

# Opioid Tolerance and Hyperalgesia

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Opioids are well recognized as the analgesics of choice, in many cases, for treating severe acute and chronic pain. Exposure to opioids, however, can lead to two seemingly unrelated cellular processes, the development of opioid tolerance and the development of opioid-induced pain sensitivity (hyperalgesia). The converging effects of these two phenomena can significantly reduce opioid analgesic efficacy, as well as contribute to the challenges of opioid management. This article will review the definitions of opioid tolerance (particularly to the analgesic effects) and opioid-induced hyperalgesia, examine both the animal and human study evidence of these two phenomena, and discuss their clinical implications. The article will also differentiate the phenomena from other aspects related to opioid therapy, including physical dependence, addiction, pseudoaddiction, and abuse.

## Opioid tolerance and opioid-induced hyperalgesia

Opioid tolerance is a phenomenon in which repeated exposure to an opioid results in decreased therapeutic effect of the drug or need for a higher dose to maintain the same effect [1]. There are several aspects of tolerance relevant to this issue [2]:

*Innate tolerance* is the genetically determined sensitivity, or lack thereof, to an opioid that is observed during the first administration. *Acquired tolerance* can be divided into pharmacodynamic, pharmacokinetic, and learned tolerance [3].

*Pharmacodynamic tolerance* refers to adaptive changes that occur within systems affected by the opioid, such as opioid-induced changes in receptor density or desensitization of opioid receptors, such that response to a given

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concentration of the drug is reduced. There is increasing evidence that many of the mechanisms related to this type of tolerance involve the N-methyl-D-aspartate (NMDA) receptor.

*Pharmacokinetic tolerance* refers to changes in the distribution or metabolism of the opioid after repeated drug administrations that result in reduced concentrations of the opioid in the blood or at the sites of drug action. The most common mechanism of this phenomenon is an increase in the rate of metabolism of the opioid.

*Learned tolerance* is a reduction in the effects of an opioid as a result of mechanisms that are learned. One type of learned tolerance is *conditioned or associative tolerance*, which is a learned mechanism that develops when environmental cues are consistently paired with the administration of the drug. When the opioid affects homeostasis by causing sedation or decreasing gut motility, there is a reflex counteraction or adaptation to restore homeostasis, which prevents the full manifestation of the drug's effect. If the opioid is taken under novel circumstances, its effects are enhanced and tolerance is reduced.

Despite the above classifications of opioid tolerance, the clinical utility of such classifications remain to be seen. However, understanding various aspects of opioid tolerance would be likely to aid the investigation into the mechanisms of opioid tolerance.

There have been many studies that have reported that opioid administration can unexpectedly cause hyperalgesia (enhanced pain response to noxious stimuli) and allodynia (pain elicited by innocuous stimuli). This phenomenon can be seen with both acute and chronic administration of opioids and high doses of opioids, and has been observed in both animals and humans. A review of the clinical experiences of more than 750 patients receiving epidural or spinal morphine over a mean period of 4 months showed that many patients developed hyperesthesia (increased sensitivity to sensory stimuli) and allodynia [4]. Studies have shown that the NMDA receptor is also involved in hyperalgesia, as well as other receptors and neuropeptides.

The relative contribution of opioid tolerance versus opioid-induced hyperalgesia to the overall clinical picture is not known from either animal or human studies. What has been known is that the effect of the combination of these two phenomena is seen as an apparent decrease in analgesic efficacy (*apparent opioid tolerance*). It is important for clinicians to be familiar with these two mechanisms so that a decrease in opioid analgesic efficacy is not automatically interpreted as opioid tolerance and treated with dose escalation. Rather, clinicians should consider that increased pain might be a result of opioid tolerance, opioid-induced hyperalgesia, or disease progression and manage the opioid regimen accordingly.

### **Evidence from animal studies for opioid antinociceptive tolerance**

Many studies have demonstrated the development of tolerance in various animal species. The administration of opioids will evoke a dose-dependent

increase in the latency of response to thermal, chemical, and mechanical nociceptors [5,6]. However, with repeated exposure, the effect produced by a given dose of opioid will decrease in magnitude or the duration of action of the opioid will decrease. In addition, studies using continuous opioid infusions by different routes have shown tolerance to be dose-dependent, time-dependent, and receptor-specific, as well as reversible [7,8].

Tolerance to the analgesic effect of opioids is best shown pharmacologically by a rightward displacement of the analgesic dose-effect curve. Studies in the 1970s showed that repeated daily systemic injections of morphine to mice or rats produced significant rightwards shifts in the antinociceptive effects of the opioid [9,10]. Repeated systemic or intrathecal injections of morphine also produced a rightward shift in dose-response curves for intrathecal morphine in the hot-plate and tail-flick tests [11]. Also, prolonged exposure to morphine pellets implanted subcutaneously produced a shift to the right in the dose-effect curves for test doses of morphine given either supraspinally or intrathecally [12].

### **Evidence from animal studies for opioid-induced hyperalgesia**

Many studies using various animal models also have demonstrated opioid-induced hyperalgesia, either with systemic or spinal administration of opioids. Large doses of intrathecal morphine are associated with nonspecific hyperalgesic and hyperesthetic responses [13]. In another study, rats given large (50 µg) intrathecal bolus injections of morphine showed nonspecific pain-related behaviors such as biting and scratching at dermatomes corresponding to the injection site, and aggressive behaviors in response to light brushing of the flanks [14].

More recent studies [15] also show that repeated opioid administration, at a clinically relevant dose range, can lead to a progressive and lasting reduction of baseline nociceptive thresholds, resulting in an increase in pain sensitivity. Rats receiving repeated intrathecal morphine administration (10 or 20 µg) over a 7-day period show a progressive reduction of baseline nociceptive thresholds [16–18]. This reduction is also seen in animals after subcutaneous fentanyl boluses using the Randall-Sellitto test, in which a constantly increasing pressure is applied to a rat's hind paw [19,20]. The decreased baseline nociceptive thresholds lasted as long as 5 days after the cessation of four fentanyl bolus injections. A similar phenomenon has been observed in animals with repeated heroin administration [21].

Opioid-induced hyperalgesia has also been observed with opioid withdrawal. It is possible that decreased baseline nociceptive thresholds observed in animals treated with opioid boluses may reflect a subliminal withdrawal in which changes in baseline nociceptive thresholds might precede other withdrawal signs such as wet-dog shaking and jumping. In this regard, a progressive reduction of baseline nociceptive thresholds has also been demonstrated in animals receiving continuous intrathecal opioid infusion via

osmotic pumps. Moreover, opioid-induced pain sensitivity including thermal hyperalgesia and tactile allodynia is observed in these animals even when an opioid infusion continues [16,22], suggesting the involvement of active cellular mechanisms in the process.

### **Evidence from human studies for opioid analgesic tolerance**

There are case reports and studies [23] that provide evidence for the development of acute tolerance to the analgesic effects of opioids. A study of pediatric scoliosis surgery patients who were either given a continuous infusion of remifentanyl or intermittent morphine intraoperatively showed that there was a 30% higher postoperative morphine requirement in patients who received continuous remifentanyl, with no difference in pain and sedation scores [24]. Another study of abdominal surgery patients also showed that those patients receiving large-dose intraoperative remifentanyl had significantly higher postoperative pain scores and morphine requirement [25].

The evidence for the development of tolerance to the analgesic effects of opioids with chronic administration has been mixed. Many of the studies were in cancer patients with severe pain and showed that they maintained a stable opioid dose (for weeks to years) even with different routes of administration [3,4,26]. Although it is generally agreed that tolerance to the analgesic properties of opioids occurs in patients with malignant pain, dose escalation is thought to be mostly a result of disease progression rather than the development of pharmacodynamic tolerance.

There have been fewer studies of patients with nonmalignant chronic pain. Although chronic pain patients have been observed to require escalating opioid doses to maintain adequate analgesia, several studies have not shown dose escalation and tolerance to be a significant problem. A study of intrathecal morphine in nonmalignant pain showed that dose escalation was related to worsening pathology [27]. Other retrospective studies, including one of patients in an orthopedic spine clinic, have also shown that opioid dosages remained stable over a period of 3 years [3,28]. Indeed, the controversy of development of tolerance to the analgesic effects of opioids with chronic administration may be the result of incorrectly using dose escalation as a measure of tolerance. This is because dose escalation can be affected by many other variables, including disease progression and coexisting psychological issues such as depression and anxiety. Recently, there was a preliminary prospective study in which six chronic low back pain patients were assessed for both opioid tolerance and opioid-induced hyperalgesia using quantitative sensory testing (cold and heat) before and after the institution of oral morphine therapy [29]. Preliminary results showed hyperalgesia and tolerance with cold but no hyperalgesia with heat or analgesic tolerance to heat pain.

### **Evidence in human studies for tolerance to opioid side effects**

Side effects of opioids after initial administration include sedation, nausea, vomiting, respiratory depression, miosis, constipation, and euphoria/dysphoria. Studies have shown that tolerance to sedation, nausea, and respiratory depression can occur rapidly, while tolerance to constipation and miosis is minimal.

Tolerance to the sedative and cognitive effects of opioids can occur rapidly. Usually sedation and cognitive impairment occur at the start of treatment or after a dose increase. One study showed that patients had significant cognitive impairment after a dose increase while patients on a stable regimen had no impairment [30]. In addition, patients seemed to be less aware of cognitive impairment compared with other side effects. If patients continue to be impaired by sedation, one can consider changing the dosing regimen to smaller and more frequent administrations. Alternatively, one could also use oral methylphenidate or modafinil to reduce sedation, if the opioid dose escalation is considered to be necessary for pain management.

The incidence of nausea has been estimated to occur in 40% of patients, while vomiting has been estimated to occur in 15% of patients. These effects usually resolve in a few days and patients can be given antiemetics while they have these symptoms [3].

Respiratory depression is a significant side effect of opioid administration as all opioids can depress the respiratory center in the brainstem. Tolerance to this effect develops rapidly and especially with repeated dosing but it is important for clinicians to be aware of the potential for respiratory arrest, especially in opioid-naïve patients receiving large doses or certain opioids (eg, methadone) with different pharmacokinetic profiles.

Constipation is a common side effect of opioid treatment and one to which there is little development of tolerance. Since opioids bind directly to peripheral opioid receptors in the gastrointestinal tract, there is decreased peristalsis; decreased biliary, pancreatic, and intestinal secretions; and increased ileocecal and anal sphincter tone. This leads to increased stool transit time and dessication of feces. In severe cases, patients can get narcotic bowel syndrome, which consists of nausea and vomiting, stomach discomfort, constipation, abdominal distention, and colonic obstruction. For these reasons, patients should always be on an aggressive bowel regimen while undergoing opioid treatment.

### **Evidence from human studies for opioid-induced hyperalgesia**

Unlike laboratory animal studies in which changes in baseline nociceptive thresholds are measured in a controlled setting, it is difficult to determine whether changes in pain levels occur clinically following opioid administration [15]. It is challenging to distinguish pharmacological tolerance from hyperalgesia when efficacy of analgesia is usually based on subjective pain

scores. However, there is still some evidence that suggests that opioid-induced hyperalgesia may be present clinically.

As previously discussed, there have been reports and studies showing decreased analgesic efficacy after intraoperative remifentanyl infusion [22–24]. It should be noted these observations do not adequately distinguish whether what appears on the surface to be the development of opioid tolerance is actually due to pharmacologic tolerance, opioid-induced hyperalgesia, or both. One indication for the presence of opioid-induced hyperalgesia is the observation that patients treated intraoperatively with remifentanyl reported more postoperative pain than the matched nonopioid controls. The level of postoperative pain should be comparable between the two groups if there was only the development of pharmacologic tolerance without opioid-induced hyperalgesia.

Empirical observations have suggested that pain sensitivity differs between normal subjects and those with opioid addiction [31–33]. Recently it has been reported that pain sensitivity to experimental pain stimulation is increased in opioid addicts [34]. Furthermore, those former opioid addicts maintained on methadone reported additional enhancement of pain sensitivity as compared with matched former opioid addicts not on methadone maintenance, suggesting that a prolonged methadone maintenance program may further worsen abnormal pain sensitivity in former opioid addicts.

There have been many recent case reports of cancer patients with high-dose opioid-induced hyperalgesia whose pain resolved after reduction in dose [35–37]. This has also been observed in chronic nonmalignant pain patients [38]. However, except for one recent preliminary study (see Chu and colleagues [29]), there is lack of controlled clinical studies and such studies are urgently needed to further evaluate clinical approaches to differentiation and management of pharmacologic tolerance versus opioid-induced hyperalgesia.

### **Mechanisms mediating opioid-induced hyperalgesia and antinociceptive tolerance**

Studies suggest that opioid-induced hyperalgesia and antinociceptive tolerance may have mechanisms in common with neuropathic pain after peripheral nerve injury [39]. Both are associated with greatly reduced analgesic effect of morphine and are sensitive to reversal by NMDA antagonists. Activation of NMDA receptors by glutamate causes sensitization of spinal neurons. NMDA receptor-mediated central sensitization has been associated with opioid-induced hyperalgesia and enhanced nociception in chronic pain states. Blockade and reversal of opioid tolerance by NMDA receptor antagonists have been observed, demonstrating the importance of the NMDA receptor in the development of tolerance. Studies have also shown that hyperalgesia caused by fentanyl or heroin, as well as

naloxone-mediated opiate withdrawal, was also blocked by NMDA receptor antagonists.

Recent evidence (see Mao [15]) also suggests that prolonged exposure to opioids induces neuroplastic changes resulting in the enhanced ability of the neuropeptides cholecystokinin (CCK) to excite pathways arising from the rostromedial medulla (RVM). This mechanism enhances morphine-induced pain and tolerance and leads to an up-regulation of spinal dynorphin content. Pathologically elevated levels of dynorphin then promote the release of excitatory neurotransmitters, which is pronociceptive and clinically manifests as increased pain and is seen as antinociceptive tolerance.

### **Clinical implications of opioid-induced hyperalgesia and antinociceptive tolerance**

A diminishing opioid analgesic efficacy during opioid treatment is often considered a sign of pharmacological tolerance, assuming there is no apparent disease progression. Escalation of opioid doses has been a common approach to improve analgesia. However, this conventional practice of dose escalation needs to be revisited in light of both animal and human study evidence of paradoxical opioid-induced hyperalgesia. Apparent opioid tolerance is not synonymous with pharmacological tolerance, which calls for an increase in opioid dose, but may be the first sign of opioid-induced hyperalgesia, suggesting, instead, a need for opioid dose reduction. The important issue is how to distinguish the elements of apparent opioid tolerance and consider the “differential diagnosis” [40] for increased pain in clinical settings.

There are two other main categories of factors that can contribute to declining analgesia, besides tolerance: increased activity in nociceptive pathways and psychological processes. Increased activity in nociceptive pathways can include (1) increasing activation of nociceptors in the periphery because of mechanical factors (tumor growth) biochemical changes (inflammation), or peripheral neuropathic processes (neuroma formation) and (2) increased activity in central nociceptive pathways because of central neuropathic processes (sensitization, shift in receptive fields, or change in modulatory processes).

Psychological processes can include increased psychological distress (anxiety or depression), change in the cognitive state leading to altered pain perception or reporting (delirium), and conditioned pain behavior that is independent of the drug. There are several issues related to opioid-induced hyperalgesia, as discussed in the following paragraphs.

#### *Opioid-induced hyperalgesia versus preexisting pain*

Several features of opioid-induced pain observed in animal and human studies would be helpful in making distinctions between opioid-induced

and preexisting pain. First, since opioid-induced hyperalgesia would conceivably exacerbate a preexisting pain condition, pain intensity should be increased above the level of preexisting pain following opioid treatment in the absence of apparent disease progression. Second, opioid-induced hyperalgesia would be diffuse, less defined in quality, and beyond the distribution of a preexisting pain state, given that the underlying mechanisms of opioid-induced hyperalgesia involve neural circuits and extensive cellular and molecular changes. Third, quantitative sensory testing may reveal changes in pain threshold, tolerability, and distribution patterns associated with the development of hyperalgesia. These parameters may also help make distinctions between the exacerbation of preexisting pain and opioid-induced pain. Fourth, undertreatment of a preexisting pain or the development of pharmacologic tolerance may be overcome by a trial of opioid dose escalation. On the contrary, opioid-induced pain could be worsened following an increase in opioid doses.

#### *Opioid regimens and opioid-induced hyperalgesia*

Several factors regarding an opioid regimen may influence the development of opioid-induced hyperalgesia. First of all, it remains to be investigated as to what opioid dose ranges lead to opioid-induced pain sensitivity. Opioid doses given through neuraxial or systemic routes in animal studies are comparable to moderate opioid doses in clinical settings. Second, there may be differences between different categories of opioid medications (eg, morphine versus methadone) in terms of their ability to induce hyperalgesia. Some evidence suggests that the development of opioid-induced hyperalgesia may differ between individual opioid medications [34]. Furthermore, is there cross pain sensitivity to other opioids following the treatment with one opioid? Last, the temporal correlation between opioid therapy and the development of opioid-induced hyperalgesia remains unknown, although opioid-induced hyperalgesia has been demonstrated in patients receiving a short intraoperative course of opioids. With a given dose of opioid treatment, how long would it take to develop opioid-induced hyperalgesia in a clinical setting? Conceivably opioid-induced pain sensitivity would be more likely to develop in patients receiving high opioid doses with a sustained treatment course.

#### *Opioids and preemptive analgesia*

While the clinical relevance and effectiveness of preemptive analgesia remains an issue in debate, several reasons may argue against the use of opioids as the main agent for preemptive analgesia. A large dose of intraoperative opioids may activate a pronociceptive system leading to the development of hyperalgesia postoperatively. This may confound the postoperative pain assessment and counteract the opioid analgesic effects. Also, the idea of preemptive analgesia

calls for preemptive inhibition of neural plastic changes largely mediated through the activation of the central glutamatergic system. Opioids are thought to inhibit the nociceptive input that could activate the central glutamatergic system. However, neural mechanisms of opioid tolerance and opioid-induced hyperalgesia may interact with those of pathological pain and pathological pain could be exacerbated with opioid administration [41].

### **Approach to a patient on opioid regimen with increased pain**

In evaluating a patient receiving opioid treatment who has increased pain, it is important to systematically review the various aspects of the “differential diagnosis” stated above. Once increased nociceptive activities (eg, disease progression) or psychological processes have been ruled out as the primary contributors to the patient’s worsened pain, one is left with the task of differentiating between pharmacologic tolerance and opioid-induced hyperalgesia. It will not be unreasonable to give a trial of opioid dose escalation at this point. If the patient’s pain improves, the cause of the pain is more likely to be tolerance. However, if the patient’s pain worsens or does not consistently respond to the dose escalation, it could be a result of opioid-induced hyperalgesia and the dose should be decreased or even weaned off. The patient may also exhibit other features of opioid-induced hyperalgesia as described previously, which can help confirm this diagnosis.

In addition, one can consider opioid rotation, as patients can get better relief of their pain using a different medication, often at lower equi-analgesic dosages. We also recommend using adjuvant pain medication treatments to minimize the amount of opioid the patient is taking, thereby reducing the risk of tolerance and hyperalgesia occurring. Last, one should also consider the history of the patient’s pain and its responsiveness to opioids. A patient who was previously on a stable opioid regimen and now complains of worsening pain is much different than one whose pain never improved with opioids. In the latter case, the patient should be weaned off the opioid and a nonopioid regimen pursued, instead of having continued dose escalations.

### **Differentiation of related phenomena in the context of opioid therapy**

*Physical dependence* occurs when there is a withdrawal syndrome after abrupt cessation or dose reduction of the opioid or after administration of an antagonist drug [1]. Physical dependence is a reflection of neurophysiologic adaptation, thought to occur at peripheral and central neurons as a result of changes induced in opioid receptors [42]. Some of the signs and symptoms of withdrawal are listed below.

*Symptoms of withdrawal:* restlessness, irritability, increased sensitivity to pain, craving for opioids, nausea, abdominal cramps, myalgias, dysphoria, anxiety, insomnia.

*Signs of withdrawal:* sweating, piloerection, tachycardia, vomiting, diarrhea, hypertension, papillary dilation, yawning, fever, rhinorrhea.

It is not known clinically as to how long or what dose can increase a patient's likelihood of developing physical dependence. It should be assumed that the patient is predisposed after repeated doses over several days. Patients on opioids for a short period (several weeks) followed with the cessation of administration may often have very mild withdrawal symptoms that they do not recognize. Patients on long-acting opioids, such as methadone, can also have mild withdrawal symptoms even with abrupt cessation because of slow elimination. Severe withdrawal symptoms can, however, be precipitated with administration of naloxone, an opioid antagonist. Indeed, symptoms can occur even in individuals after one to two doses of an opioid, with no history of opioid dependence [43].

The withdrawal symptoms, although extremely unpleasant, are not considered to be life threatening. However, it is the fear of withdrawal that is a positive reinforcer both for continued self-administration of morphine in animals [44] and for continued drug-seeking behavior in patients who try to avoid these symptoms. It is important to note that physical dependence and this type of drug-seeking behavior do not necessarily indicate addiction.

*Addiction* is defined as a behavioral pattern of drug use, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and the high tendency to relapse after withdrawal [42]. It is a group of maladaptive behaviors, including loss of control, preoccupation with drug use, and results in adverse consequences of use. Addiction is distinct from physical dependence and it should be noted that addiction is a psychological and behavioral process.

*Pseudoaddiction* describes an iatrogenic syndrome of behavioral changes that is similar to addiction, but develops as a result of inadequate pain management [45]. Severe and uncontrolled pain can result in increasing demands and drug-seeking behavior from the patient. This behavior may result in increasing suspicions on the part of the clinician that the patient is "addicted" and unwillingness to provide more opioids. The patient then becomes increasingly angry and distrustful of the clinician because of the inadequate treatment of the pain as well as the suspicions of addiction. It is important for the clinician to be aware of this syndrome and continually reevaluate the patient's clinical status with alterations in the therapeutic management.

The evidence of the development of addiction in patients with chronic administration of opioids has been mixed. Several studies have not shown abnormal drug-seeking behavior in patients with post-herpetic neuralgia, phantom limb pain, and chronic spinal pain [3]. But another study by Maruta and colleagues [46] showed that 65% of 144 consecutive patients referred for chronic nonmalignant pain management were abusing or "dependent on" weak and strong opioid drugs and had a strong family history of alcohol abuse. Because of the wide range of responses to opioid therapy

in chronic pain patients, Portenoy [47] has suggested redefining addiction in these patients as

- (1) an intense desire for the drug and overwhelming concern about its continued availability (psychological dependence);
- (2) evidence of compulsive drug use (characterized, for example, by unsanctioned dose escalation, continued dosing despite significant side effects, use of drug to treat symptoms not targeted by therapy, or unapproved use during period of no symptoms); or
- (3) evidence of one or more of a group of associated behaviors, including manipulation of the treating physician or medical system for the purposes of obtaining additional drug (altering prescriptions, for example), acquisition of drugs from other medical sources or from a nonmedical source, drug hoarding or sales, or unapproved use of other drugs (particularly alcohol or other sedatives/hypnotics) during opioid therapy.

*Abuse* describes the use of a medication by the patient in a way that may cause harm to him- or herself or to others, or the use of the medication for an indication other than that intended by the prescribing clinician. An abuser may or may not be physically dependent or addicted to the opioid [42].

## Summary

In summary, the phenomena of opioid tolerance and opioid-induced hyperalgesia have been well documented and contribute to the decreased analgesic efficacy of opioids. In the clinical setting, patient reports of increased pain require a systematic approach in consideration of the possible etiologies. In addition, there should be awareness that increasing the opioid dose may not always be the answer. Under certain circumstances, less opioid may be more effective in pain reduction. This approach may be combined with opioid rotation or addition of nonopioid adjuvant medications. In addition, opioid tolerance and opioid-induced hyperalgesia need to be differentiated from physical dependence, addiction, pseudoaddiction, and abuse.

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