Review Article

Opioid-Induced Hyperalgesia: Is It Clinically Relevant for the Treatment of Pain Patients?

■■■ *Robert B. Raffa, PhD,[*] and Joseph V. Pergolizzi Jr, MD[†,‡]*

■ Abstract:

There is a curious and paradoxic phenomenon, reliably demonstrated in animal models, that consists of an increased sensitivity to pain that is apparently induced by the very opioid drugs used to ameliorate the pain. This phenomenon is termed "opioid-induced hyperalgesia." Whether opioid-induced hyperalgesia occurs in humans, and, if so, to what extent and consequence, is far less established. This is a critical question for attempting to treat pain. If opioid-induced hyperalgesia develops in a patient, it would masquerade as tolerance (because the clinical effectiveness of the opioid would be diminished), yet the appropriate clinical adjustment would be precisely the opposite to that of tolerance. It would be to decrease, rather than increase, the dose of opioid. We review the evidence, particularly the clinical evidence, about opioid-induced hyperalgesia and the postulated mechanisms. We conclude that given the clinical ramifications, opioid-induced hyperalgesia is one of the most understudied important aspects of opioid research.

*From the *Temple University School of Pharmacy, Philadelphia, Pennsylvania; [†]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [‡]Department of Anesthesiology, Georgetown University School of Medicine, Washington, D.C.*

Address correspondence to Robert B. Raffa, PhD, Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, PA 19401. E-mail: robert.raffa@temple.edu

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The notion that opioids might have pronociceptive effects might have been suspected as early as the American Civil War (Mitchel, 1905). Today there is convincing and growing preclinical evidence and possibly some clinical evidence to support a phenomenon of opioid-induced hyperalgesia (OIH). Early clinical investigation focused on a heightened pain sensitivity observed in drug addicts (Compton, 1994; Doverty, White, Somogyi, Bochner, Ali, & Ling, 2001), but current interest in OIH includes the implications for pain management in the general patient population. There is no definitive answer yet because the clinical presentation of OIH mimics tolerance; in fact, OIH would be conclusively diagnosed only retrospectively, i.e., if a reduction in opioid consumption provided greater pain relief (Angst, Chu, & Clark, 2010). Thus, although there is convincing evidence in the preclinical literature, clinical demonstration of OIH remains nebulous and its significance, even existence, in patients has been disputed

(Bannister & Dickenson, 2010; Fishbain, Cole, Lewis, Gao, & Rosomoff, 2009). The present article presents an introduction and broad overview of what is known about OIH and its possible clinical relevance in pain management—an important, controversial, and challenging clinical dilemma.

The phenomenon of OIH in preclinical studies can probably be most simply depicted as in Figure 1. In this representation of results from an animal model, a pain-free animal is administered a constant dose of some opioid for an extended period. The animal's baseline for detection of a nociceptive (presumptive painful) stimulus is assessed over the duration of opioid administration. A common measure is the time that it takes (latency) for the animal to withdraw its tail or foot from the source of noxious input. It has been observed that the animal's baseline latency decreases over time, i.e., the animal paradoxically becomes *more* sensitive to a painful stimulus over the course of extended opioid exposure. This finding is reliably reproduced. Note that this is not tolerance, because there is no overt analgesic effect. The measure is *pain threshold* in a previously pain-free animal.

If this same phenomenon occurs in pain patients there is an obvious, and as yet unresolved, dilemma about treating patients with opioid "analgesics." However, animal models might be fundamentally different from the clinical situation. The animal models typically assess baseline latency, whereas opioid analgesics are used to reduce pain to the baseline level. We review both aspects of this puzzling, but important issue, concentrating on the studies in humans.

GENERAL CONSIDERATIONS

When and Why Would Opioid-Induced Hyperalgesia Occur?

Just as pain is complex, the concept of OIH is complex. It appears that OIH is not merely more pain or increased painful sensations associated with the original site of pain. What typically is detected in humans is hyperalgesia at a different location surrounding the original pain site and having different characteristics than the original pain (Ali, 1986; Devulder, 1997; Ossipov, Lai, King, Vanderah, & Porreca, 2005). For example, in a study of chronic pain patients taking oral opioids and nonopioid medications (n = 100), no overt abnormal sensitivity to cold pain was observed, but more of the patients taking opioid analgesics had less neuronal activity related to endogenous pain inhibition compared with patients taking nonopioid analgesics (Ram, Eisenberg, Haddad, & Pud, 2008).

It would seem logical that if OIH exists, it would most likely occur under circumstances of sustained exposure to opioids (as in persistent or chronic pain) or aggressive titration in the postoperative period. But it is not clear why OIH would occur. Such hyperalgesia has been called a form of "abnormal" pain, compared to physiologic or "normal" pain (Werz & MacDonald 1982; Yaksh, Harty, & Onofrio, 1986). From the viewpoint of adaptation, it could be argued that antinociception occurs to reduce pain during times of danger when pain might hinder an appropriate response, but nociception in the form of heightened pain sensitivity occurs when the patient is safe but needs to recuperate (Simonnet & Rivat, 2003). Following this line of thinking, hyperalgesia would be the body's natural response following antinociception, a sort of postscript to "fight or flight." Thus, a patient who experiences acute pain is experiencing a natural antinociception (release of endogenous endorphins and enkephalins), which analgesic medications may further promote, but when the "danger" has passed, the body heightens pain sensitivity to assure that the patient rests to recover from the attack. According to such thinking, OIH may be an adaptive homeostasis process (Leknes, Brooks, Wiech, & Tracy, 2008) that corresponds to a time when the body releases transmitters with pronociceptive activity (such as cholecytokinin, substance-P, or dynorphin) (Kiss, Degryse, Bardin, Gomez de Segura, & Colpaert, 2005; Rivat, Laulin, Corcuff, Célèrier, Pain, & Simonnet, 2002). Opioid-binding sites become desensitized, possibly as part of an adaptive pain process (nociception opposing antinociception) (Chakrabarti, Yang, Law, & Loh, 1997; Cvejic, Trapaidze, Cyr, & Devi, 1996). Thus, OIH may be part of an adaptive response rather than only drug mediated. Although there is general agreement that an opioid-initiated up-regulation of the excitatory *N*-methyl-D-aspartic acid (NMDA) receptors occurs during OIH in animals (Célèrier, Rivat, Jun, et al., 2000; Cvejic et al., 1996; Mao, Price, & Mayer, 1994, 1995), the adaptive function of OIH remains speculative.

As an alternative or complementary view, when hyperalgesia from trauma, inflammation, viral infection, metabolic derangements, and other pathophysiologies occur, peripheral mechanisms that mediate or promote inflammation heighten the body's sensitivity to pain. Such underlying neural mechanisms are similar to those involved in the development of neuropathic pain (Mao 2002). If OIH is neurally mediated, as has been proposed (Ueda 2010), the mechanisms of OIH may overlap with those involved in the development of chronic neuropathic pain (Ling & Compton 2010). Many chronic pain patients have neuropathy or a neuropathic component to their pain (Vorobeychik, Chen, Bush, & Mao, 2008); it is possible that the primary

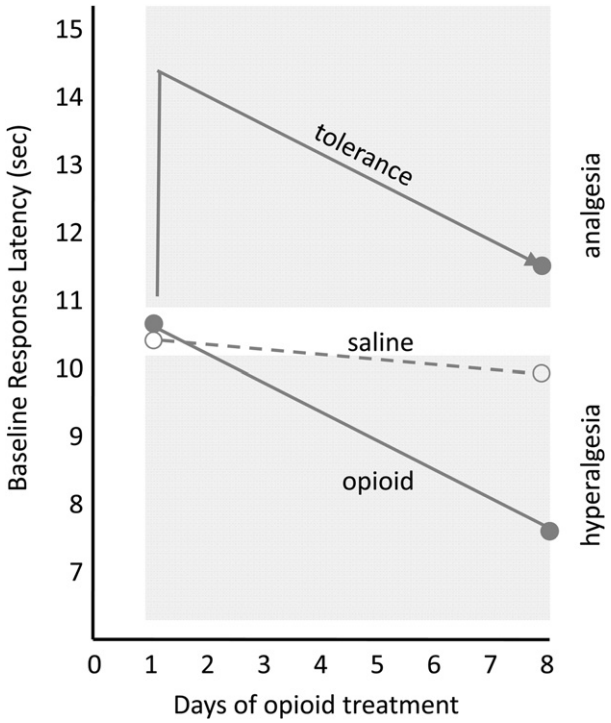

Figure 1. ■ Graphical representation of opioid-induced hyperalgesia. In this rendering of the results from the typical animal model (mice or rats), a pain-free animal is administered a constant dose or infusion of an opioid over an extended period. The measurement, plotted on the ordinate, is the animal's baseline for the response to some painful stimulus (commonly the time it takes for the animal to withdraw its tail, foot, or so on, from the painful stimulus). Pain sensitivity (threshold) is plotted against time on the abscissa. Opioid-induced hyperalgesia is inferred when the animal's baseline latency decreases, i.e., the animal becomes more sensitive to a painful stimulus, over the duration of exposure of opioid. This differs from tolerance, because there is no overt analgesic effect. Based on (Mao 2010).

hyperalgesia in some patients associated with this neuropathy might be inappropriately attributed to OIH, which is a secondary hyperalgesia. Perhaps it is not coincidental that buprenorphine, a drug that is effective in treating neuropathic pain (Induru & Davis 2009), has also been reported to prevent OIH (Silverman 2009). It suggests that OIH and neuropathy might share some common mechanisms.

The relationship between inflammatory pain and OIH is unclear. Fentanyl-induced hyperalgesia in rats without inflammatory pain can be reversed with relatively low concentrations of sevoflurane (1.0%), but not when inflammatory pain is present (Richebe, Rivalan, Rivat, et al., 2009). This suggests that inflammatory pain mechanisms might be distinct from the mechanisms of OIH.

Opioid-Induced Hyperalgesia and Tolerance

Both OIH and tolerance have the same clinical presentation: inadequate analgesia at previously adequate doses. The similarities in clinical presentation have even led to suggestion that they are the same thing (Ballantyne 2010; Mao 2006). Although OIH has been readily observed in several preclinical studies, equivocal results in human studies have caused some to challenge its existence as an independent entity (Fillingim, Doleys, Edwards, & Lowery, 2003; Reznikow, Pud, & Eisenberg, 2005). Perhaps there might be some value in more circumspect wording such as "apparent OIH," as there is in the term "apparent opioid tolerance" (Colpaert, 1996). Clearly distinct mechanistic boundaries between tolerance and OIH have yet to be drawn.

Treatment strategies would differ fundamentally for tolerance versus OIH, in that tolerance is effectively addressed by judicious and monitored increase in opioid dose, whereas OIH would be treated by decreasing the opioid dose. For this reason, it is clinically important to be able to differentiate OIH from tolerance.

Although tolerance and OIH have superficial similarities, there are crucial distinctions. OIH typically involves pain intensity greater than the original pain (despite the absence of progression of disease), and it often extends beyond the original site of pain (Mao, 2002, 2006, 2010). Furthermore, OIH has been associated with changes in pain threshold (the point at which a noxious stimulus is registered as pain) and pain tolerance (the point at which prolonged noxious stimulation is perceived as unbearable); this is not the case with opioid tolerance (Angst, Chu, & Clark, 2010). Pharmacologic tolerance occurs with adaptive cellular changes associated with processes such as a reduction in the turnover rate and number of opioid receptors or desensitization of opioid receptors to opioid ligand, or both (Ballantyne & Mao, 2003; Ueda & Ueda, 2009). Tolerance is a desensitization process, and, as such, does not increase baseline pain sensitivity. OIH increases sensitivity to pain. Tolerance has been defined as a rightward shift in the dose-effect curve and OIH as a downward shift (Angst, 2010).

Despite the obvious external differences, tolerance and OIH might share some common cellular mechanisms (DuPen, Shen, & Ersek, 2007), in that cholecystokinin-mediated changes in descending modulatory pathways (King, Ossipov, Vanderah, Porreca, & Lai, 2005) and changes in NMDA receptors (Mao et al., 1994; Mao, 2002) have been implicated in both. In mice, treatment with ultralow doses (10 ng/kg

subcutaneously) of nontoxic B-subunit of cholera toxin (CTX-B), which binds selectively to GM1 gangliosides, blocks the excitatory—but not the inhibitory—effects of morphine and other bimodally acting opioids, increasing the net inhibitory opioid effect and blocking the hyperalgesic effects produced by morphine agonists (Shen & Crain, 2001). Chronic coadministration of CTX-B and morphine in mice reduces the development of both opioid tolerance and OIH. Other animal studies have also shown an association between development of morphine tolerance and morphine-induced thermal hyperalgesia (Mao et al., 1995; Ossipov, Lopez, Nichols, Bian, & Porreca, 1995; Vanderah, Gardell, Burgess, et al., 2000; Wegert, Ossipov, Nichols, et al., 1997).

Chronic morphine reduces regional glutamate homeostasis control, increasing the level of extracellular glutamate, which in turn increases the likelihood of activation of excitatory amino acid receptors, such as the NMDA receptor (NMDAR) (Mao, Sung, Ji, & Lim, 2002b). Both morphine tolerance and morphine-induced thermal hyperalgesia can be prevented in rats by blocking NMDARs (Mao et al., 1995).

Chronic intrathecal or continuous intravenous morphine produces a dose-dependent down-regulation of glutamate transporters EAAC1 and GLAST in the dorsal horn of the spinal cord of rats (Suzuki, Porreca, & Dickenson, 2006). This down-regulation is temporally correlated with the development of both morphine tolerance and thermal hyperalgesia (Mao, Sung, Ji, & Lim, 2002b). Thus, spinal glutamate transporters might contribute to the neural mechanisms of both morphine tolerance and morphine-induced hyperalgesia through their regulation of regional glutamate homeostasis.

Transition from Acute to Chronic Pain

The transition from acute to chronic pain is poorly understood. Medical definitions offer no mechanistic distinction between acute and chronic pain, only a temporal one (Reichling & Levine, 2009). Furthermore, it is unclear why certain patients pass from acute to chronic pain whereas other, seemingly similar, patients do not. Risk factors have been identified in the surgical model to include fear, anxiety, and depression (Wang, Myunghae Hah, & Carroll, 2009) and genetic predisposition (Katz & Seltzer, 2009). Added to the list of risk factors is the use of opioids in the management of acute pain (Webster, Verma, & Gatchel, 2007).

Although chronic pain is currently defined by duration, there might be a mechanistic distinction between acute pain and chronic pain (Kovacs, Abraira, Zamora, & Fernandez, 2005; Young Casey, Greenberg, Nicassio, Harpin, & Hubbard, 2008). According to this view, prolonged pain is actually acute pain of extended duration rather than true chronic pain, although extended acute pain can transform into chronic pain (Wang et al., 2009). During the transition, the patient may experience a diminishing responsiveness to pain treatment (Biondi, 2006). For example, "hyperalgesic priming" occurs when an acute inflammatory insult or environmental stress induces neuronal plasticity in primary afferent nociceptors, triggering a hypersensitivity of these nociceptors to inflammatory cytokines (Reichling & Levine, 2009). Hyperalgesic priming, which has been modeled in rats (Ferrari, Bogen, & Levine, 2010; Joseph, Reichling, & Levine, 2010), depends on the epsilon isoform of protein kinase C and a switch in intracellular signaling pathways mediating cytokine-induced nociceptor hyperexcitability.

Chronic pain also can develop when peripheral injury increases the excitability of peripheral nociceptors, leading to peripheral sensitization or primary hyperalgesia (Wang et al., 2009). This can lead to exaggerated central nervous system inputs, which increase and prolong the excitability of central nervous system neurons, leading to central sensitization. When central sensitization occurs, the patient exhibits secondary hyperalgesia with increased sensitivity to painful stimuli in areas of undamaged tissue distant from the site of injury. During the course of peripheral nerve injury, a variety of physiologic changes take place that contribute to depolarization of injured nociceptors. When injured nociceptors depolarize, associated neurons can spontaneously fire without further exogenous stimulation (Wang et al., 2009).

Surgical pain involves multiple components (Woolf & Salter, 2000). Part of surgical pain is induced by acute nociceptive stimuli; the intensity of this pain depends directly on the intensity and duration of the stimuli. Sensitization may be induced by the nociceptive inputs, but it might also be induced by the use of opioid analgesics. For that reason, some investigators have suggested that opioids should not be administered for preemptive analgesia (Eisenach 2000), out of concern that they may expedite the transition from acute to chronic pain.

Opioid Withdrawal and Opioid-Induced Hyperalgesia

Hyperalgesia is a recognized phenomenon of opioid withdrawal. Hyperalgesia can be induced by abstinence-induced (Devillers, Boisserie, Laulin, Larcher, & Simonnet, 1995; Dunbar & Pulai, 1998; Ekblom, Hammarlund-Udenaes, & Paalzow, 1993; Grilly & Gowans, 1986; Johnson & Duggan, 1981) or antagonist-precipitated (Kaplan & Fields, 1991; Martin & Eades, 1964; Martin, Gilbert, Jasinski, & Martin,

1987; Tilson, Rech, & Stolman, 1973; Yaksh et al., 1986) withdrawal. In preclinical studies, hyperalgesia following opioid withdrawal has been shown to occur after chronic opioid use as well as after a one-time exposure (Bederson, Fields, & Barbaro, 1990; Goldfarb, Kaplan, & Jenkins, 1978; Kim, Barbaro, & Fields, 1988). Hyperalgesia during antagonist-induced opioid withdrawal after a single exposure to morphine has been demonstrated in humans (Compton, Athanasos, & Elashoff, 2003). For this reason, OIH has been associated with withdrawal. However, in animal studies, OIH has been induced and perpetuated during opioid infusion (Mao et al., 2002a; Vanderah, Ossipov, Lai, Malan, & Porreca, 2001), which suggests that withdrawal-induced hyperalgesia is distinct from OIH.

Preclinical Studies of Opioid-Induced Hyperalgesia

The fundamental dilemma regarding OIH is that it is reliably demonstrated in animal models but preclinical studies might not adequately reflect the human experience of pain (Morgan, Carter, DuPree, Yezierski, & Vierck, 2008). Therefore, the studies in animal models are only briefly summarized here; the studies in humans are discussed in more detail subsequently.

In several studies, intrathecal morphine (10 or 20 μg) administered to rats over 7 days progressively reduced the nociceptive threshold in foot-withdrawal latency to thermal stimulation (Mao et al., 2002a, 2002b), and the depressed threshold persisted for several days after morphine was discontinued (Mao et al., 1994). Subcutaneous boluses of fentanyl produced similar reductions in nociceptive threshold in rats in the Randall-Selitto test (mechanical pressure to the hind paw), which persisted up to 5 days after fentanyl was discontinued (Célèrier, Laulin, Corcuff, le Moal, & Simonnet, 2001; Célèrier et al., 2000; Laulin, Maurette, Corcuff, Rivat, Chauvin, & Simmonet, 2002). Animals administered heroin displayed a similar decrease in nociception (Célèrier et al., 2001). Such decreases in nociceptive threshold are equivalent to an increase in pain sensitivity or OIH.

Genetic variation is believed to play a role in expression of OIH (Trang, McNaull, Quirion, & Jhamandas, 2004). For example, genetic variants of the β_2 adrenoreceptor gene can explain the differences between strains of mice that do and do not develop OIH (Liang, Liao, Wang, et al., 2006). But to our knowledge, no genetic studies of OIH in humans have been conducted (Jensen, Lonsdorf, Schalling, Kosek, & Ingvar, 2009).

Ketamine administered to animals was able to attenuate or prevent OIH (Minville, Fourcade, Girolami, & Tack, 2010; Richebe, Rivat, Laulin, Maurette, & Simonnet, 2005; Rivat et al., 2002). Although ketamine had antihyperalgesic effects in rats who had hyperalgesia induced by remifentanil, similar results did not occur in pediatric patients undergoing scoliosis surgery (Engelhardt, Zaarour, Naser, et al., 2008), but ketamine did prevent postoperative remifentanil-induced hyperalgesia in adults undergoing abdominal surgery (Joly, Richebe, Guignard, et al., 2005). Ketamine's role in preventing OIH supports the notion that NMDAR activation contributes to or supports OIH, because ketamine is an NMDAR antagonist. Subcutaneous pretreatment with ketamine (10 mg/kg) prevented the development of thermal hyperalgesia induced by remifentanil in rats (Gu, Wu, Liu, Cui, & Ma, 2009). When ketamine was administered alone, it had no apparent effect on nociceptive threshold, suggesting that ketamine has antihyperalgesic properties rather than antinociceptive properties in this model. Interestingly, ketamine interacts with NMDAR sites by binding to its phencyclidine site (Vorobeychik, 2010), which can only occur when the receptor is activated (MacDonald, Bartlett, Mody, et al., 1991).

Clinical Studies of Opioid-Induced Hyperalgesia

Some of the first human studies of OIH involved testing of a heightened sensitivity to pain coincidentally observed in opioid addicts (Compton 1994; Compton, Charuvastra, Kintaudi, & Ling, 2000; Compton, Charuvastra, & Ling, 2001; Doverty, Somogyi, White, et al., 2001; Doverty, White, et al., 2001; Dyer, Foster, White, Somogyi, Menelao, & Bochner, 1999; Schall, Katta, Pries, Klöppel, & Gastpar, 1996). By and large, these studies reported that opioid addicts are more sensitive to cold pressor pain than are healthy control subjects and former drug users. These studies found no hypersensitivity to mechanically induced pain. Although the studies could associate hyperalgesia with regular opioid addiction, it was unclear whether opioid addicts were perhaps hyperalgesic or whether hyperalgesia, as an independent phenomenon, might lead an occasional drug user to become a more chronic user. More study is needed to answer this question.

A summary of representative OIH human studies is presented in Table 1. OIH was observed in surgical patients when it was found that patients who received high doses of intraoperative opioids for their surgical pain had larger postsurgical opioid analgesic consumption than similar patients receiving lower doses of opioids (Chia, Liu, Wang, Kuo, & Ho, 1999; Cooper, Lindsay, Ryall, Kokri, Eldabe, & Lear, 1997; Guignard, Bossard, Coste, et al., 2000). A study of surgical patients by Cortínez et al. failed to establish OIH (Cortínez, Brandes, Muñoz, Guerrero, & Mur, 2001),

Table 1.
Human Studies of Opioid-Induced Hyperalgesia

Study	n	Design	Drugs	End Points	Results	Comments
Cooper et al., 1997	60 cesarean section patients	Randomized to receive fentanyl or saline solution with intrathecal bupivacaine IV during C-section	0.5 mL (25 μg) fentanyl or 0.5 mL saline solution; all patients received 0.5% plain bupivacaine (2 mL)	Postoperative PCA (morphine) use over 23 hours	Fentanyl patients used 63% more morphine 6-23 h after operation than control	Results significant after 6-23 h but not before
Cohen et al., 2008	355 patients scheduled for interventional procedure evaluated pain intensity and unpleasantness intensity before and after lidocaine injection	Controlled study, not blinded; patients ranged from 7.5 to 3,000 mg MED per day	Patients were previously on opioid therapy, with majority taking oxycodone; doses and medications varied	Pain and unpleasantness intensity scores on scale of 0 to 10	Patients on high doses of opioids (≥30 MED) had significantly higher preinjection pain scores than control ($p = .001$)	Unpleasantness scores tended to be higher than pain scores for patients taking ≥30 MED per day
Crawford et al., 2006	30 pediatric patients undergoing scoliosis surgery	Randomized, controlled, blinded	Continuous infusion of remifentnil starting at 0.25 μg/kg/min and titrated in increments of 0.05 μg/kg/min according to hemodynamic response in test group; control patients received intermittent morphine boluses of 50 μg/kg per hemodynamic response	Use of PCA (morphine), sedation, pain	Use of PCA morphine significantly greater in remifentanil patients, 30% more at 24 h ($p < .0001$)	Pain and sedation did not differ significantly
Guignard et al., 2000	50 adult patients undergoing abdominal surgery	Randomized controlled study	Desflurane at 0.5 minimum alveolar concentration and titrated remifentanil based on autonomic responses; control group received remifentanil (0.1 μg/kg/min) and desflurane titrated to autonomic responses	Pain scores and morphine consumption through 24 h after surgery	Remifentanil patients had significantly higher pain scores and took almost twice as much morphine in 24 h, 59 mg vs. 32 mg ($p < .01$)	Mean remifentanil infusion rate was 0.3 ± 0.2 μg/kg/min in the active agent group
Fillingim et al., 2003	240 patients with chronic back or neck pain (35% women)	Cross-sectional data analysis	Patients self-reported drugs, pain, and disability and underwent clinical assessment	Clinical variables of opioid use and gender	Opioid use not associated with greater pain severity	Opioid use was associated with lower affective distress in women and higher affective stress in men
Koppert et al., 2005	15 adults	Randomized, double-blind, placebo-controlled crossover study	0.15 mg buprenorphine IV assessed at various points up to 150 min after administration	Responses as antihyperalgesic or hyperalgesic	Antihyperalgesic responses occurred more often	Half-life of buprenorphine-induced analgesic and antihyperalegesic effects were 171 and 288 min, respectively

MED = morphine equivalent dose; PCA = patient-controlled analgesia.

possibly because the doses (infusion rate and duration) were too low to evoke OIH, suggesting a dose-dependent relationship for OIH (Angst & Clark, 2006). Although these studies strongly suggest that OIH can develop when high doses of opioids are administered in the surgical setting, it is not the only explanation for the results. It is possible that high doses of opioids result in rapid-onset acute tolerance, which would also manifest itself as an increased postsurgical opioid consumption.

In a study of healthy volunteers with an induced hyperalgesic skin lesion, opioids exacerbated the preexisting hyperalgesia in response to mechanical pain (Angst, Koppert, Pahl, Clark, & Schmelz, 2003; Koppert, Angst, Alsheimer, et al., 2003; Koppert, Sittl, Scheuber, Alsheimer, Schmelz, & Schüttler, 2003) and this effect was observed to last as long as four hours after opioid discontinuation (Hood, Curry, & Eisenach, 2003). There was no exacerbation of heat pain sensitivity (Angst, Koppert 2003; Hood, Curry, et al., 2003). Because opioids have been associated with heightened sensitivity to cold pain (Compton et al., 2003; Compton, Miotto, & Elashoff, 2004), OIH might vary by type of pain, which might suggest clues to its underlying mechanism (s). It should be noted that pain tests conducted on a single type of pain, such as cold pain, may produce an incomplete picture of pain sensitivity. Different types of pain were compared in 272 healthy volunteers. In that study, responses differed based on whether the painful stimulus was thermal (heat and cold), electrical, or mechanical (Neziri, Curatolo, Nüesch, et al., 2011). This suggests that different pain pathways are involved with different types of pain, supporting the prevailing opinion that pain is multimodal. Studies may rely on a single type of pain, e.g., cold pain, for practical reasons. Results from such studies are useful, but they must be considered within the context of the multimodal nature of pain.

In a study of fentanyl (0.5 mL or 25 μg) versus placebo (saline solution) along with intrathecal 0.5% bupivacaine (2 mL) administered in cesarean section patients randomized to either fentanyl or control groups (n = 60), fentanyl patients required significantly more ($p < .05$) patient-controlled morphine analgesia 6-23 hours after the procedure (Cooper et al., 1997). The question is whether fentanyl induced acute spinal opioid tolerance, as the investigators reported, or perhaps OIH.

In a randomized study of pediatric scoliosis surgery patients (n = 30), patients received an intraoperative continuous infusion of remifenatil or intermittent morphine (control) (Crawford, Hickey, Zaarour, Howard, & Naser, 2006). Postsurgical consumption of patient-controlled analgesia (morphine), pain scores, and sedation scores were assessed by blinded investigators for the first 4 hours after surgery and then every 4 hours through 24 hours. Remifentanil patients consumed significantly more postoperative morphine than did the control group at each time point up to 24 hours ($p < .0001$), and at 24 hours, remifentanil patients had taken 30% more morphine than control patients. Other end points, sedation and pain scores, were not significantly different by group.

High-dose intraoperative remifentanil has also been associated with greater postoperative pain levels and more postoperative morphine consumption in adult patients undergoing abdominal surgery (Guignard et al., 2000). Three-hundred fifty-five patients on analgesic therapy, including opioid therapy using any of several opioids, were divided into opioid and nonopioid patients and, among opioid patients, by dosage. In this study, high-dose opioid patients were those who received ≥30 morphine-equivalent doses daily. Twenty-seven control volunteers with no pain and currently taking no analgesics were also enrolled. All patients, including control subjects, received a subcutaneous injection of lidocaine before a full dose of a local anesthetic agent. Patients were asked to rate their pain and unpleasantness scores on an 0–10-point analog scale. Patients on high-dose opioid therapy (≥30 morphine-equivalent doses daily) had significantly higher pain scores before injection than control subjects ($p = .0001$). Postinjection pain intensity and unpleasantness scores were significantly higher in opioid patients (all doses) than in those taking nonopioid analgesics or control patients ($p < .001$) (Cohen, Christo, Wang, et al., 2008). This suggests that OIH may influence pain threshold but also may involve mechanisms of pain modulation or pain processing. In fact, it has been suggested that the unpleasantness component, along with heightened pain perception, might be a reliable indicator of OIH (Doverty et al., 2001; Pud, Cohen, Lawental, & Eisenberg, 2006).

In patients taking morphine, OIH has been found to develop in as little as a month (Chu, Clark, & Angst, 2006). However, there are fewer studies of OIH in patients on chronic opioid therapy and specifically in cancer pain, although opioid analgesia is a mainstay of palliative cancer care (Mao et al., 2002b). Although one study of cancer pain patients (n = 224) failed to show a significant difference between opioid users and nonopioid users in punctate pain, thermal pain, or pain thresholds, the study involved "commonly" used doses of oral opioid and nonopioid medications (Reznikov et al., 2005). Therefore, it is not clear whether the absence of OIH should be attributed to

cancer pain as a distinct type of pain or whether the lack of OIH could be associated with oral analgesic administration, lower drug doses, or the mixtures of opioids used.

Opioid-induced hyperalgesia has been reported in a variety of other settings where opioids are used to treat pain, including musculoskeletal pain (Crofford, 2010) and migraine (Saper & Lake, 2008). A case study in the literature reports that a reduction in opioid dose improved pain relief in a patient with recurrent squamous cell lung carcinoma and spinal metastases (Vorobeychik et al., 2008). However, chronic opioid therapy in pain patients does not always result in OIH (Fillingim et al., 2003).

Possible Sites/Mechanisms of Opioid-Induced Hyperalgesia

No physiologic mechanism has been definitely proven to underlie OIH. However, a number of explanations have been put forward. It is possible that some combination of causes is required or that some temporal sequence of events is necessary. A sample of some of the major postulated mechanisms is given here.

Neuroplasticity in the Rostral Ventral Medulla or the Spinal Cord. It has been proposed that opioids have the capacity to provoke systems-level adaptations in descending facilitation, up-regulation of spinal dynorphins, and an exaggerated release of excitatory transmitters from primary afferents, all leading to increased pain perception (Ossipov, Lai, King, et al., 2004). For example, morphine applied to the rostral ventromedial medulla elicits antinociception, which is mediated through inhibitory pathways which diminish pain signals delivered to the spine, but the rostral ventromedial medulla is also the source of descending pathways that facilitate nociceptive signals at the spinal level. Perhaps morphine also activates these pathways, heightening sensitivity to pain (hyperalgesia) (Ossipov et al., 2004).

Opioid-induced hyperalgesia has been linked to neuroplasticity in the rostral ventromedial medulla and the dorsolateral funiculus of the spinal cord (Gardell, King, Ossipov, et al., 2006; Gardell, Wang, Burgess, et al., 2002; Meng & Harasawa, 2007; Vera-Portocarrero, Zhang, Ossipov, et al., 2006; Vera-Portocarrero, Zhang, King, et al., 2007; Xie, Herman, Stiller, et al., 2005).

In particular, the down-regulation of glutamate transporters in the spinal cord and the activation of NMDARs have been associated with OIH (Mao 2002; Mao & Mayer 2001; Mao et al., 2002b; Inturrisi, 2005). Ketamine, an NMDA antagonist, has been reported to counteract OIH (Laulin et al., 2002; Richebé et al., 2005; Singla, Stojanovic, Chen, & Mao, 2007; Vorobeychik, 2010), supporting the notion that NMDA activation plays a role in OIH. Hyperalgesia induced in rats by remifentanil is accompanied by enhancement of tyrosine phosphorylation of the NMDAR 2B subunit in the spinal cord, which is inhibited by pretreatment with ketamine (Gu et al., 2009).

Sex Steroids. Gender may play a role in this process, because morphine-induced hyperalgesia is preferentially blocked in male mice (Juni, Klein, Kowalczyk, Ragnauth, & Kest, 2008), implicating the influence of sex steroids (Juni, Cai, Stankova, et al., 2010). In a study of opioid use and hyperalgesia in humans, women experienced greater pain intensity and more unpleasantness of treatment scores (Cohen et al., 2008). In rodent studies, the analgesic effects of opioids are typically more pronounced in male and the hyperalgesic effects more pronounced in female animals (Bodnar & Kest, 2010). There clearly is a need for greater investigation into the role of gender in OIH.

Glial Cells. Glial cells are nonneuronal cells that support and protect the neurons of the brain, maintain homeostasis, and produce myelin. Glial cells play a role in nociception in peripheral nerve injury. Opioids activate glial cells, which are associated with opioid-mediated analgesia. In this process, opioids induce glial cells to release proinflammatory cytokines, including tumor necrosis factor, which has been associated with opioid tolerance, dependence and reward (Hutchinson, Bland, Johnson, Rice, Maier, & Watkins, 2007; Watkins, Hutchinson, Johnston, & Maier, 2005; Watkins, Milligan, & Maier, 2001) and, more recently, OIH (Hutchinson, Lewis, Coats, et al., 2010). Toll-like receptor 4 (TLR4) signaling has been implicated in this process (Hutchinson et al., 2010). The involvement of TLR4 signaling suggests opioid selectivity, because morphine-3-glucuronide (a morphine metabolite with little opioid receptor activity) is associated with substantial TLR4 activation and the active morphine metabolite, morphine-6-glucuronide, is not. The fact that activation of glial cells by TLR4 signal transduction induced by opioids may play a role in OIH merits further research and may lead to better understanding of OIH.

Receptor Types. Opioid therapy has been associated with lowered nociceptive thresholds (de Conno, Caraceni, Martini, Spoldi, Salvetti, & Ventafridda, 1991). The mechanism for OIH is unknown, but one that has been suggested is a receptor-mediated mechanism in which opioids sensitize the spinal neurons and thereby increase sensitivity to pain by acting on some opioid receptors coupled to excitatory cholera toxin-sensitive G-proteins (Crain & Shen, 2000). Selective activation of these receptors by low systemic doses of morphine (~0.1 μg/kg) produces acute hyperalgeisa,

and selective blockade of these receptors with the use of ultralow doses of naltrexone (~1-100 pg/kg) unmasks potent morphine analgesia in mice (Crain & Shen, 2001). Acute injection of the NMDAR antagonist MK-801 reduces hyperalgesia in morphine-treated mice given naltrexone, suggesting that the NMDAR may play a role in OIH that is not related to the effect that NMDARs have on analgesia (Juni, Klein, & Kest, 2006). Injecting MK-801 during opioid infusion in control mice reversed hyperalgesia but had no such effect in triple-knockout mice (mice without μ, δ, or κ opioid receptors) (Juni, Klein, Pintar, & Kest, 2007). This suggests that OIH is independent of NMDA-mediated analgesia. Naltrexone pellets implanted in mice administered opioids eliminated analgesia but not hyperalgesia. NMDAR antagonism reversed OIH in mice (Juni et al., 2008).

Once NMDARs are activated, ongoing peripheral inputs are no longer necessary to maintain a sensitized state (Coderre & Melzack, 1985). Morphine has no detectable binding affinity to NMDARs (Mao, 1999) and would therefore not directly activate NMDARs. OIH associated with NMDAR activation appears to be indirectly triggered (Fig. 2).

The involvement of μ-opioid receptors in OIH was demonstrated in a preclinical study that found that selective μ-opioid receptor agonists can cause OIH in normal mice, but not in μ-opioid receptor–deficient knockout mice under the same conditions (Li, Angst, & Clark, 2001a). Spinal opioid receptors might be involved in mediation of OIH, because intermittent intrathecal morphine has been associated with thermal hyperalgesia (Dunbar & Pulai, 1998; Ibuki, Dunbar, & Yaksh, 1997). Thus, it appears that OIH might involve both opioid receptor–mediated and nonopioid receptor–mediated pathways.

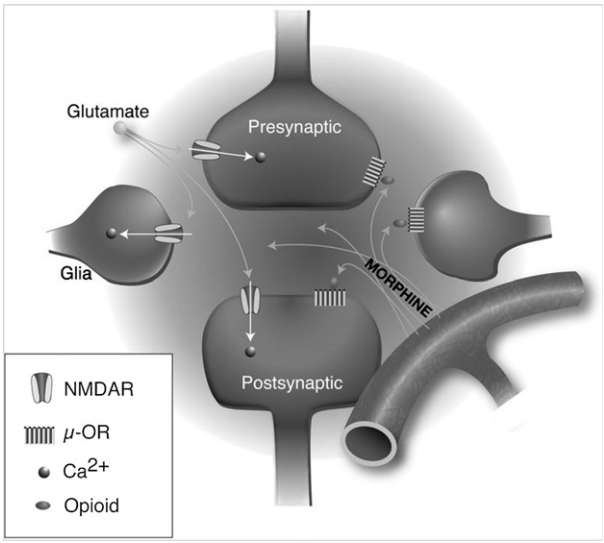

Figure 2. ■ Artist's rendering of the hypothesized interplay between neurons and glia cells in opioid-induced hyperalgesia. Opioids, such as morphine, bind to seven-transmembrane G protein-coupled opioid receptors located on pre- and post-synaptic neurons and on glia cells. Endogenous glutamate activates NMDA receptor channels located on neurons and glia cells that selectively increase Ca^{2+} influx.

Opioid-Induced Excitatory Actions. Opioids might evoke a direct excitatory effect, which can be demonstrated in isolated sensory neurons (Crain & Shen, 1990; Wang & Burns, 2006). This excitatory effect has been demonstrated for a variety of opioids in human and animal studies (Angst et al., 2003; Célèrier et al., 2000, 2001; Kiss et al., 2005; Mao et al., 1994; Vinik & Kissin, 1998). Pure μ-opioid receptor agonists, such as sufentanil and remifentanil, have been observed to exert a bimodal effect, whereby inhibitory action is followed by an excitatory effect; the latter can be subsequently unmasked by naloxone (Freye & Levy, 2010). Remifentanil administered to mice at 4, 6, and 8 nmol/L causes significant mean increases in NMDA peak current amplitudes over control animals, and these NMDA enhancements paralleled the development of hyperalgesia and tolerance (Zhao & Joo, 2008). NMDA enhancement was shown to depend on both μ- and δ-receptors, but could be induced entirely by δ-receptors alone.

Neuropeptides. Prolonged exposure to morphine increases the activity of sensory neuropeptides, e.g., calcitonin gene–related peptide and substance P, and their downstream signaling messengers, prostaglandins, lipoxengenase metabolites, and endocannibinoids (Trang et al., 2004; Trang, Sutak, & Jhamandas, 2007) in addition to increasing the neurokinin (NK) 1 receptor expression in the dorsal horn of the spinal cord (King, Gardell, Wang, et al., 2005). Sensory neuropeptides are involved in many brain functions, including analgesia.

NK-1 receptor–expressing neurons play a part in the neuroplastic changes that are associated with the spinal excitability manifested as thermal and tactile hypersensitivity (Vera-Protocarerero et al., 2007). Pronociceptive events are likely related to the opioid-induced up-regulation of spinal dynorphin levels that amplify input from primary afferent nociceptors. Adaptive neuroplastic changes are elicited, which increase sensitivity to pain while simultaneously diminishing the effectiveness of opioid analgesia (Ossipov et al., 2004; Xie et al., 2005).

Ca^{2+}/Calmodulin–Dependent Protein Kinase II. Ca^{2+}/calmodulin–dependent protein kinase II (CaMKII) is a multifunctional serine/threonine protein

kinase that is colocalized with the μ-opioid receptor in the superficial laminae of the dorsal horn of the spinal cord and in the small-to-medium-diameter primary afferent neurons in the dorsal root ganglia (Bruggemann, Schulz, Wiborny, & Holt, 2000; Carlton, 2002). CaMKII is activated by elevated levels of intracellular Ca^{2+} and activated calmodulin. Spinal CaMKII-α activity is significantly increased in morphine-treated mice displaying OIH. When mice were administered a CaMKII inhibitor (KN93), OIH was dose-dependently and time-dependently reversed in parallel with CaMKII (Chen, Yang, & Wang, 2010).

Serotonin. Stimulation of serotonin 1A receptors induces a mirror image of OIH, in that it evokes paradoxic analgesia and inverse tolerance (Xu, Colpaert, & Wiesenfeld-Hallin, 2003). A complex theory involving acute and chronic opioids and signal transduction has been advanced to explain the phenomenon. In this hypothesis, a single input causes two stimuli with opposing effects. For example, a brief positive input, such as stimulation of a peripheral nociceptor, causes an immediate positive response (stimulation), but then a delayed second-order opposing force occurs. Accordingly, when morphine stimulates an opioid receptor, it produces dual responses of both analgesia (first-order response) and hyperalgesia (second-order response). Administration of an opioid antagonist, such as naloxone, not only reverses analgesia, but also promotes hyperalgesia, i.e., the opposite response (Le Bars, Guilbaud, Jurna, & Besson, 1976). This has been interpreted to mean that stimulation of opioid receptors can trigger a compensatory or opposing response of longer duration than the stimulation (Simonnet & Rivat, 2003).

Opioid-Induced Hyperalgesia and Its Relation to Specific Opioids

It would be instructive to know if some opioids produce OIH more than others. We provide here a short summary by drug (additional details are presented in other sections).

Methadone. Methadone is thought to have NMDAR antagonist properties, and NMDAR activation has been implicated in OIH. The literature reports a case study in which OIH was resolved by substituting methadone for morphine in a cancer patient (Sjøgren, Jensen, & Jensen, 1994). There is other evidence suggesting that methadone may be less likely to induce hyperalgesia than certain other opioids (Compton et al., 2001). Although methadone is a pure μ-opioid receptor agonist, it is a racemate in which the *d*-isomer is an NMDAR antagonist, which may account for the attenuation of OIH (Davis & Inturrisi, 1999). Methadone has a relatively long half-life (24-35 hours) and may be prescribed for pain relief (Heit, Covington, & Good, 2004). However, methadone has been reported in a few cases to induce hyperalgesia (Davis & Inturrisi, 1999, Davis, Shaiova, & Angst, 2007). It would be interesting to test the *d*-isomer of methadone alone.

Morphine. High doses of morphine have been reported to induce OIH (Ali, 1986; de Conno et al., 1991; Potter, Reid, Shaw, Hackett, & Hickman, 1989; Sjøgren, Jonsson, Jensen, Drenck, & Jensen, 1993). In rodents, continuous systemic morphine (Li, Angst, & Clark 2001a, 2001b; Xie et al., 2005) and intermittent subcutaneous morphine were associated with OIH (Liang et al., 2006). In human studies, daily subcutaneous morphine induced hyperalgesia (Petersen, Meadoff, Press, Peters, LeComte, & Rowbotham, 2008), and OIH has been reported in patients administered intrathecal morphine (Arner, Rawal, & Gustafsson, 1988).

Fentanyl, Remifentanil, Sufentanil. Fentanyl, a selective μ-opioid receptor agonist, has been reported to induce hyperalgesia in rats (Célèrier et al., 2000; Richebé et al., 2009) and in humans (Chia et al., 1999; Cooper et al., 1997). Opioid-induced hyperalgesia has been reported to develop more often and more rapidly with potent short-acting opioids, such as remifentanil, compared with longer-acting opioids (Derrode, Lebrun, Levron, Chauvin, & Debaene, 2003; Joly et al., 2005). Remifentanil has been associated with OIH in animals (Freye & Levy, 2010; Gu et al., 2009; Zhao & Joo, 2008) and humans (Koppert et al., 2003; Luginbühl, Gerber, Schnider, Petersen-Felix, Arendt-Nielsen, & Curatolo, 2003). In particular, high-dose remifentanil was associated with significantly greater postoperative morphine consumption (59 mg vs. 32 mg) in adult abdominal surgery patients as well as increased levels of pain versus control subjects (but not versus another opioid) (Guignard et al., 2000). However, not all studies of remifentanil reached the same conclusion (Cortínez et al., 2001). Sufentanil has been associated with OIH in animals (Minville et al., 2010).

Buprenorphine. A study of buprenorphine in humans reported an antihyperalgesic effect (Koppert, Ihmsen, Körber, Wehrfritz, Sittl, & Schüttler, 2005). This may owe in part to the relationship of buprenorphine to dynorphins, opioid peptides produced by the brain. Dynorphins increase when opioids are taken and modulate the body's pain response, but sometimes in seemingly contradictory ways. Dynorphins have been associated with both reducing and causing pain in ways not yet fully understood (Lai, Luo, Chen, et al., 2006). Dynorphins exert their effect at the κ-opioid receptors, where they act as agonists. Among other properties, buprenorphine is a κ-receptor antagonist (Silverman, 2009). Buprenorphine has been

shown to block central sensitization (Induru & Davis, 2009). In a study of patients who developed OIH when treated with fentanyl, switching the opioid to buprenorphine reduced hyperalgesia (Koppert et al., 2005).

Dose Dependence and Duration of Opioid-Induced Hyperalgesia

Exposure to high-dose intravenous and intrathecal opioids has been reported to lead to the development of OIH in humans (Ali, 1986; de Conno et al., 1991; Devulder, 1997; Potter et al., 1989; Sjøgren et al., 1993). The literature also reports that such cases of OIH resolve quickly with dose reduction or drug discontinuation (Sjøgren et al., 1994). OIH has been reported also when drug dosage in chronic opioid therapy is abruptly reduced (Devulder, Bohyn, Castille, de Laat, & Rolly, 1996; Miser, Chayt, Sandlund, Cohen, Dothage, & Miser, 1986; Lipman & Blumenkopf, 1989). In rats, thermal hyperalgesia could be induced after several days of intermittent systemic morphine or continuous delivery of morphine interrupted by naloxone (Ibuki et al., 1997; Mayer, Mao, Holt, & Price, 1999; Tilson et al., 1973).

Very low doses of morphine (<1 μg/kg) provoke acute thermal hyperalgesia in otherwise normal opioid-naïve mice (Crain & Shen, 2001). This low-dose OIH is thought to be mediated by the selective activation of excitatory opioid receptor function, because it can be effectively blocked by an ultralow-dose opioid antagonist (naltrexone). An early study of low-dose morphine taken by former addicts unexpectedly revealed a dose-dependent biphasic response to morphine in 12% of patients (7/57), who became mildly hypersensitive to heat pain at low doses but not at higher doses (Andrews, 1943). OIH has been reported in humans with very high doses, rapidly escalating doses, and ultralow doses of opioids (Angst et al., 2010).

After a single large dose of one or more opioids, hyperalgesia is often first observed once the antinociceptive effects of the opioids subside. It has been suggested that the hyperalgesia occurs simultaneously with the opioid administration but is effectively masked by the more powerful antinociceptive effects of the drug (Célèrier, Laulin, Larcher, le Moal, & Simonnet, 1999; Célèrier et al., 2000; Larchner, Laulin, Célèrier, le Moal, & Simonnet, 1998). This suggests that short-term exposure to opioids may produce a rebound hyperalgesic effect. In a study of mice treated with heroin, hyperalgesia was not detected until the mice were administered naloxone. The naloxone effectively unmasked the hyperalgesia, which had been obscured by the more powerful effects of heroin (Larcher et al., 1998). Thus, it is possible that brief exposure to opioids may result in hyperalgesia that goes undetected, at least in the short term.

CLINICAL RELEVANCE IN THE TREATMENT OF CHRONIC PAIN PATIENTS

This, of course, is the big question. It is fairly well established that OIH exists in animal models. Whether it occurs in humans, and to what extent and consequence, is less well established.

Opioid-induced hyperalgesia often presents together with hyperesthesia (increased sensitivity to sensory stimuli) and allodynia (pain elicited by otherwise innocuous sensory stimuli) (Arner et al., 1988), which can markedly exacerbate patient distress. Therefore, OIH might be one part of a spectrum of processes that might present with different features in different patients. This would make OIH difficult to discern. Quantitative sensory testing (Chen, Malarick, Seefeld, Wang, Houghton, & Mao, 2009) and assessment of the magnitude of diffuse noxious inhibitory control (Ram, Eisenberg, Haddad, & Pud, 2008) might be useful tools for assessing OIH. When suspecting OIH, clinicians would need to rule out tolerance, disease progression, flares, and comorbidities. In short, there are many reasons why patients taking opioids may suddenly find pain control inadequate; OIH is just one of them. But if OIH exists, it could create a vicious cycle of escalating dosages and exacerbated pain.

The most concerning ramifications of OIH in humans is its potential impact on pain therapy. Aggressive opioid therapy, once thought to be suitable in certain surgical or palliative settings, may result in a net heightened effect of pain rather than its alleviation. Long-term opioid therapy to manage chronic pain may actually exacerbate it. If opioids can in some instances provoke OIH, this would limit their role in certain pain management settings. For that reason, more study is needed to understand when and how OIH occurs and how it can be better diagnosed.

Opioid-induced hyperalgesia should be considered when the effect of opioid therapy lessens in the absence of disease progression and if the patient reports diffuse pain in an area not associated with the original site of pain (McCarberg, 2010). It could be tested by reducing the opioid dose and monitoring the response; alleviation of pain with decreasing dosage would suggest OIH. Patients suffering from OIH may be reticent about reducing the dose of their pain medication, thinking that their pain is already undertreated or even out of control.

Opioid-induced hyperalgesia may have broader implications. The nonmedical use of opioids is

increasing in the United States with prescription painkiller use (mainly opioids) only surpassed by marijuana (Substance Abuse and Mental Health Services Administration, 2006). Beyond the legal and societal ramifications of widespread illicit opioid use are the clinical ramifications. Physicians can expect to treat many patients who regularly take opioids, not all of whom will be forthcoming about their drug use. Therefore, tolerance or hyperalgesia may be present yet undisclosed in some patients at the outset of treatment. It is unclear how this sort of preexisting OIH or tolerance should be best managed. Opioids are beneficial for treating moderate to severe chronic pain, and their appropriate role in such therapy should not be undermined by fear of OIH.

CONCLUSIONS

A phenomenon of OIH is fairly well established in animal models, and there is ongoing debate about its occurrence in some patients treated with opioids. Although it might be more common in patients treated with high doses of infused opioids, OIH has been reported with low doses, oral opioids, and in a variety of acute and chronic settings. OIH might be misinterpreted as opioid tolerance, a related but distinct phenomenon. However, tolerance is overcome with dose increase; OIH, on the other hand, would be overcome with dose decrease. OIH occurs during opioid withdrawal, but can also be present when opioids are maintained. The exact mechanisms of OIH remain unclear, but they appear to relate to excitatory influence of NMDARs and may have roots in beneficial adaptive pain responses that cause the body to follow pain attenuation with heightened pain sensitivity. Although human clinical trials are relatively few, OIH appears to be more associated with morphine and fast-acting opioids such as remifentanil and less associated with methadone (although evidence is conflicting) and buprenorphine. However, this might relate to the relative amount and pattern of use of the particular opioid drugs. Currently, it is not clear which patients are at greater risk of developing OIH. Further study into OIH is required, particularly because the number of chronic pain patients is expected to significantly grow in coming years and because opioid therapy—a valuable therapeutic tool for treating pain—could be compromised by unrecognized or unaddressed OIH. Until then, it is left to the practitioner to be diligent to the possibility of OIH and to provide the appropriate informed care.

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