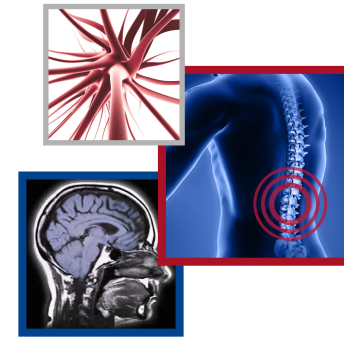
Review

Pain Management



Mechanisms, diagnosis, prevention and management of perioperative opioid-induced hyperalgesia

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Practice points

- Opioid-induced hyperalgesia (OIH) occurs when opioids paradoxically enhance pain.
- Controversy remains over the classification of OIH as a distinct medical phenomenon.
- While the precise mechanism for OIH is not fully understood, it is likely the result of multifactorial changes, and the impact of opioid exposure on the descending modulatory system suggests important mechanisms for targeted prevention and treatment.
- Appropriate treatment requires differentiating OIH, opioid tolerance, withdrawal, and opioid use disorder.
- Recent studies suggest that OIH may be preventable with screening and delaying elective surgery when needed.
- Operations requiring short-term exposure to high potency opioids should utilize the lowest possible infusion doses (remifentanil <0.2 μg/kg/min), which are tapered before infusion cessation.
- Non-opioid analgesics can assist with opioid dose reduction and may play a role in OIH prevention.
- Treatment of OIH requires tapering opioids and use of alternative pain management techniques.

Opioid-induced hyperalgesia (OIH) occurs when opioids paradoxically enhance the pain they are prescribed to ameliorate. To address a lack of perioperative awareness, we present an educational review of clinically relevant aspects of the disorder. Although the mechanisms of OIH are thought to primarily involve medullary descending pathways, it is likely multifactorial with several relevant therapeutic targets. We provide a suggested clinical definition and directions for clinical differentiation of OIH from other diagnoses, as this may be confusing but is germane to appropriate management. Finally, we discuss prevention including patient education and analgesic management choices. As prevention may serve as the best treatment, patient risk factors, opioid mitigation, and both pharmacologic and non-pharmacologic strategies are discussed.

Lay abstract: Opioid-induced hyperalgesia (OIH) occurs when opioid medications worsen rather than decrease pain. We present an educational review of the disorder. Although mechanisms of OIH are thought to primarily start in the brain or brainstem before traveling through the spinal cord to the area of pain in the body, there are likely many causes. We provide a suggested clinical definition and a pathway for clinical differentiation of OIH from other diagnoses to help with management. Finally, we discuss prevention including patient education and medication management choices. As prevention may serve as the best treatment, patient risk factors for OIH, decreased opioid use, and both medication and non-medication strategies are discussed.

Tweetable abstract: Opioid-induced hyperalgesia occurs when opioids worsen pain. Our review provides a clinical definition and pathway for differentiation from other diagnoses. Screening, patient education, and medication management choices offer opportunities for prevention.

Future Medicine

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Opioid-induced hyperalgesia (OIH) is nociceptive sensitization following acute or chronic exposure to opioids. OIH occurs when opioid administration results in the paradoxical enhancement of the noxious stimuli they are prescribed to ameliorate. OIH should be suspected with worsening widespread pain in the absence of a novel injury coupled with: exacerbation of pain with a higher opioid dose or analgesic improvement with a lower opioid dose. OIH can occur in both the opioid naive patients, often with acute exposure, and non-opioid naive patients. Even in the absence of a chronic pain condition, after up to 5 months of opioid abstinence, increased pain sensitivity persists, as shown via quantitative sensory testing in recovering heroin addicts [1]. Similarly, a large Norwegian epidemiological study showed that regular users of opioids have increased pain sensitivity associated with more analgesic use [2].

Despite mounting experimental and clinical evidence over the last two decades, controversy remains over the classification of OIH as a distinct medical phenomenon [3]; this is due to a multitude of reasons. Although animal research supports the existence of OIH as distinct from opioid tolerance [4,5], well-designed clinical studies examining OIH in the perioperative setting are scarce. The few studies examining OIH development in the perioperative period that do exist are limited to short-acting phenylpiperidine and piperidine opioids (remifentanil, alfentanil and fentanyl) with less focus on phenanthrene opioids (morphine and hydromorphone) [6–10]. Furthermore, clinical differentiation of OIH and opioid tolerance remains challenging without an opioid taper; however, withholding opioid-based analgesia for many patients is difficult in the perioperative period. Additionally, few clinical studies of OIH have demonstrated analgesic improvement with decreased opioid dosing, and of those, hyperalgesia is often described as resulting from chronic as opposed to acute opioid treatments [11]. Moreover, the prevalence of OIH is not known [12], and most reports attempting to quantify OIH prevalence are anecdotal and related to chronic high-dose opioid use [13,14]. In fact, a recent survey of Canadian physicians working in anesthesiology, chronic pain or palliative care found physicians to perceive that OIH is a rare medical condition with a low prevalence among their patients (0.002% per patient per physician practice year among non-pain physicians, 0.01% among chronic pain physicians) [15]. In another survey among physicians specializing in pain management, less than half acknowledged that OIH affects >5% of chronic pain patients [16]. It is unclear if physicians are unaware of OIH or simply misdiagnose OIH as opioid tolerance, perioperative stress response, catastrophizing or even anxiety. In sum, OIH is a controversial but critical topic requiring more educational awareness.

Although several reviews have been written on OIH [17–19], our review will focus on the perioperative patient and include several clinically relevant new studies and guidelines. First, we discuss mechanisms of OIH because they suggest essential areas for targeted treatment (section 1). Next, we summarize the recent controversy in the diagnosis of OIH, and provide a proposed compromised definition and path to differential diagnosis (section 2). In particular, our review provides an expanded focus on steps in the perioperative setting in which preventative steps can be taken to prevent OIH (section 3). Because opioids remain the commonly used postoperative analgesic, it is imperative to advance the prevention of OIH at this time. Finally, when OIH occurs, we provide guidelines for tapering and suggestions for treatment (section 4). This educational review focuses on the current understanding of OIH and suggestions for improving perioperative patient care, significantly impacting the long-term quality of life.

Mechanism of OIH

The impact of opioid exposure on the descending modulatory system suggests important mechanisms for targeting OIH. While the precise mechanism is not fully understood, OIH is likely to result from multifactorial changes that occur with opioid exposure. Before developing OIH, opioids elicit their effects by binding to opioid receptors located in peripheral tissue, spinal cord and throughout the brain, impacting multiple organ systems [20]. Opioids affect numerous central circuits to induce euphoria, increase sedation and alter reflexes – which profoundly affects behavior and pain reporting [21]. Opioid inhibition of both the dorsal horn and supraspinal circuits is needed to provide adequate systemic opioid analgesia [22,23]. In addition, opioid-sensitive neurons in the rostral ventral

Table 1. Comparison of opioid-induced hyperalgesia, tolerance, withdrawal and opioid use disorder.

	Opioid-induced hyperalgesia	Opioid tolerance	Opioid withdrawal	Opioid use disorder
Mechanism	Drug-induced pain sensitization within the CNS (central sensitization)	Decreased drug efficacy Desensitization of μ-receptor to opioids	Absence of μ-receptor stimulation Increased NE levels result in systemic symptoms	Uncontrolled use of opioids despite adverse outcomes Possible desensitization to opioids
Opioid escalation	Pain not overcome with opioid dose escalation	Pain overcome with opioid dose escalation	Symptomatic improvement with opioid escalation	Variable response to dose escalation
Other symptoms	Pain worse with dose escalation	Tolerance to many opioid side effects but not central apnea or constipation	Symptoms include muscle spasm, abdominal cramp, anxiety, palpitations, and hot flashes	Symptoms of tolerance and withdrawal, depending on the presence or lack of opioid use

CNS: Central nervous system; NE: Norepinephrine.

medulla play an essential role in the facilitation of hyperalgesia and the development of chronic pain by exciting dorsal horn neurons [24,25]. In summary, it must be appreciated that some analgesic effects of opioids are due to the descending inhibition of the spinal cord, but many alternative circuits likely contribute as well.

It is largely believed that OIH is due to dysfunctional facilitation of descending nociceptive pathways of the spinal cord by the rostral ventral medulla. While ablation of this descending modulatory pathway can block OIH [26,27], animal models have shown that repeated administration of opioids can also increase pain sensitivity via cellular mechanisms outside of the brainstem. Both signaling pathways for reducing antinociceptive systems and amplifying pronociceptive signals have been implicated in OIH [28]. Central factors including microglial activation [29] and upregulation of the central glutaminergic system and N-methyl-D-aspartate (NMDA) receptors [30] are thought to be important drivers of OIH. Peripherally, opioid receptor activity results in hyperalgesia priming of prostaglandin [31] and alterations in transient receptor potential channel function [32]. Notably, the primary literature highlights that the same pathways involved in OIH are also involved in opioid tolerance, opioid-induced analgesia and chronic pain. Thus, while differentiating these diseases is essential, processes that improve descending modulation or produce analgesia without using opioids are most beneficial, regardless of the diagnosis. Notably, interventions do not need to be pharmacologic, as exercise has been shown to aid in preventing OIH in animals via a descending modulatory-mediated mechanism [33]. Although the mechanisms of sleep and OIH have not been adequately studied, it is well known that sleep greatly affects descending modulation [25] and fragmented or inadequate sleep can exacerbate acute [34] or chronic [35] pain.

Differential diagnosis of OIH

OIH should be distinguished from opioid tolerance, withdrawal and opioid use disorder (OUD) [36]. Whereas OIH is a state of enhanced nociception related to acute or chronic exposure to opioids, 'opioid tolerance' is a pharmacologic effect in which a higher dose of opioid is needed to achieve a given analgesic effect. Opioid 'withdrawal' is a set of clinical signs of symptoms that develops from opioid cessation. Conversely, individuals with OUD, the uncontrolled use of opioids despite adverse outcomes, may have tolerance and withdrawal symptoms, depending on the presence or lack of opioid use.

Characteristics of OIH, opioid tolerance, withdrawal and OUD are presented in Table 1. These diagnoses may occur concomitantly and have similar causes or presentations. Both opioid tolerance and OIH may be associated with a decreased analgesic response despite increased opioid administration. Both OIH and opioid tolerance may result from acute (e.g., continuous remifentanil administration) [37] or chronic opioid exposure and present with increased opioid requirements in the perioperative setting. Both withdrawal and OIH can occur with opioid cessation, and OIH has also been observed in both patients deescalating from high doses of opioids and those maintained on chronic methadone therapy [38–40]. As opioid tolerance and withdrawal may complicate the diagnosis of OIH, further discussion is warranted.

Tolerance occurs as repeated exposure to opioids results in adaptation and desensitization in the brain, GI tract and other organ systems [41], causing the medication's analgesic effects to diminish over time. As opioid tolerance renders equivalent dosages ineffective, the mechanisms of opioid withdrawal may present in tandem. Ordinarily, stimulation of μ-receptors by opioids results in less norepinephrine (NE) release by locus coeruleus and elicits opioid side effects (i.e., a decrease in respiration, blood pressure and muscle tone) [42,43]. However, with repeated drug exposure, neurons become tolerant, and NE levels normalize. Thus, in addition to decreased analgesia, opioid tolerance may also decrease opioid side effects including nausea, respiratory depression and sedation [44]. Thus

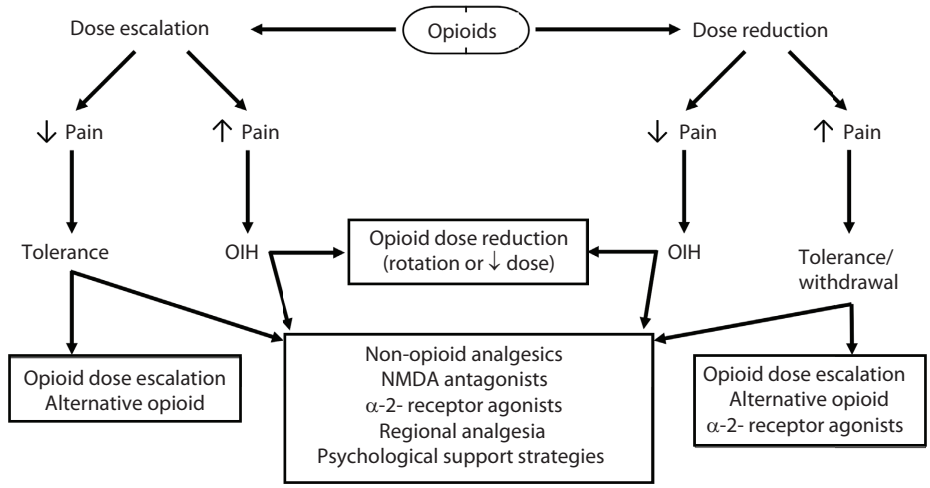

Figure 1. Clinical differentiation and management of opioid-induced hyperalgesia & opioid tolerance.

opioid cessation results in increased NE levels and elicits the symptoms of opioid 'withdrawal' including muscle spasms, abdominal cramps, anxiety, palpitations and hot flashes [45]. Withdrawal symptoms for short-acting opioids (e.g., heroin, oxycodone and hydrocodone) typically occur within 12 h of cessation, peak at 36–72 h and taper over 4–7 days [46]. This timeline highlights another critical difference between tolerance/withdrawal and OIH, as OIH potentially has much longer-lasting effects.

Although OIH and opioid tolerance may have similar clinical presentations, they require different management strategies (Figure 1). Tolerance occurs following prolonged opioid administration with pain resulting from reduced efficacy and requires increasing opioid doses. As tolerance is often a magnification of the patient's baseline pain, increasing the dosage or changing opioids can overcome the effect. Conversely, OIH typically presents as a clinical syndrome of tolerance to opioid analgesia combined with hypersensitivity to painful stimuli [44]. Simply, OIH should be suspected when increased doses of opioids exacerbate pain or the subject's pain changes in terms of characterization (e.g., burning) or dermatomal location without evidence of a new pain source or injury [47].

Although clinical criteria for diagnosing OIH have been described [47], a specific test or exam to confirm OIH is lacking and definitive diagnoses remain difficult. In fact, the lack of consensus surrounding a clinical definition is currently impeding recognition and progress [48]. One suggestion for verification of OIH is to deliver an increased opioid dose. Improved analgesia likely indicates tolerance, whereas more pain likely indicates OIH [49]. Alternatively, analgesia that improves after decreasing the opioid dose is also a sign of OIH [47]. Because complex taxonomies for characterizing OIH are in development [48], we propose a simple interim definition encompassing both of these prior suggestions: *"OIH could be defined as the exacerbation of widespread pain in the absence of an alternative explanatory factor (e.g., infection, stroke, spinal cord injury and disease progression), in which the pain either worsens with a higher opioid dose or improves with a lower opioid dose"*. As our suggested definition is a compromise to provide a foundation for research to building a consensus definition, we strongly encourage others to validate a definition for OIH.

Screening for risk & prevention of OIH

The best treatment for OIH is likely prevention. OIH may be preventable with screening and delaying elective surgery when needed. The perioperative period is associated with high rates of opioid exposure. Prevention strategies may be implemented in the pre-operative, intra-operative and postoperative arena, but ultimately should occur throughout the perioperative period.

In the pre-operative period, opioid education, chronic opioid cessation or tapering and risk assessment are imperative (Figure 2). Pre-operative patient education regarding opioid use can decrease opioid consumption and improve postoperative opioid cessation [50,51]. In these successful prospective studies on patient education [50,51], education consisted of provider education, physician & nurse discussion with printed materials, or a short video. Even coaching by an athletic trainer on opioids and pain management at a pre-operative clinic visit is helpful [52]. Online courses and mobile device apps may also help with this process [53,54].

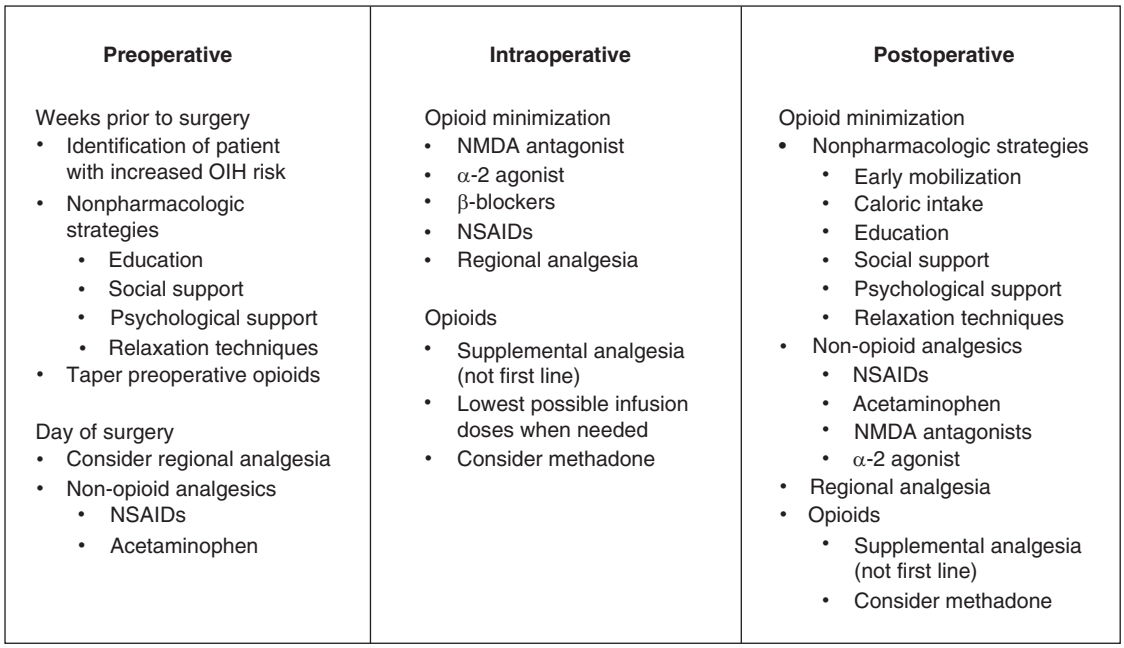

Figure 2. Perioperative strategies to prevent or minimize opioid-induced hyperalgesia.

Similarly, cessation of chronic opioids before surgery decreases the risk of chronic postoperative opioid use [55]. Although retrospective publications suggest a benefit for opioid tapering before surgery [56,57], large prospective studies are still needed. However, these studies and guidelines by the American Society for Enhanced Recovery and Perioperative Quality Initiative advocate the utilization of a biopsychosocial model and multimodal pain management methods to taper opioid use by 50% before surgery [58]. Delaying elective surgery in these patients and higher risk patients (discussed below) for 10–12 weeks is recommended to allow them to participate in a multidisciplinary pain management program [58]. Although further research is needed to establish the threshold opioid dose level, there is a particular concern for patients taking 60-mg morphine equivalents or higher within 90 days of surgery according to current guidelines [58].

Generally, screening for the same recommended factors that should be screened for adverse opioid outcomes could help prevent for OIH [58,59]. Ineffective pain management with opioids suggestive of OIH is associated with fibromyalgia survey scores, more neuropathic pain symptoms and higher levels of depression. Notably, in this cohort, patients were rarely diagnosed with fibromyalgia (<5%), but more than 40% met the survey criteria for this condition that seldom responds to opioids [59]. Pre-operative setting use of a fibromyalgia questionnaire has shown to identify patients at risk for developing chronic and poorly managed pain, even accounting for prior opioid use [60,61].

Intra-operative analgesics

While the overall evidence of whether specific agonists are responsible for OIH is mixed, certain medications may increase the risk of OIH development. A retrospective study found that higher doses of intra-operative fentanyl (>3 g/kg) were associated with accelerated postoperative pain onset compared with lower doses, suggestive of acute OIH [62]. Similarly, an earlier meta-analysis suggested high intra-operative doses of remifentanil were associated with an increased likelihood of OIH [8]. However, a more recent meta-analysis found little evidence of high intra-operative opioid administration levels contributing to postoperative pain [63]. Thus, although additional research is needed to clarify the importance of selecting a specific opioid agonist or dose for the risk of developing OIH, there is a basis in the earlier literature for suggesting caution and opioid minimization strategies may minimize OIH. Operations requiring short-term exposure to high potency opioids should utilize the lowest possible infusion doses (remifentanil <0.2 μg/kg/min), which are tapered before infusion cessation [64–66].

Alternatively, non-opioid analgesics can assist with opioid dose reduction and may play a role in OIH prevention. As the central glutaminergic system and NMDA receptor activation are thought to be important drivers of OIH,

ketamine and methadone are often prescribed to prevent and treat OIH [67,68]. In diabetic mice, ketamine reversed remifentanil induced hyperalgesia and allodynia [69]. Clinically, patients randomized to intravenous perioperative ketamine demonstrated reduced opioid consumption[67] and a reduced incidence of chronic post surgical pain (CPSP) [70]. However, acetaminophen has also been shown to block substance P [71,72] and NMDA [71], in animal models, resulting in the prevention of hyperalgesia. Although NSAIDs also reduce prostaglandin release, decreasing nociceptive signaling [73] and opioid consumption [74,75], it is not certain that NSAIDs reduce OIH. Although cyclooxygenase inhibition prevented hyperalgesia in one animal model,[76] indomethacin had limited effects in an animal model of OIH [77].

Similarly, α-2-receptor agonists, clonidine and dexmedetomidine improve analgesia [68,78,79] and have also been used to treat OIH [17,68]. They are also used to treat symptoms associated with opioid withdrawal [80]. As OIH often improves with opioid reduction, which may lead to withdrawal, α-2-receptor agonist administration should be considered to ameliorate analgesia and withdrawal symptoms when OIH is suspected.

Although few studies have assessed multimodal analgesia in regards to OIH, use of two or more non-opioid analgesics can reduce both opioid analgesic requirements and adverse opioid side effects including respiratory depression [81,82]. For example, α-2-receptor agonists may be more efficacious in reversing hyperalgesia when used in combination with ketamine, rather than as a sole agent [68]. Therefore, administration of more than one non-opioid adjunct likely has a synergistic effect and may have a greater ability to mollify or prevent OIH.

Regional anesthesia & systemic local anesthetics

Regional anesthesia may also impact central sensitization and decrease hyperalgesia after surgery. Besides lessening acute postoperative pain, local anesthetics decrease acute inflammation, early cytokine production and central markers of pain sensitization [83–85]. In an animal model of incisional pain, sciatic blocks placed prior to incision for hind foot surgery and continued postoperatively, decreased postoperative hyperalgesia, central sensitization and pain chronicization [86]. This publication was the first to demonstrate reductions in acute pain and acute hyperalgesia from regional anesthesia in animals, combined with a decrease in central sensitization. Notably, regional anesthesia was not able to reverse central sensitization induced by high doses of intra-operative fentanyl. In another animal model, sufentanil induced OIH hyperalgesia was inhibited in diabetic and non-diabetic mice with a single injection sciatic nerve block before incision [87]. In patients undergoing thoracotomy and randomized to IV morphine by patient-controlled analgesia thoracic epidural or thoracic epidural initiated pre- or post-operatively, the IV patient-controlled analgesia group had a greater incidence (78%; $p = 0.0233$) and intensity ($p = 0.014$) of chronic post-thoracotomy pain at 6 months compared with the pre-operative epidural group (45%) [88]. Further, in patients undergoing laparotomy and randomized to intravenous analgesics (lidocaine, clonidine and morphine) or neuraxial analgesics (bupivacaine, clonidine and sufentanil) in the intra- and post-operative periods, the incidence of CPSP 6 and 12 months after laparotomy was greatly reduced in patients receiving intra-operative neuraxial local anesthetic (intra- and post-operative epidural, 0%; intra-operative epidural analgesics with postoperative intravenous analgesics, 11%) compared with patients treated with IV medications (intra- and post-operative intravenous analgesics; 45%) [89]. Notably, punctate hyperalgesia areas in acute postoperative period did not differ if the patients received epidural local anesthetic at some time in the perioperative period (intra-operative and/or postoperative). These studies indicate that regional anesthesia should be used prior to surgery for intra-operative analgesia and intra-operative opioid reduction, reducing the risk for central sensitization and OIH. Conversely, some authors suggest that the timing of regional anesthesia placement pre-, intra- or post-operative period is less significant than the presence of regional analgesia in the acute postoperative period [90]. This perspective was examined in a trial of patients undergoing open nephrectomy and randomized to IV opioids, thoracic epidural analgesia, or continuous, subcutaneous wound infiltration [91]. In the postoperative period, both continuous wound infiltration and epidural analgesia decreased opioid consumption and the area of wound hyperalgesia, while improving analgesia and patient rehabilitation.

Studies have also reported that systemic local anesthetics may also act as NMDA antagonists [92,93], perhaps providing another indication for regional anesthesia techniques in the management and prevention of OIH. In diabetic rats administered systemic (peritoneal lidocaine) or localized (intraplantar levobupivacaine) local anesthetic, allodynia was inhibited with intraplantar administration, while systemic administration did not differ from saline (placebo) [94]. Similarly, in the earlier mentioned laparotomy study, patients randomized to intravenous analgesics (lidocaine, clonidine and morphine) in both the intra- and post-operative periods had the greatest incidence of CPSP, compared with patients receiving intra-operative epidural analgesics, despite the use of intravenous lidocaine

throughout the perioperative period [89]. Combined, these studies and a recent meta-analysis [95], question the beneficial impact of perioperative intravenous lidocaine for analgesia. Thus, systemic lidocaine likely does not decrease the risk of OIH.

Alternative opioids

When opioids are required for patients with suspected OIH, an alternative is to utilize opioids with properties that may mitigate OIH. The contribution of NMDA receptors to OIH and the ability of ketamine to block OIH suggest NMDA antagonism as an important target for OIH prevention [96–98]. Although methadone is a μ-receptor agonist, it is a racemic mixture and the d-isomer is an NMDA receptor antagonist [99]. Methadone also exhibits incomplete cross-tolerance and remains potent even in patients on chronic opioid regimens. Methadone may therefore promote an opioid reduction of 40–50% while providing NMDA receptor antagonism and minimizing the risk of opioid withdrawal. While publications have described single-dose, intra-operative methadone administration [100–102], initiation of methadone otherwise in the perioperative period is not well described. Additionally, due to its long half-life and risk of delayed respiratory depression, methadone should be titrated slowly for long-term outpatient management. Thus, it may not be practical to initiate long-term methadone therapy in the acute, perioperative period. Buprenorphine, a kappa receptor antagonist, may also have a mitigating effect on OIH development. Levels of spinal dynorphin, a kappa receptor agonist, rise with intrathecal opioid administration in rats, contributing to OIH; however, thermal hyperalgesia and allodynia were reversed with dynorphin antiserum [103]. In an experimental clinical model utilizing transcutaneous stimulation for hyperalgesia, the antihyperalgesic effects of buprenorphine were more pronounced than the analgesic effects [104].

Non-pharmacological strategies

Non-pharmacological therapies should also be utilized for OIH prevention. This is best noted in the multitude of Enhanced Recovery After Surgery protocols that incorporate early mobilization, caloric intake, patient education and additional techniques that indirectly improve pain outcomes, in addition to medication-based therapy and regional anesthesia techniques to optimize analgesia. Exercise is helpful in the prevention of OIH in animal models via a descending modulatory-mediated mechanism [33]. Perioperative patient education regarding opioid related risk and guidance on managing pain without opioids can decrease postoperative opioid consumption [51]. Analgesic strategies can include passive range or motion, moist heat or ice therapy. Further, relaxation, behavioral instruction and other psychological support strategies may have utility for analgesia and should be considered to prevent OIH [105–107].

Treatment of OIH

In theory, OIH treatment is simple: remove the opioid and hyperalgesia will eventually abate. In the perioperative setting, regional techniques and non-opioid pharmacological infusions (such as ketamine), may replace the need for opioid treatment. While this simplistic approach of avoiding all opioids may not be possible for patients suffering from chronic or malignant pain, it should serve as a starting point. In the postoperative setting implementing non-opioid pharmacological therapy, coupled with proper psychological counseling, rehabilitation and interventional pain treatment is required for pain management and functional recovery without OIH development. In patients on opioid therapy who are experiencing pain exacerbation despite opioid dose escalation and the absence of new clinical findings should be examined for potential OIH. Practical treatment options may include decreasing the total daily opioid dose or transitioning to an opioid with NMDA receptor antagonism function, such as methadone.

Although additional research is needed, guidelines for tapering including a conceptual model, have been generated [108]. These guidelines emphasize the importance of a combination of careful physician-patient communication and patient development of coping skills. In particular, the usage of open-ended questions for the development of individualized tapering plans is recommended. The individual tapering plan may include physician-initiated strategies (e.g., physical therapy and treatment of comorbid depression), but should also include patient-initiated strategies (e.g., meditation and 12-step programs).

A total daily opioid dose decrease may be accomplished by a 10–20% reduction per week [109]. Although tapering as high as 50% per week may be necessary in some cases, further research is needed to determine whether it is associated with increased noncompliance [109]. As incomplete cross-tolerance exists among various opioids, the total daily dose of opioids could be decreased by 30–50% with opioid rotation, likely to improve OIH symptoms [110]. Concurrent with opioid reduction, non-opioid analgesics and non-pharmacologic therapies should also be initiated to minimize pain exacerbation. Similarly, withdrawal symptoms may be minimized with anti-emetics, muscle

relaxants and α-2 adrenergic agents [45]. Finally, long-term opioid reduction has been associated with an improved success rate for other pain management strategies such as spinal cord implantation [111].

As NMDA receptors play a central role in pain modulation, neuronal plasticity and hyperalgesia development, NMDA receptor antagonists may provide a useful target in treatment of OIH [67,68]. Extensive research supports perioperative use of ketamine in treatment of heightened nociceptive and neuropathic states; however, ketamine is not readily available for treatment of outpatient chronic pain as outpatient ketamine infusions are not routinely reimbursable and may be unattainable to many patients. Although clearly of value in the acute pain setting, ketamine administered for chronic pain conditions provides a significant yet transient analgesic response [112,113]. Another alternative is an opioid rotation to an opioid with NMDA receptor inhibition such as methadone [114,115] or buprenorphine. In clinical studies, this approach has been associated with significant and sustainable analgesic benefits. Methadone has a long and well-established history of efficacy in treating hyperalgesic states, and there is growing evidence in its use for OIH. However, its complex pharmacokinetics and potential for significant side effects may raise concerns [114,115]. In comparison, buprenorphine may have a superior safety profile and a lower abuse risk, making it attractive for OIH treatment [116–118]. However, buprenorphine may return to eliciting hyperalgesia over time [119].

Conclusion

OIH remains controversial. While this is potentially due to a lack of research, OIH is increasingly recognized as a clinical problem in the perioperative period. Through the education of our colleagues, residents, patients, patient families, and surgeons, OIH can be more adequately considered in our differential diagnosis in a patient with poorly controlled perioperative pain. In the interim, the following recommendations should be considered:

- Pre-operative
  - Patient education regarding opioids
  - Chronic opioid reduction or cessation
  - Identification of patients at increased risk for OIH
- Analgesics
  - Administration of the lowest possible opioid infusion doses (remifentanil <0.2 μg/kg/min), which are tapered before infusion cessation, in operations requiring short-term exposure to high potency opioids;
  - Administer a combination of ketamine and α-2 agonists as administration of more than one non-opioid adjunct likely has a synergistic effect and may have a greater ability to mollify or prevent OIH;
  - Utilize perioperative regional anesthesia to decrease acute inflammation, cytokine production, and central markers of pain sensitization.

Future perspective

There are many valuable opportunities for improvement of screening, prevention and treatment in OIH. Although pre-operative screening for chronic post surgical pain risk has rarely been effectively applied, quantitative sensory testing is predictive in small studies [120]. As quantitative sensory testing methods are not yet convenient or common for pre-operative screening, only questionnaire screening and patient history are recommended by guidelines [58]. However, future research into quantitative sensory testing methods coupled with a consensus definition of OIH, could improve screening and prevention. Because the current guidelines for opioid tapering are in the absence of large-scale randomized trials, more research on this topic is desperately needed [108]. Finally, there are many promising new avenues for additional therapies in the treatment of OIH. The efficacy of dextromethorphan (an NMDA receptor antagonist), duloxetine [121], cyclooxygenase-2 inhibitors [73], melatonin [122], dexmedetomidine [79,80] and clonidine [68] are promising non-opioid drugs that could ameliorate OIH, but require further investigation. New biased opioid ligands with tailored signaling properties may also decrease the undesirable side effects of opioids, and specifically OIH [123]. Successful prospective randomized trials of non-opioid and biased opioid targets would herald the promise of eliminating OIH and even reversing the opioid epidemic.

Author contributions

SH Wilson, KM Hellman, and A Chandrakantan participated in the manuscript design. SH Wilson, KM Hellman, D James, AC Adler, and A Chandrakantan participated in manuscript creation. All authors contributed to literature search and interpretation, and manuscript drafting and revision. All authors have approved the final manuscript and agree to be accountable for the integrity of the article.

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• **This is a large European study looking at mediators of pain tolerance in a population-based cohort.**

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