 2018; 21:869–80
96. Al-Hasani R, Bruchas MR: Molecular mechanisms of opioid receptor-dependent signaling and behavior. Anesthesiology 2011; 115:1363–81
97. Torrecilla M, Quillinan N, Williams JT, Wickman K: Pre- and postsynaptic regulation of locus coeruleus neurons after chronic morphine treatment: A study of GIRK-knockout mice. Eur J Neurosci 2008; 28:618–24
98. Ross SE, Mardinly AR, McCord AE, Zurawski J, Cohen S, Jung C, Hu L, Mok SI, Shah A, Savner EM, Tolias C, Corfas R, Chen S, Inquimbert P, Xu Y, McInnes RR, Rice FL, Corfas G, Ma Q, Woolf CJ, Greenberg ME: Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. Neuron 2010; 65:886–98
99. Huang J, Polgár E, Solinski HJ, Mishra SK, Tseng PY, Iwagaki N, Boyle KA, Dickie AC, Kriegbaum MC, Wildner H, Zeilhofer HU, Watanabe M, Riddell JS, Todd AJ, Hoon MA: Circuit dissection of the role of somatostatin in itch and pain. Nat Neurosci 2018; 21:707–16
100. Acton D, Ren X, Di Costanzo S, Dalet A, Bourane S, Bertocchi I, Eva C, Goulding M: Spinal neuropeptide Y1 receptor–expressing neurons form an essential excitatory pathway for mechanical itch. Cell Rep 2019; 28:625–39.e6

101. Bourane S, Duan B, Koch SC, Dalet A, Britz O, Garcia-Campmany L, Kim E, Cheng L, Ghosh A, Ma Q, Goulding M: Gate control of mechanical itch by a subpopulation of spinal cord interneurons. Science 2015; 350:550–4
102. Sultan P, Gutierrez MC, Carvalho B: Neuraxial morphine and respiratory depression: Finding the right balance. Drugs 2011; 71:1807–19
103. Ngan Kee WD, Khaw KS, Ng FF, Ng KK, So R, Lee A: Synergistic interaction between fentanyl and bupivacaine given intrathecally for labor analgesia. Anesthesiology 2014; 120:1126–36
104. Horta ML, Morejon LC, da Cruz AW, Dos Santos GR, Welling LC, Terhorst L, Costa RC, Alam RU: Study of the prophylactic effect of droperidol, alizapride, propofol and promethazine on spinal morphine-induced pruritus. Br J Anaesth 2006; 96:796–800
105. Anwari JS, Iqbal S: Antihistamines and potentiation of opioid induced sedation and respiratory depression. Anaesthesia 2003; 58:494–5
106. Roth T, Roehrs T, Koshorek G, Sicklesteel J, Zorick F: Sedative effects of antihistamines. J Allergy Clin Immunol 1987; 80:94–8
107. Cohen SE, Ratner EF, Kreitzman TR, Archer JH, Mignano LR: Nalbuphine is better than naloxone for treatment of side effects after epidural morphine. Anesth Analg 1992; 75:747–52
108. Rzasa Lynn R, Galinkin JL: Naloxone dosage for opioid reversal: Current evidence and clinical implications. Ther Adv Drug Saf 2018; 9:63–88
109. Kendrick WD, Woods AM, Daly MY, Birch RF, DiFazio C: Naloxone *versus* nalbuphine infusion for prophylaxis of epidural morphine-induced pruritus. Anesth Analg 1996; 82:641–7
110. Charuluxananan S, Kyokong O, Somboonviboon W, Narasethakamol A, Promlok P: Nalbuphine *versus* ondansetron for prevention of intrathecal morphine–induced pruritus after cesarean delivery. Anesth Analg 2003; 96:1789–93
111. Sarvela PJ, Halonen PM, Soikkeli AI, Kainu JP, Korttila KT: Ondansetron and tropisetron do not prevent intraspinal morphine- and fentanyl-induced pruritus in elective cesarean delivery. Acta Anaesthesiol Scand 2006; 50:239–44
112. Yazigi A, Chalhoub V, Madi-Jebara S, Haddad F, Hayek G: Prophylactic ondansetron is effective in the treatment of nausea and vomiting but not on pruritus after cesarean delivery with intrathecal sufentanil-morphine. J Clin Anesth 2002; 14:183–6
113. Siddik-Sayyid SM, Aouad MT, Taha SK, Azar MS, Hakki MA, Kaddoum RN, Nasr VG, Yazbek VG, Baraka AS: Does ondansetron or granisetron prevent subarachnoid morphine-induced pruritus after cesarean delivery? Anesth Analg 2007; 104:421–4
114. Kyriakides K, Hussain SK, Hobbs GJ: Management of opioid-induced pruritus: A role for 5-HT3 antagonists? Br J Anaesth 1999; 82:439–41
115. Bonnet MP, Marret E, Josserand J, Mercier FJ: Effect of prophylactic 5-HT3 receptor antagonists on pruritus induced by neuraxial opioids: A quantitative systematic review. Br J Anaesth 2008; 101:311–9
116. Törn K, Tuominen M, Tarkkila P, Lindgren L: Effects of sub-hypnotic doses of propofol on the side effects of intrathecal morphine. Br J Anaesth 1994; 73:411–2
117. Warwick JP, Kearns CF, Scott WE: The effect of subhypnotic doses of propofol on the incidence of pruritus after intrathecal morphine for caesarean section. Anaesthesia 1997; 52:270–5
118. Anand S: Gabapentin for pruritus in palliative care. Am J Hosp Palliat Care 2013; 30:192–6
119. Yesudian PD, Wilson NJ: Efficacy of gabapentin in the management of pruritus of unknown origin. Arch Dermatol 2005; 141:1507–9
120. Akhan A, Subasi FD, Bosna G, Ekinci O, Pamuk H, Batan S, Ateser RY, Turan G: Comparison of mirtazapine, gabapentin and ondansetron to prevent intrathecal morphine–induced pruritus. North Clin Istanb 2016; 3:53–9
121. Kharasch ED, Clark JD, Kheterpal S: Perioperative gabapentinoids: Deflating the bubble. Anesthesiology 2020; 133:251–4
122. Horta ML, Ramos L, Gonçalves ZR: The inhibition of epidural morphine-induced pruritus by epidural droperidol. Anesth Analg 2000; 90:638–41
123. Wood PB: Role of central dopamine in pain and analgesia. Expert Rev Neurother 2008; 8:781–97
124. McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, Lau J, Carr D; Americal Pain Society: Management of opioid side effects in cancer-related and chronic noncancer pain: A systematic review. J Pain 2003; 4:231–56
125. Liao CC, Chang CS, Tseng CH, Sheen MJ, Tsai SC, Chang YL, Wong SY: Efficacy of intramuscular nalbuphine *versus* diphenhydramine for the prevention of epidural morphine-induced pruritus after cesarean delivery. Chang Gung Med J 2011; 34:172–8
126. Eldor J, Fishelev V, Levine S, Guedj P, Dudakova I: Prevention of epidural morphine pruritus by intramuscular promethazine in parturients. Reg Anesth 1994; 19:433–4
127. Millington GWM, Collins A, Lovell CR, Leslie TA, Yong ASW, Morgan JD, Ajithkumar T, Andrews MJ, Rushbook SM, Coelho RR, Catten SJ, Lee KYC, Skellett AM, Affleck AG, Exton LS, Mohd Mustapa MF, Levell NJ: British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018. Br J Dermatol 2018; 178:34–60

128. Kamei J, Hirano S, Miyata S, Saitoh A, Onodera K: Effects of first- and second-generation histamine-H1-receptor antagonists on the pentobarbital-induced loss of the righting reflex in streptozotocin-induced diabetic mice. J Pharmacol Sci 2005; 97:266–72
129. Dunteman E, Karanikolas M, Filos KS: Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. J Pain Symptom Manage 1996; 12:255–60
130. Somrat C, Oranuch K, Ketchada U, Siriprapa S, Thipawan R: Optimal dose of nalbuphine for treatment of intrathecal-morphine induced pruritus after caesarean section. J Obstet Gynaecol Res 1999; 25:209–13
131. Juneja MM, Ackerman WE 3rd, Bellinger K: Epidural morphine pruritus reduction with hydroxyzine in parturients. J Ky Med Assoc 1991; 89:319–21
132. Miller JL, Hagemann TM: Use of pure opioid antagonists for management of opioid-induced pruritus. Am J Health Syst Pharm 2011; 68:1419–25
133. Kjellberg F, Tramèr MR: Pharmacological control of opioid-induced pruritus: A quantitative systematic review of randomized trials. Eur J Anaesthesiol 2001; 18:346–57
134. Maxwell LG, Kaufmann SC, Bitzer S, Jackson EV Jr, McGready J, Kost-Byerly S, Kozlowski L, Rothman SK, Yaster M: The effects of a small-dose naloxone infusion on opioid-induced side effects and analgesia in children and adolescents treated with intravenous patient-controlled analgesia: A double-blind, prospective, randomized, controlled study. Anesth Analg 2005; 100:953–8
135. Levy JH, Brister NW, Shearin A, Ziegler J, Hug CC Jr, Adelson DM, Walker BF: Wheal and flare responses to opioids in humans. Anesthesiology 1989; 70:756–60
136. Charuluxananan S, Kyokong O, Somboonviboon W, Lertmaharit S, Ngamprasertwong P, Nimcharoendee K: Nalbuphine *versus* propofol for treatment of intrathecal morphine–induced pruritus after cesarean delivery. Anesth Analg 2001; 93:162–5
137. Lawhorn CD, McNitt JD, Fibuch EE, Joyce JT, Leadley RJ Jr: Epidural morphine with butorphanol for postoperative analgesia after cesarean delivery. Anesth Analg 1991; 72:53–7
138. Lee H, Naughton NN, Woods JH, Ko MC: Effects of butorphanol on morphine-induced itch and analgesia in primates. Anesthesiology 2007; 107:478–85
139. Goletiani NV, Mendelson JH, Sholar MB, Siegel AJ, Skupny A, Mello NK: Effects of nalbuphine on anterior pituitary and adrenal hormones and subjective responses in male cocaine abusers. Pharmacol Biochem Behav 2007; 86:667–77
140. Gunter JB, McAuliffe J, Gregg T, Weidner N, Varughese AM, Sweeney DM: Continuous epidural butorphanol relieves pruritus associated with epidural morphine infusions in children. Paediatr Anaesth 2000; 10:167–72
141. Bailey AG, Valley RD, Freid EB, Calhoun P: Epidural morphine combined with epidural or intravenous butorphanol for postoperative analgesia in pediatric patients. Anesth Analg 1994; 79:340–4
142. Hawi A, Alcorn H Jr, Berg J, Hines C, Hait H, Sciascia T: Pharmacokinetics of nalbuphine hydrochloride extended release tablets in hemodialysis patients with exploratory effect on pruritus. BMC Nephrol 2015; 16:47
143. Reszke R, Szepietowski JC: End-stage renal disease chronic itch and its management. Dermatol Clin 2018; 36:277–92
144. Inan S, Torres-Huerta A, Jensen LE, Dun NJ, Cowan A: Nalbuphine, a κ opioid receptor agonist and μ opioid receptor antagonist attenuates pruritus, decreases IL-31, and increases IL-10 in mice with contact dermatitis. Eur J Pharmacol 2019; 864:172702
145. Smith MC, Williamson J, Yaster M, Boyd GJ, Heitmiller ES: Off-label use of medications in children undergoing sedation and anesthesia. Anesth Analg 2012; 115:1148–54
146. Umeuchi H, Togashi Y, Honda T, Nakao K, Okano K, Tanaka T, Nagase H: Involvement of central μ-opioid system in the scratching behavior in mice, and the suppression of it by the activation of κ-opioid system. Eur J Pharmacol 2003; 477:29–35
147. Togashi Y, Umeuchi H, Okano K, Ando N, Yoshizawa Y, Honda T, Kawamura K, Endoh T, Utsumi J, Kamei J, Tanaka T, Nagase H: Antipruritic activity of the κ-opioid receptor agonist, TRK-820. Eur J Pharmacol 2002; 435:259–64
148. Kozono H, Yoshitani H, Nakano R: Post-marketing surveillance study of the safety and efficacy of nalfurafine hydrochloride (Remitch® capsules 2.5 μg) in 3,762 hemodialysis patients with intractable pruritus. Int J Nephrol Renovasc Dis 2018; 11:9–24
149. Akiyama T, Carstens MI, Piecha D, Steppan S, Carstens E: Nalfurafine suppresses pruritogen- and touch-evoked scratching behavior in models of acute and chronic itch in mice. Acta Derm Venereol 2015; 95:147–50
150. Mores KL, Cummins BR, Cassell RJ, van Rijn RM: A review of the therapeutic potential of recently developed G protein-biased κ agonists. Front Pharmacol 2019; 10:407
151. European Medicines Agency: Assessment report: Winfuran. European Medicines Agency. Committee for Medicinal Products for Human Use; 2013
152. Brust TF, Morgenweck J, Kim SA, Rose JH, Locke JL, Schmid CL, Zhou L, Stahl EL, Cameron MD, Scarry SM, Aubé J, Jones SR, Martin TJ, Bohn LM: Biased agonists of the κ opioid receptor suppress pain and

itch without causing sedation or dysphoria. Sci Signal 2016; 9:ra117
153. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H: Effect of a novel κ-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: A phase III, randomized, double-blind, placebo-controlled study. Nephrol Dial Transplant 2010; 25:1251–7
154. Grangier L, Martinez de Tejada B, Savoldelli GL, Irion O, Haller G: Adverse side effects and route of administration of opioids in combined spinal-epidural analgesia for labour: A meta-analysis of randomised trials. Int J Obstet Anesth 2020; 41:83–103
155. Norris MC, Grieco WM, Borkowski M, Leighton BL, Arkoosh VA, Huffnagle HJ, Huffnagle S: Complications of labor analgesia: Epidural *versus* combined spinal epidural techniques. Anesth Analg 1994; 79:529–37
156. George RB, Allen TK, Habib AS: Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing cesarean delivery with intrathecal morphine: A systematic review and meta-analysis. Anesth Analg 2009; 109:174–82
157. Morales M, Battenberg E, Bloom FE: Distribution of neurons expressing immunoreactivity for the 5HT3 receptor subtype in the rat brain and spinal cord. J Comp Neurol 1998; 402:385–401
158. Marinelli S, Vaughan CW, Schnell SA, Wessendorf MW, Christie MJ: Rostral ventromedial medulla neurons that project to the spinal cord express multiple opioid receptor phenotypes. J Neurosci 2002; 22:10847–55
159. Zhao ZQ, Liu XY, Jeffry J, Karunarathne WK, Li JL, Munanairi A, Zhou XY, Li H, Sun YG, Wan L, Wu ZY, Kim S, Huo FQ, Mo P, Barry DM, Zhang CK, Kim JY, Gautam N, Renner KJ, Li YQ, Chen ZF: Descending control of itch transmission by the serotonergic system via 5-HT1A-facilitated GRP-GRPR signaling. Neuron 2014; 84:821–34
160. Borgeat A, Wilder-Smith OH, Saiah M, Rifat K: Subhypnotic doses of propofol relieve pruritus induced by epidural and intrathecal morphine. Anesthesiology 1992; 76:510–2
161. Gunal AI, Ozalp G, Yoldas TK, Gunal SY, Kirciman E, Celiker H: Gabapentin therapy for pruritus in haemodialysis patients: A randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant 2004; 19:3137–9
162. Sheen MJ, Ho ST, Lee CH, Tsung YC, Chang FL: Preoperative gabapentin prevents intrathecal morphine–induced pruritus after orthopedic surgery. Anesth Analg 2008; 106:1868–72
163. Chiravanich W, Oofuvong M, Kovitwanawong N: Single dose of gabapentin for prophylaxis intrathecal morphine–induced pruritus in orthopedic surgery: A randomized controlled trial. J Med Assoc Thai 2012; 95:186–90
164. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, Leblanc G, Cossi MJ, Neveu X, Turgeon AF; Canadian Perioperative Anesthesia Clinical Trials (PACT) Group: Perioperative use of gabapentinoids for the management of postoperative acute pain: A systematic review and meta-analysis. Anesthesiology 2020; 133:265–79
165. Horta ML, Vianna PT: Effect of intravenous alizapride on spinal morphine-induced pruritus. Br J Anaesth 2003; 91:287–9
166. Jackson CW, Sheehan AH, Reddan JG: Evidence-based review of the black-box warning for droperidol. Am J Health Syst Pharm 2007; 64:1174–86
167. Arendt K, Segal S: Why epidurals do not always work. Rev Obstet Gynecol 2008; 1:49–55