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REVIEW ARTICLE

Mechanisms and treatment of opioid-induced pruritus: Peripheral and central pathways

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Abstract

Background and Objective: Pruritus (also known as itch) is defined as an unpleasant and irritating sensation of the skin that provokes an urge to scratch or rub. It is well known that opioid administration can cause pruritus, which is paradoxical as itch and pain share overlapping sensory pathways. Because opioids inhibit pain but can cause itching. Significant progress has been made to improve our understanding of the fundamental neurobiology of itch; however, much remains unknown about the mechanisms of opioid-induced pruritus. The prevention and treatment of opioid-induced pruritus remains a challenge in the field of pain management. The objective of this narrative review is to present and discuss the current body of literature and summarize the current understanding of the mechanisms underlying opioid-induced pruritus, and its relationship to analgesia, and possible treatment options.

Results: The incidence of opioid-induced pruritus differs with different opioids and routes of administration, and the various mechanisms can be broadly divided into peripheral and central. Especially central mechanisms are intricate, even at the level of the spinal dorsal horn. There is evidence that opioid receptor antagonists and mixed agonist and antagonists, especially μ-opioid antagonists and κ-opioid agonists, are effective in relieving opioid-induced pruritus. Various treatments have been used for opioid-induced pruritus; however, most of them are controversial and have conflicting results.

Conclusion: The use of a multimodal analgesic treatment regimen combined with a mixed antagonist and κ agonists, especially μ-opioid antagonists, and κ-opioid agonists, seems to be the current best treatment modality for the management of opioid-induced pruritus and pain.

Significance: Opioids remain the gold standard for the treatment of moderate to severe acute pain as well as cancer pain. It is well known that opioid-induced pruritus often does not respond to regular antipruritic treatment, thereby posing a challenge to clinicians in the field of pain management. We believe that our review makes a significant contribution to the literature, as studies on the

mechanisms of opioid-induced pruritus and effective management strategies are crucial for the management of these patients.

1 | INITIAL CONSIDERATIONS

In this review, the authors present and discuss the currently available literature and summarize the current knowledge of the mechanisms underlying opioid-induced pruritus, their relationship with pain aspects, and the possible treatment options to counteract this phenomenon. The review by Nguyen et al., published in June 2021 in *Anesthesiology*, summarizes the clinical aspects related to opioid-induced pruritus and empathizes some genetic aspects and new emerging preclinical treatments, such as nalfurafine. Although the two reviews show similarities in the sections summarizing the incidence and peripheral and central mechanisms of opioid-induced pruritus, they also show some dissimilarities.

Compared with the review by Nguyen et al., 2021 the focus of the current review is more on the clinical itch treatment outcomes. In the current review, the authors present a detailed overview of the itch mechanisms, including the similarities and differences between pain mechanisms, which is essential for understanding the paradoxical phenomenon of 'opioids inhibiting pain but causing itch'. The present review illustrates, in detail, the fibres and receptors involved in itch perception and underlines the molecular aspects of specific mechanisms of opioid-induced itch.

This review presents various treatment modalities that may be effective for pruritus from the perspective of the relationship between pain and itch mechanisms. Opioid-induced pruritus is a common condition, but due to its low severity, patients are traditionally prescribed antihistamines and thereby left with insufficient antipruritic efficacy. As there are limited clinical studies based on current evidence, further studies are required to address the clinical and off-label use of drugs for the treatment of opioid-induced pruritis.

2 | INTRODUCTION

Although several types of analgesics are available, opioids remain the gold standard for the short-term treatment of moderate to severe acute pain and cancer pain (Bonnet et al., 2010). Spinal and epidural morphine are highly effective for the management of postoperative pain and are widely used for analgesia during caesarean sections (*Anesthesiology*, 2016; Duale et al., 2003; Sharpe et al., 2020). Opioids are effective; however, they frequently cause pruritus (also known as itch) as a side effect, with the highest incidence (30%–90%) observed following neuraxial administration (Bonnet et al., 2010; Colbert, O'Hanlon, Galvin, et al., 1999).

Pruritus can be more troubling than pain, and it can significantly impair the quality of life of patients (Ballantyne et al., 1988; Tan et al., 2019). Since itch and pain rely on proportions of the same population of sensory neurons, especially small unmyelinated nerve fibres (C-fibres) (Carstens, 2016; Colbert, O'Hanlon, Galvin, et al., 1999; LaMotte et al., 2014; Yosipovitch & Bernhard, 2013), it is not fully understood why opioids relieve pain but elicit itch (Ikoma et al., 2006; Reich & Szepietowski, 2010; Schmelz, 2009) that is difficult to treat and is refractory to conventional antipruritic treatments (Kumar & Singh, 2013). Therefore, the prevention and treatment of opioid-induced pruritus remain challenging in the field of pain management.

The purpose of this review is to summarize the basic and clinical findings and discuss the possible mechanisms underlying opioid-induced pruritus and possible ways to counteract this effect. The literature source for this review was obtained by searching the database of PubMed for reports published in English between 1978 and 2023.

3 | SIMILARITIES AND DISSIMILARITIES BETWEEN ITCH AND PAIN

There are several similarities and dissimilarities between itch and pain. Both sensations are uncomfortable and protect the body from harmful stimuli, and organisms learn from past experiences to avoid future exposures (Hachisuka et al., 2018). Itch is defined as an unpleasant sensory perception that causes an intense desire to scratch to remove the irritant, whereas an acute pain stimulus causes a withdrawal response. Thus, itch and pain have distinct sensations and characteristic nocifensive behaviours; however, counter stimuli, such as scratching, lead to the suppression of the itch sensation, and opioids are contradictory in suppressing pain but enhancing itch. Several points of similarity or dissimilarity exist across the transmitting pathway: primary afferents, neurotransmitters, and the dorsal horn (Carstens et al., 2021). Several experiments involving animals and humans have been conducted to elucidate how these sensations can be distinguished. The somatosensory pathways of itch and pain are closely related. The transduction fibres that transmit both signals include unmyelinated C-fibres and thinly

myelinated A-fibres (Davidson, 2021). These fibres can be classified as peptidergic and non-peptidergic or based on mechanical, thermal, and chemical sensitivities (LaMotte et al., 2014). Noxious stimulation activates pruritic-responsive neurons as well as nociceptive neurons; therefore, it is unclear whether the signal is transmitted by identical fibres or labelled lines. Several itch-provoking mediators, such as histamine and serotonin (5-HT), also induce pain, and several receptors or ion channels, such as transient receptor potential cation channel V1 (TRPV1) and transient receptor potential ankyrin1 (TRPA1), play a pivotal role in itch and pain transduction (Ross, 2011). For instance, allyl isothiocyanate activates TRPA1 and TRPV1, causing pain and, to some extent, itch (Sheahan et al., 2018).

In mouse experiments, three neuronal populations, the mas-related G protein-coupled receptor (Mrgpr) A3 population, Mrgpr D neurons, and somatostatin neurons, have been found to be sensitive to pruritogens (Ringkamp, 2021). The central axons of MrgprA3-expressing primary sensory neurons connect with gastrin-releasing peptide receptor (GRPR)-expressing neurons in the spinal dorsal horn, and it has been demonstrated that they represent itch-specific neuronal pathways (Han et al., 2013). The results of mouse experiments favour the labelled line theory; however, itching remains controversial in primates.

It is shown that μ-receptor agonists such as morphine have analgesic effects without inhibition of itch sensation, whereas μ-receptor antagonists such naloxone inhibit itch but not pain (Akiyama et al., 2010). This could indicate that central specificity exists for the separate sensations of itch and pain, even though pruritic and algesic stimulation excite overlapping populations of nociceptors, spinal neurons, and ascending sensory pathways. The neural mechanisms and theories of itch-pain discrimination between them have been discussed for more than a century, and several theories have been advocated in the field. (1) Specificity theory (Labelled line theory): Primary afferent fibres selectively conveyed in signalling itch or pain connect to the central pathway. (2) Intensity theory: With changes in the neuron firing rate, strong sensory perception causes pain, and less perception causes itching. (3) Selectivity theory: It basically follows the specific theory, but it involves inhibitory modulation of itch transmission through inhibitory interneurons by nociceptive inputs. (4) Leaky gate theory: Like the intensity theory, a common population of GRP-expressing spinal neurons is excited by both pruriceptive and nociceptive inputs, signalling itch and pain simultaneously. Pain is inhibited through enkephalinergic feed-forward inhibition by strong nociceptive input. (5) Spatial contrast theory: Nociceptive nerve endings elicit itch sensations by focal stimulation, on the other hand, pain is induced by the mobilization of a larger nociceptor population (Carstens et al., 2020).

4 | MECHANISM OF PRURITUS

4.1 | General mechanism of pruritus

Free nerve endings of primary afferents in the skin are responsible for detecting pruritogens (Roosterman et al., 2006). A subset of nociceptive mechano-insensitive unmyelinated C-fibres transmits histaminergic itch via histamine receptors, such as histamine 1 and 4 receptors, which have been detected in dorsal root ganglion (DRG) neurons (Han et al., 2006). The histamine receptor is a G-protein-coupled receptor that activates an intracellular second messenger signalling cascade leading to the activation of TRPV1. After stimulating the phospholipase A2 and lipoxygenase pathways, the sensory neurons are excited as a result (Kim et al., 2004). Antihistamines have limited effects on opioid-induced pruritus, and a possible sedative effect may suppress the itch-scratch cycle (Krajnik & Zylicz, 2001). As histamine-induced itch is related to TRPV1, intrathecal TRPV1 antagonists can suppress morphine-induced itch without causing hyperthermia or morphine-induced antinociception in mice (Sakakibara et al., 2019). Conversely, it has been reported that TRPV1 antagonists may not effectively alleviate pruritus induced by histamine and cowhage in healthy volunteers (Gibson et al., 2014).

Based on the labelled line theory, protease-activated receptor 2 (PAR2)-mediated mast cell tryptase-induced itch signalling is distinct from histamine-induced itch; thus, a subset of nociceptive mechano-heat C-fibres (or 'polymodal nociceptors') transmits non-histaminergic itch (e.g., PAR2 signalling pathway) via TRPA1 (Figure 1; Carstens & Akiyama, 2016; Jian et al., 2016; LaMotte et al., 2014; Schmelz et al., 1997). PAR-2 interaction with tryptase initiates a signalling cascade involving TRPV1/4 and TRPA1 activation via phospholipase C (PLC) and protein kinase A/C (PKA/PKC) (Chen et al., 2011). There is an association between serotonin administration and 5-HT7 activation, which leads to the activation of downstream TRPA1 through phospholipase beta 3 (Imamachi et al., 2009; Morita et al., 2015).

The descending modulation pathway is also important for the pruriceptive pathway as well as for nociceptive signalling. The descending 5-hydroxytryptamine serotonergic pathway facilitates GRP-GRPR signalling via 5-HT1A (Zhao et al., 2014). Moreover, the descending noradrenergic system affects the continuous inhibition of itch signalling in the spinal cord, possibly by activating the inhibitory interneurons (Braz,

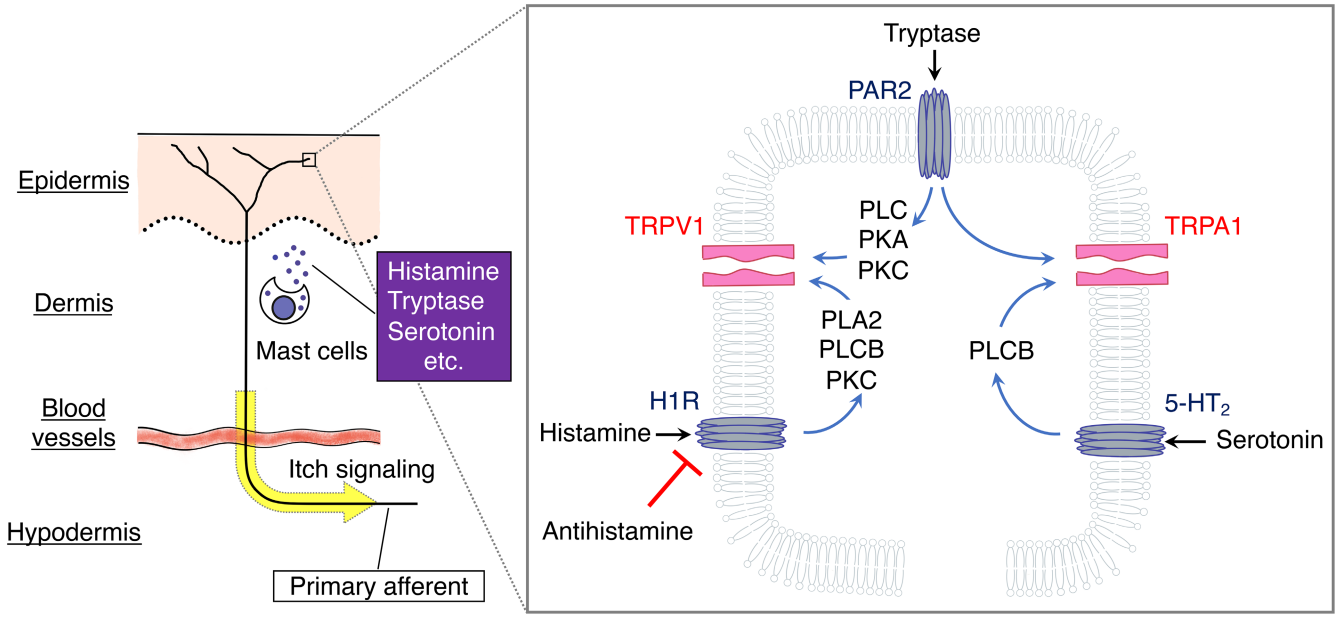

FIGURE 1 Peripheral itch pathway involving mast cell degranulation. Activated mast cells release histamine, tryptase, serotonin, and other substances. G protein-coupled receptors (gray transmembrane receptors) require ion channels (pink channels) such as TRPV1 and TRPA1. Histamine activates TRPV1 and serotonin-induced itch associated with 5-HT activation and downstream TRPA1 activity. PAR2 is involved with both TRPA1 and TRPV1. 5-HT_2 5-hydroxytryptamine; H1R, histamine 1 receptor; PAR2, protease-activated receptor 2; PKC, protein kinases C; PLA2, phospholipase A_2; PLCB, phospholipase Cβ; TRPA1, transient receptor potential ankyrin1; TRPV1, transient receptor potential vanilloid 1.

Solorzano, et al., 2014; Carstens & Akiyama, 2016; Gotoh et al., 2011). Nguyen et al. identified that rostral ventromedial medulla κ-opioids receptor neurons inhibit nociception and itch sensation through a descending modulation pathway (Nguyen et al., 2022).

4.2 | Specific mechanism of opioid-induced pruritus

The various mechanisms underlying opioid-induced pruritus can be broadly divided into peripheral and central (Reich & Szepietowski, 2010). The peripheral effect is assumed to be mainly mediated via mast cell destabilization (Adler et al., 1979; Casale et al., 1984; McNeil & Dong, 2012), whereas the central effect is mainly mediated via spinal disinhibitory mechanisms (Hagermark, 1992; Ikoma et al., 2006; McMahon & Koltzenburg, 1992).

Opioid receptor agonists and antagonists have been shown to cause mast cell degranulation in the skin (Hermens et al., 1985; Levy et al., 1989). Morphine, codeine, and meperidine cause a non-immunologic release of histamine (Waxler et al., 2005) that stimulates the H1R present on itch-specific C-fibres in humans (Schmelz et al., 1997) and after the intradermal injection of morphine in mice (Nakasone et al., 2016). However, Ko et al. showed that histamine release due to mast cell degranulation may not be the predominant mechanism in primates (Ko et al., 2004), and they concluded that, in mice, the antipruritic effect of centrally acting antihistamines on neuraxial morphine-induced itch is caused by a secondary sedative effect (Nguyen et al., 2021). The opioid receptor antagonist naloxone does not inhibit morphine-induced histamine release in the human skin (Hermens et al., 1985). Studies using intradermal microdialysis suggested that mast cell degranulation induced by codeine and meperidine did not depend on μ-opioid receptors but on the direct activation of the G-proteins of mast cells (Blunk et al., 2004). Morphine can release histamine from mast cells. However, antihistamines are often ineffective for patients (Krajnik & Zylicz, 2001). This is because mast cells can release histamine as well as other itch-related chemical mediators, such as tryptase and interleukin-4 (Metcalfe et al., 1997), and mast cell mediators, serotonin, leukotriene, and sphingosine-1-phosphate that directly stimulate Natriuretic Polypeptide type-B (NPPB) sensory neurons and convey itch signals through the gastrin-releasing peptide (GRP) pathway in the spinal dorsal horn (Solinski et al., 2019).

In contrast, several neuropeptides, such as substance P (Carstens et al., 2010), GRP (Sun et al., 2009; Tang et al., 2007), and NPPB, are released from the central terminals of pruriceptors. Nppb is a pivotal peptide for histaminergic and non-histaminergic itch (Figure 2; Mishra & Hoon, 2013). It has been suggested that the

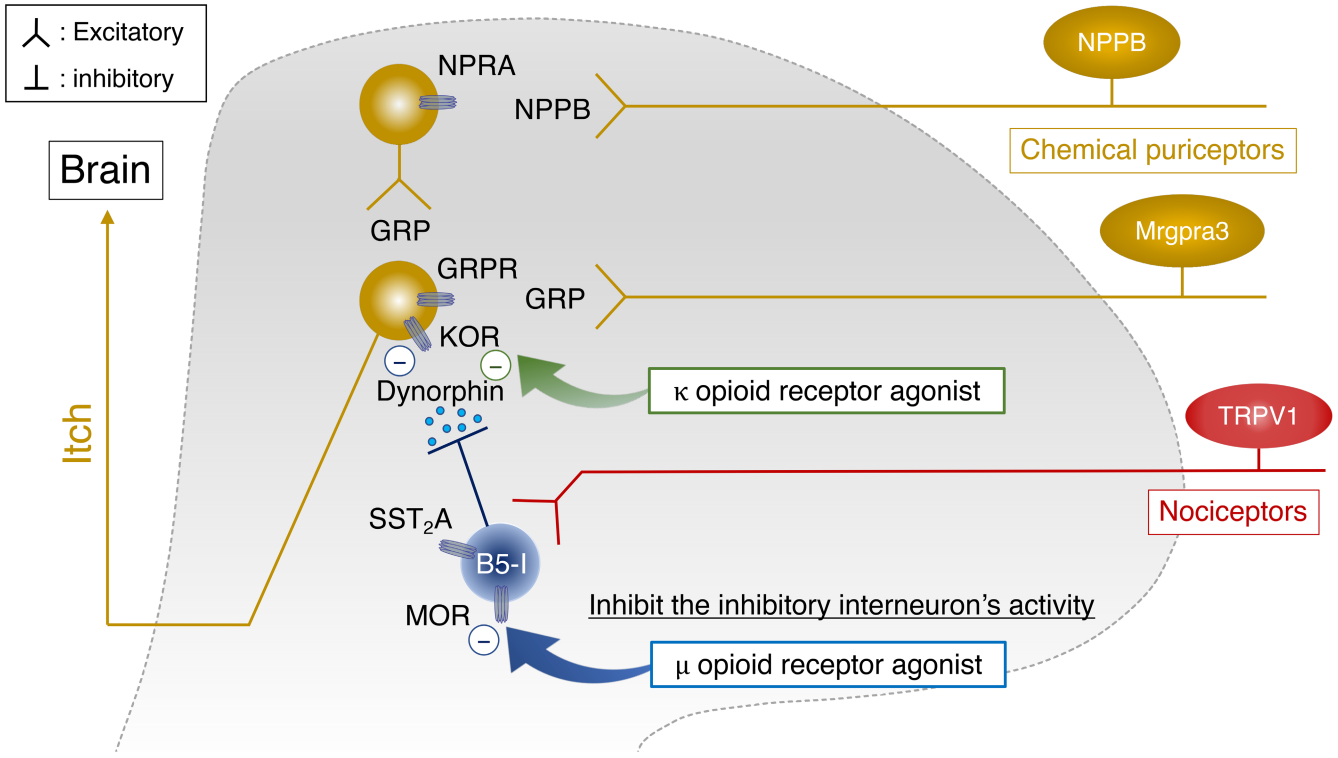

FIGURE 2 Hypothetical schematic drawing of the relationship between pruriceptors and nociceptors in the spinal dorsal horn. Nociceptive stimulation usually inhibits itching via B5-I interneurons in the dorsal horn. The μ-opioid receptor agonists alleviate the inhibition via inhibitory interneurons, and the disinhibited pruriceptive neurons convey the itch signal as a result. Since B5-I neurons contain dynorphin, κ-opioid receptor agonists seem to be effective in suppressing itch signalling in the spinal dorsal horn. B5-I, class B basic helix loop helix protein 5 interneuron; GRP, gastrin-releasing peptide; GRPR, gastrin-releasing peptide receptor; MOR, μ opioid receptor; Mrgpra3, Mas-related G protein-coupled receptor A3; NPPB, natriuretic peptide B; NPRA, natriuretic peptide receptor A; SST_2A, somatostatin receptor 2a; TRPV1, transient receptor potential vanilloid 1.

same population of sensory neurons and small unmyelinated C-fibres transmit pain as well as pruritus (Colbert, O'Hanlon, Galvin, et al., 1999), whereas several types of counter-stimuli such as scratching, noxious heat, cool, and menthol relieve the itch sensation (Bromm et al., 1995; Ward et al., 1996; Yosipovitch et al., 2007). Kardon et al., 2014 showed that class B basic helix-loop-helix protein 5 (Bhlhb5), a transcription factor, is required for the survival of spinal inhibitory interneurons required for normal itch signalling (Ross et al., 2010). They referred to Bhlhb5-expressing spinal inhibitory interneurons as B5-I neurons that inhibit the itch sensation and release dynorphin, an endogenous κ-opioid receptor agonist, as a key neuromodulator of pruritus (Figure 2; Kardon et al., 2014).

Neuraxial opioid-induced pruritus appears to act via μ-opioid receptors (Ko et al., 2004). Approximately 75% of μ-opioid receptors are expressed at the axon terminal of primary afferents in rat dorsal horns, whereas the remaining are expressed at postsynaptic sites (Besse et al., 1990). Most of the cells in the superficial dorsal horn, which express μ-opioid receptors, are excitatory (Kemp et al., 1996); thus, they contribute to analgesia. However, dynorphin can inhibit itch, suggesting exogenous κ-opioid receptor agonists can be a potential anti-pruritic itch treatment, as previously indicated (Kardon et al., 2014). Although the postsynaptic targets of B5-I neurons are unknown, κ-opioids seem to act on or downstream of GRPR neurons because κ-opioid receptor agonists inhibit itch via GRP (Kardon et al., 2014). Most B5-I neurons (90%) express somatostatin receptor 2a and dynorphin. A recent study reported that inhibitory interneurons expressing the opioid receptor μ1 express neuropeptide Y or prodynorphin; however, morphine-induced itch is mediated by neuropeptide Y neurons and prodynorphin neurons without affecting the analgesic effect (Figure 2; Nguyen et al., 2021). It has been demonstrated that neuropathic itch in Bhlhb5-deficient mice can be treated by transplant restoration; cell-mediated restoration of inhibitory interneurons can effectively ameliorate symptoms of chronic itch (Braz, Juarez-Salinas, et al., 2014). Furthermore, experiments in mice on delta opioid receptors have shown that δ-agonists suppress itching while antagonists cause itching (Smith et al., 2023).

5 | TREATMENT OF OPIOID-INDUCED ITCH

5.1 | Opioid receptor antagonist—Opioid receptor

Primates studies have shown that κ-opioid receptors and δ-opioid receptor agonists do not induce scratching behaviour, whereas nociceptin/orphanin FQ receptor agonists produce antinociceptive efficacy without evoking scratching behaviour (Ko et al., 2006; Ko, Lee, Harrison, et al., 2003; Thomas et al., 1992). The μ-opioid receptor antagonist nalmefene showed that intrathecal morphine-induced itch scratching is mediated by μ-opioid receptors (Ko & Naughton, 2000). Furthermore, pretreatment with clocinamox, a selective μ-opioid receptor antagonist, suppressed intrathecal morphine-induced scratching (Ko et al., 2004). These studies suggest that μ-opioid receptors mediate neuraxial opioid-induced itch in primates.

Naloxone, a classic opioid receptor antagonist that acts as an μ-opioid receptor antagonist, has been shown to be effective in preventing or treating neuraxial opioid-induced pruritus (Waxler et al., 2005). It is evident that opioid antagonists are most effective for the treatment of opioid-induced pruritus; however, naloxone and naltrexone may also antagonize the effective analgesic effect of opioids (Charuluxananan et al., 2001; Charuluxananan et al., 2003; Kendrick et al., 1996; Okutomi et al., 2003). Due to their attenuated analgesic effect, the use of μ-opioid antagonists in outpatients is currently impractical. Although clinicians are unsure about the appropriate use of opioids, low-dose continuous intravenous infusion of naloxone seems appropriate for the prevention of opioid-induced pruritus (Miller & Hagemann, 2011). An intravenous dose of 0.25–1 μg/kg/h of naloxone may be the most effective without affecting analgesia (Gan et al., 1997), and a systematic review showed that doses above 2 μg/kg/h are likely to reverse opioid-induced analgesia (Kjellberg & Tramer, 2001). In clinical practice, titration of antagonists using continuous infusion is more effective with less fluctuation of the antagonist concentration; however, its use is a future challenge as the appropriate dosage varies from patient to patient and may antagonize analgesic effects. Naloxone has a short serum half-life of approximately 60 min, which necessitates continuous administration when used in the treatment of opioid-induced pruritus. Goldfrank et al. devised a naloxone continuous infusion dose nomogram to overcome the short effect duration of naloxone in the treatment of opioid adverse effects. They concluded that the initial bolus dose should be clinically determined to avoid overdose and accelerated withdrawal of naloxone, but that once this value is determined, an infusion equivalent to two-thirds of this initial dose per hour should be sufficient to prevent the recurrence of respiratory and neurological depression (Goldfrank et al., 1986).

5.2 | Mixed agonist-antagonist opioid—Opioid receptor

Nalbuphine, a mixed agonist-antagonist drug with μ-partial agonist and κ-agonist properties, may reverse pruritus, even more effectively than naloxone without impairing analgesia (Cohen et al., 1992). It is used clinically in the treatment of moderate to severe pain conditions and the pharmacological profile is similar to those of butorphanol and pentazocine. Primate experiments indicate that κ-opioid receptor activation attenuates morphine-induced pruritus without interfering with nociception, and mixed agonist and antagonists (μ-opioid receptor antagonists and κ-opioid receptor agonists) are effective in relieving intrathecal morphine-induced pruritus (Ko, Lee, Song, et al., 2003; Lee et al., 2007; Togashi et al., 2002). A recent systematic review showed that nalbuphine appears to reduce the incidence of opioid-induced pruritus. The antipruritic effect of nalbuphine seems to be related to decreased IL-31 and increased IL-10 levels (Tubog et al., 2019); however, this treatment may be associated with increased drowsiness (Waxler et al., 2005).

A single 15-mg dose of intravenous pentazocine, a κ-receptor agonist and partial μ-receptor agonist or antagonist, reduces both the incidence and severity of pruritus in women who have received subarachnoid opioids during caesarean delivery (Hirabayashi et al., 2017). In addition, it has been suggested that the intravenous administration of 15 mg of pentazocine is superior to the administration of 4 mg of ondansetron, a specific 5-HT3 antagonist, for the treatment of intrathecal morphine-induced pruritus in caesarean delivery (Tamdee et al., 2009).

Some randomized controlled trials (RCTs) have suggested that intravenous or epidural administration of butorphanol, a μ2-opioid receptor antagonist, μ1-opioid receptor agonist or antagonist, and κ-opioid receptor agonist, reduced spinal morphine-induced pruritus without reversing the analgesic effects of opioid therapy (Wu et al., 2012, 2014). It has been used to alleviate intractable pruritus based on its potential anti-pruritus effect (Du et al., 2013; Gunter et al., 2000; Lawhorn et al., 1991; Wu et al., 2012). A single 3-mg dose of butorphanol added to epidural morphine for analgesia for caesarean section decreased the incidence of pruritus (Lawhorn et al., 1991). Moreover, the continuous administration of epidural butorphanol was found to be effective in relieving epidural morphine-induced pruritus in children (Gunter et al., 2000). One systematic review concluded that buprenorphine, a partial μ-opioid receptor agonist and

κ-opioid receptor antagonist, is associated with a lower incidence of pruritus than morphine (White et al., 2018).

In conclusion, central μ-opioid receptors play an important role in the process of itching induced by both central and peripheral pruritogens. The antipruritic mechanism underlying the systemic administration of μ2-opioid and κ-opioid receptor agonists may be the blockade of the itch pathway by antagonizing the activation of central μ-opioid receptors. This can be an alternative treatment with opioid rotation if morphine causes pruritus in patients requiring analgesia. Thus, opioid agonists and antagonists are among the best medicines for treating opioid-induced itch without affecting analgesia.

The mechanisms of opioid-induced pruritus involve several targets, including the spinal nucleus of the trigeminal nerve, the medullary dorsal horn, and the serotonergic pathway. Pruritus due to spinal opioids usually affects the face, neck, or upper thorax (Kumar & Singh, 2013). The facial area innervated by the trigeminal nerve is at the highest risk (Krajnik & Zylicz, 2001). Scott and Fischer reported that the highest incidence of opioid-induced itching occurs within the distribution of the facial trigeminal nerve, particularly in the spinal nucleus of the trigeminal nerve (Scott & Fischer, 1982), which contains the majority of opioid receptors and is continuous with the substantia gelatinosa and the Lissauer tract at the C3-C4 level (Kam & Tan, 1996; Kumar & Singh, 2013). Moreover, a high density of 5-HT subtype 3 (5-HT3) receptors is present in the superficial layers of the dorsal horn and in the spinal nucleus of the trigeminal nerve located superficially in the medulla, which integrates sensory input from the face and may act as an 'itch center' (Kumar & Singh, 2013). Compared with placebo, 5-HT3 antagonism has been reported not to reduce intrathecal morphine-induced pruritus (Kung et al., 2014), and the activation of 5-HT3 receptors by opioids may be important for neuraxial opioid-induced pruritus and opioid-induced nausea and vomiting (Ganesh & Maxwell, 2007; Waxler et al., 2005). Taken together, spinal pruriceptive neurons are usually inhibited by B5-I interneurons of the dorsal horn. The administration of μ-opioids can attenuate this inhibition; as a result, the disinhibited itch neurons may become activated without the stimulation of the primary afferents (Schmelz, 2009).

5.3 | 5-HT3 antagonist—Serotonin

Serotonin plays a notable role in regulating the transmission of nociceptive information at various levels, directly stimulating the peripheral nerves and promoting inflammation and hypersensitivity, while pain and itch sensations are tuned in the central nervous system. There are seven serotonin receptors, 5-HT1 to 5-HT7, which are categorized within the G-protein-coupled receptor superfamily except for 5-HT3. The only 5-HT3 receptor is a cation-selective ligand-gated ion channel for serotonin (Derkach et al., 1989). 5-HT3 receptor antagonists are known to reduce nausea and vomiting in patients as well as potentially reduce pain (Ernberg et al., 2000). There are abundant 5-HT3 receptors in the dorsal horn of the spinal cord and the spinal tract of the trigeminal nerve in the medulla (Kumar & Singh, 2013). Morphine can activate the serotonergic pathways (Shiomi et al., 1978; Vasko & Vogt, 1982; Yaksh & Tyce, 1979). An animal study suggested that morphine may produce part of its analgesic effect through the release of serotonin (Richardson, 1990), and the inhibition of serotonin receptors can attenuate pruritus (Bonnet et al., 2008). The interaction between opioids and 5-HT3 receptors plays an important role in the generation of neuraxial opioid-induced pruritus (Bonnet et al., 2008; Yeh et al., 2000). Ondansetron and other specific 5-HT3 antagonists, including granisetron and dolasetron, have been used to prevent neuraxial opioid-induced pruritus in larger studies (Bonnet et al., 2008). Ondansetron is more effective than placebo for the prevention of intrathecal morphine-induced pruritus after caesarean delivery (Charuluxananan et al., 2003; Yeh et al., 2000), and it is also likely to attenuate intrathecal fentanyl-induced pruritus (Gulhas et al., 2007). In addition, the postoperative dose-dependent increase of serum serotonin levels was significantly increased after intrathecal morphine administration for caesarean delivery (Aly et al., 2018). These findings support the hypothesis that serotonin may be an important causative factor for intrathecal morphine-induced pruritus and that the serotonergic pathway is essential in intrathecal morphine-induced itch.

However, some RCTs concluded that the use of intravenous ondansetron, compared with placebo, did not decrease morphine-induced pruritus (Kung et al., 2014; Sarvela et al., 2006), and prophylactic intravenous ondansetron was also ineffective in reducing the incidence and severity of intrathecal fentanyl-induced pruritus (Wells et al., 2004). Based on these results, the use of 5-HT3 receptor antagonists remains controversial (Bonnet et al., 2008; George et al., 2009). Further large RCTs for parturients and non-pregnant patients are required to confirm these findings.

5.4 | Gabapentin—Glycine, GABA

Melzack and Wall explained the control mediated by nociceptive and non-nociceptive neuronal input as the gate control theory (Melzack & Wall, 1965), and then there is strong evidence that inhibitory interneurons have a pivotal role in maintaining the balance between nociceptive

and non-nociceptive inputs. One major neurotransmitter, γ-aminobutyric acid (GABA), is released by spinal inhibitory interneurons to control the transmission of itch and pain messages (Ross et al., 2010). Opioid-induced itching seems to block inhibitory transmitters, such as glycine and GABA, which may be responsible for itch inhibition (Ballantyne et al., 1988), and gabapentinoids may effectively suppress opioid-induced pruritus (Sheen et al., 2008). Gabapentinoids target the voltage-dependent calcium channels α2-δ1 subunit, inhibit calcium currents, and decrease excitatory transmitter release and, thereby, spinal sensitization. They also activate the descending noradrenergic inhibitory pain system coupled with spinal α2 adrenoceptors (Kremer et al., 2016). The increase in serotonin and noradrenaline levels elicits an attenuating effect on pruriceptive processing induced by acute itch conditions in mice (Miyahara et al., 2019). Several human studies have discussed the effectiveness of gabapentinoids in treating opioid-induced pruritus. Preoperative gabapentin prevents pruritus induced by the intrathecal administration of morphine in patients undergoing lower limb surgery with spinal anaesthesia (Sheen et al., 2008). Some studies concluded that gabapentin decreased the incidence and severity, delayed the onset time, and shortened the duration of intrathecal morphine-induced pruritus (Sheen et al., 2008). Gabapentin may have a multimodal antipruritic action that involves the central reduction of itch perception (Summey Jr. & Yosipovitch, 2005), modulatory action on transmitter release (Iannetti et al., 2005), which diminishes the excitability of spinal and supraspinal neurons during itch transmission, and spinal-supraspinal inhibition of serotonergic circuits (Suzuki et al., 2005). However, gabapentin should be used with caution as it can cause dizziness, drowsiness, and visual disturbances as side effects.

5.5 | Propofol—Dorsal horn transmission

Several studies have indicated the use of propofol for the treatment and prevention of opioid-induced pruritus. For example, several authors have reported that the prophylactic administration of propofol significantly decreases the incidence of intrathecal morphine-induced pruritus (Horta et al., 2006; Torn et al., 1994), and propofol in a subhypnotic dose (10–20 mg) is a suggested treatment for spinal morphine-induced pruritus (Borgeat et al., 1992; Charuluxananan et al., 2001; Torn et al., 1994). An RCT showed that administering 20 mg of propofol reduced the incidence of morphine-induced pruritus (Horta et al., 2006), whereas another study reported that propofol did not relieve pruritus in parturients who underwent caesarean section using intrathecal morphine (Beilin et al., 1998), and another RCT suggested that propofol-based general anaesthesia was associated with a higher incidence of and more severe epidural morphine-induced pruritus than thiopental-sevoflurane-based anaesthesia (Kostopanagiotou et al., 2006). The effectiveness of a subhypnotic dose of propofol remains controversial, and the exact mechanism of its antipruritic action is not fully understood; however, it is postulated that this may be due to the inhibition of dorsal horn transmission in the spinal cord (Torn et al., 1994).

5.6 | Dopamine D2 receptor antagonist—Dopamine receptor

Droperidol and alizapride, which are dopamine D2 receptor antagonists, have been used for the treatment of opioid-induced pruritus and postoperative nausea and vomiting. Droperidol shows weak anti-5HT3 activity (Kumar & Singh, 2013). Intravenous droperidol and alizapride reduced the incidence of intrathecal morphine-induced pruritus in a group of parturients undergoing caesarean section (Horta et al., 2006). Epidural droperidol has been reported to significantly suppress morphine-induced pruritus (Naji et al., 1990), and a dose-related reduction in the incidence of pruritus after epidural droperidol in patients undergoing caesarean delivery has been reported (Horta et al., 2000). Alizapride may also reduce itching after intrathecal morphine (Horta et al., 2006); however, another study reported that alizapride reduced the severity of pruritus but not its frequency (Horta & Vianna, 2003). These dopamine D3 receptor antagonists may be effective antipruritic agents, but their data are conflicting. According to the black box warning for droperidol by the US Food and Drug Administration, QT prolongation leads to torsade de pointes, a form of polymorphic ventricular tachycardia, and sudden death may occur.

5.7 | Non-steroidal anti-inflammatory drugs (NSAIDs)—PGE1, PGE2

NSAIDs are commonly used to relieve or reduce various inflammatory pain conditions. It has been suggested that the release of prostaglandins (PGE1 and PGE2) may be associated with neuraxial opioid-induced pruritus (Szarvas et al., 2003), since they enhance C-fibre transmission to the central nervous system and are known to release histamine to potentiate pruritus (Gulhas et al., 2007). NSAIDs can reduce the production of prostaglandins by inhibiting the activity of cyclooxygenase enzymes and may modulate the perception of pruritus. Treatment with tenoxicam or diclofenac decreased the incidence and severity of

postoperative pruritus in patients who received neuraxial opioids (Colbert, O'Hanlon, Chambers, & Moriarty, 1999; Colbert, O'Hanlon, Galvin, et al., 1999). However, some studies failed to demonstrate any significant antipruritic effects of lornoxicam and celecoxib following intrathecal opioid administration (Gulhas et al., 2007; Lee et al., 2004).

5.8 | N-methyl-D-aspartate (NMDA) receptor

Intrathecal co-administration of morphine with the NMDA receptor antagonists ketamine and ifenprodil alleviated morphine-induced scratching behaviour in mice without affecting antinociception (Shen et al., 2018). Moreover, intrathecal morphine increased extracellular signal-regulated kinase phosphorylation in the lumbar spinal dorsal horn, and NMDA receptor antagonists suppressed the scratching behaviour (Shen et al., 2018).

6 | MOLECULAR MECHANISM OF OPIOID INDUCED PRURITUS

The molecular mechanisms of morphine-induced itch are not completely understood; however, Liu et al. demonstrated that the μ-opioid receptor isoform (MOR1D) and GRPR play critical roles in these mechanisms (Liu et al., 2011; Tsuda, 2018). MOR1D and GRPR are colocalized in the dorsal horn, and GRPR-expressing pruriceptive neurons are further activated by MOR1D activation by morphine. The μ-opioid receptor has a role in analgesia, while MOR1D evokes morphine-induced itch, and morphine induces heterodimerization and co-internalization of MOR1D and GRPR, which activates the PLC/inositol 1, 4, 5 triphosphate/calcium signalling pathway (Liu et al., 2011; Tsuda, 2018). This PLC/inositol 1, 4, 5 triphosphate/calcium signalling pathway triggers morphine-induced itch (Liu et al., 2011). However, the presence of MOR1D in the rat spinal cord remains to be elucidated (Oldfield et al., 2008). In contrast, Ji et al., 1995 suggested that intrathecal morphine elicits itch via $GRPR^+$ neurons via vesicular gamma-aminobutyric acid (GABA) transporter-positive inhibitory interneuron disinhibition in mice (Wang et al., 2021). There seems to be no doubt that GRPR plays a pivotal role in these studies. Although the GRPR antagonist significantly attenuated intrathecal GRP-induced behaviour, it did not attenuate the scratching behaviour elicited by the intrathecal administration of the μ-opioid receptor ligand, β-endorphin (Lee & Ko, 2015). It has been reported that β-endorphin and GRP dose-dependently elicit itch behaviour, while enkephalin and nociceptin-orphanin only suppress pain without causing itching in non-human primates (Lee & Ko, 2015). The G protein-coupled receptor TGR5 was detected in peptidergic neurons of the DRG and spinal cord in mice that transmit both itch and pain (Alemi et al., 2013). Although a TGR5-selective agonist and bile acid induced hyperexcitability of DRG neurons and stimulated itching and the release of analgesia transmitters GRP and leucine-enkephalin (Alemi et al., 2013), there were no significant differences in leucine- and methionine-enkephalin in the plasma samples of patients with hepatic pruritus compared with healthy controls (Dull et al., 2021). There seems to be a weak relationship between enkephalin and itch sensation in primates, including humans.

The antipruritic mechanisms of TRPV1 antagonists for morphine-induced itch are also not well known. TRPV1 receptors are mainly expressed in the central and peripheral terminals of primary sensory neurons and colocalized with μ-opioid receptors in the superficial laminae of the dorsal horn (Sakakibara et al., 2019; Scherrer et al., 2009). Furthermore, TRPV1-expressing neurons release GRP in the dorsal horn of the spinal cord, activating the GRP–GRPR signalling pathway (Tsuda, 2018). While intrathecal TRPV1 antagonists reduce morphine-induced itch without affecting its antinociceptive effect in mice (Sakakibara et al., 2019), the loss of μ-opioid receptors in $TRPV1^+$ neurons partially reduced the antinociceptive effect of intrathecal morphine but did not affect morphine-induced itch (Wang et al., 2021). Thus, the causal relationship with TRPV1 remains controversial.

Although only μ-opioid receptor agonists have analgesic effects accompanied by itch responses, other opioid receptor subtypes, including δ and κ, and nociceptin/orphanin peptide receptors, may inhibit pain, suggesting differential actions on the different classes of opioid receptors on the small cells of sensory nerves (Wang & Wessendorf, 2001). In human studies, morphine has a stronger analgesic effect on C-fibre-mediated second pain than A-fibre-mediated first pain (Cooper et al., 1986; Yeomans et al., 1996). In addition, peripheral inflammation increases μ-opioid receptor density not only in the peripheral nerves but also in the projected dorsal root ganglia (Ji et al., 1995; Mousa et al., 2007). Ross et al. suggested that the expression of μ-opioid receptors in spinal $dynorphin^+$ neurons is necessary for morphine-induced itch using chemogenetic inhibition of $dynorphin^+$ neurons and κ-opioid receptor agonists (Figure 2; Nguyen et al., 2021).

7 | INCIDENCE OF OPIOID-INDUCED PRURITUS

The frequency and severity of morphine-induced itching vary with the dose and route of administration

TABLE 1 Pruritic and antipruritic actions of different procedures and substances in relation to opioid-induced pruritus.

Main activating site	Procedures/substances	Itch provocation	Opioid-induced itch inhibition	Effective amount
μ-opioid receptor	Neuraxial morphine	+++ (H) (Horta et al., 2000; Singh et al., 2013; Tan et al., 2019; Yeh et al., 2000)		
	Systemic (intravenous) morphine	++ (H) (Gan et al., 1997; Woodhouse et al., 1996)		
	Systemic (peroral) morphine	+ (H) (Cherny et al., 2001; Schofferman & Mazanec, 2008)		
	Neuraxial fentanyl	+++ (H) (Uppal et al., 2020)		
	Systemic fentanyl	+ (H) (Dinges et al., 2019; Lee et al., 2013; Woodhouse et al., 1996)		
	Neuraxial sufentanil	+++ (H) (Cho et al., 2008; Demiraran et al., 2006; Dewandre et al., 2010; Hu et al., 2016)		
	Systemic sufentanil	++ (H) (Dinges et al., 2019)		
	Systemic remifentanil	+ (H) (Dinges et al., 2019)		
	Systemic methadone	± (H) (Dinges et al., 2019)		
	Systemic pethidine/meperidine	± (H) (Dinges et al., 2019)		
	Epidural μ opioid receptor antagonists		−−− (H) (Okutomi et al., 2003)	0.0004% Naloxone: c.i.e.
	Systemic μ opioid receptor antagonists		−−− (H) (Kendrick et al., 1996; Kjellberg & Tramer, 2001; Okutomi et al., 2003; Waxler et al., 2005) −−− (A) (Ko et al., 2004; Ko & Naughton, 2000)	Naloxone (prophylactic): 0.25–2.4 μg/kg/h i.v.
κ-opioid receptor	Systemic κ opioid receptor agonists		−−− (A) (Ko et al., 2003, b; Togashi et al., 2002)	
	Systemic pentazocine		−−− (H) (Hirabayashi et al., 2017; Waxler et al., 2005)	Pentazocine: 15 mg i.v.
	Neuraxial butorphanol		−−− (H) (Du et al., 2013; Gunter et al., 2000; Lawhorn et al., 1991; Wu et al., 2014) −−− (A) (Lee et al., 2007)	Butorphanol: 0.004% 2 mL/h c.i.v. or 1–4 mg i.e.
	Systemic butorphanol	± (H) (Dinges et al., 2019)	−− (H) (Du et al., 2013; Wu et al., 2012) −−− (A) (Lee et al., 2007)	Butorphanol: 1–2 mg i.v.
	Systemic nalbuphine	± (H) (Dinges et al., 2019)	−−− (H) (Charuluxananan et al., 2001; Charuluxananan et al., 2003; Cohen et al., 1992; Tubog et al., 2019)	Nalbuphine: 3–10 mg i.v.
δ-opioid receptor	Systemic buprenorphine	+ (H) (Dinges et al., 2019; White et al., 2018)		

(Continues)

TABLE 1 (Continued)

Main activating site	Procedures/substances	Itch provocation	Opioid-induced itch inhibition	Effective amount
H1 receptor	Systemic antihistamine		− (H) (Krajnik & Zylicz, 2001)	
α2δ calcium subunit	Systemic gabapentinoids		−− (H) (Sheen et al., 2008; Summey Jr. & Yosipovitch, 2005) −− (A) (Miyahara et al., 2019; Suzuki et al., 2005)	Gabapentin (prophylactic): 1200 mg p.o.
5-HT3 receptor	Systemic 5-HT3 antagonists		± (H) (Bonnet et al., 2008; Charuluxananan et al., 2003; Gulhas et al., 2007; Kung et al., 2014; Sarvela et al., 2006; Wells et al., 2004; Yeh et al., 2000)	
TRPV1	Systemic TRPV1 antagonists		0 (H) (Gibson et al., 2014) −−− (A) (Sakakibara et al., 2019)	
$GABA_A$ receptor	Systemic propofol		± (H) (Beilin et al., 1998; Borgeat et al., 1992; Charuluxananan et al., 2001; Horta et al., 2006; Kostopanagiotou et al., 2006; Torn et al., 1994)	
D2 receptor	Epidural droperidol		−− (H) (Horta et al., 2000; Naji et al., 1990)	Droperidol: 5 mg i.e.
	Systemic droperidol/alizapride		± (H) (Horta et al., 2006; Horta & Vianna, 2003; Kjellberg & Tramer, 2001)	
COX	Systemic NSAIDs		± (H) (Colbert, O'Hanlon, Chambers, & Moriarty, 1999; Colbert, O'Hanlon, Galvin, et al., 1999; Gulhas et al., 2007; Lee et al., 2004)	
NMDA receptor	Intrathecal NMDA receptor antagonists		− (A) (Shen et al., 2018)	

Note: Based on the data presented, the relative pruritic potencies of different opioids and different routes of administration are summarized. In addition, the relative anti-pruritic potencies of different substances and their different routes of administration on opioid-induced pruritus are likewise summarized.Itch provocation: '+' indicates the frequency of itch provocation. '±' = rarely provoked itch; '+' = occasionally provoked itch; '++' = sometimes provoked itch; '+++' = frequently provoked itch. Opioid induced itch inhibition: '−' indicates degree of antipruritic effect on opioid-induced pruritus. '0' = no opioid-induced itch inhibition; '±' = controversial; '−' = Weak opioid-induced itch inhibition; '−−' = Moderate opioid-induced itch inhibition; '−−−' = Strong opioid-induced itch inhibition. (A), preclinical animal data; (H), human research data; 5-HT3, 5-hydroxytriptamine; c.i.e., continuous intraepidural; c.i.v., continuous intravenous; COX, cyclooxygenase; D2, dopamin2; GABA, aminobutyric acid; H1, Histamine1; i.e., intraepidural; i.v., intravenous; NMDA, N-methyl-d-aspartate; p.o., per os; TRPV1, transient receptor potential vanilloid subtype 1.

(Jannuzzi, 2016). Data from prospective studies indicate that pruritus is observed in 2–20% of patients treated systemically with oral opioids (Cherny et al., 2001; Schofferman & Mazanec, 2008). Several studies have reported an incidence rate of 40%–55% for intravenous morphine administration using patient-controlled analgesia (Gan et al., 1997; Woodhouse et al., 1996), 40% for alfentanil/morphine combination, and 23%–35% for intravenous administration of fentanyl using patient-controlled analgesia (Lee et al., 2013; Woodhouse et al., 1996). Neuraxial injections of opioids increase the risk of pruritic symptoms, especially in patients undergoing caesarean delivery, who have an incidence of approximately 20%–70% after epidural morphine (Horta et al., 2000; Singh et al., 2013; Tan et al., 2019) and 85% after intrathecal administration (Yeh et al., 2000). This increased incidence may be related to the interaction of oestrogens with μ-opioid receptors (LaBella et al., 1978); however, this aspect is not sufficiently understood. Additional detailed investigations are required.

In their systematic review, Dings et al. reported that nalbuphine, butorphanol, methadone, and pethidine/meperidine were associated with a significantly lower risk of pruritus than morphine (Dinges et al., 2019), indicating that opioids induce pruritus in different ways, which may be via different pathways or receptors.

8 | POSSIBLE WAYS TO PREVENT OPIOID-INDUCED PRURITUS

Based on the data presented, the relative pruritic and antipruritic potencies of different opioids and different routes of administration are summarized in Table 1. Various treatments have been used for opioid-induced pruritus; however, most of them are controversial and have yielded conflicting results. Therefore, there is no doubt that the administration of opioids should be kept to a minimum required dose, and analgesia should be achieved with other analgesics, such as local anaesthetics, and it is more important to prevent pruritus than to treat it.

In terms of treatment, regarding the peripheral pathway, chemical mediator-released inhibitors may have limited efficacy in stabilizing mast cells. In contrast, central mechanisms are quite intricate, even in the spinal dorsal horn. There is evidence that opioid receptor antagonists and mixed agonist and antagonists, especially μ-opioid antagonists and κ-opioid agonists, are the most effective in relieving opioid-induced pruritus (Cohen et al., 1992; Hirabayashi et al., 2017; Kendrick et al., 1996; Kjellberg & Tramer, 2001; Okutomi et al., 2003; Tubog et al., 2019). Opioids have interpatient variability governed by genetic and environmental factors (Hwang et al., 2014). Therefore, adopting a uniform treatment is not suitable for affected patients, and adjusting the doses of opioids is required to achieve satisfactory analgesic action and minimal side effects. Dose regulation is important when opioid receptor antagonists or mixed agonists/antagonists are used. Rather than relying on opioid-only treatment, the use of polymodal regimes, including NSAIDs, acetaminophen, local anaesthetics, antidepressants, anticonvulsants, and NMDA receptor antagonists, is acceptable. Some of these drug classes effectively alleviate pain and itch sensations. The use of a multimodal antipruritic treatment regime, especially those including mixed μ antagonist-agonists, seems to be optimal for managing opioid-induced pruritus, as the management paradigm has been applied for several years to multimodal pain management.

9 | CONCLUSION

If the incidence of opioid-induced pruritus differs with different opioids and routes of administration, then the optimal management is to reduce opioid doses with a multimodal analgesic regimen and then use an antipruritic treatment regimen, including mixed μ antagonists and agonists, depending on the incidence. There are overlaps in the pathways between pain and pruritus, and further research on opioid-induced pruritus is required in animals and humans to evaluate the factors that will facilitate an optimal balance between analgesia and pruritic side effects.

AUTHOR CONTRIBUTIONS

Hiroai Okutani designed and wrote the initial draft of the manuscript. Silvia Lo Vecchio assisted with the preparation of the manuscript. Lars Arendt-Nielsen critically reviewed the manuscript. All authors discussed the results and commended on the manuscript, therefore approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, SLV, upon reasonable request.

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