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The OIH Paradox:
Can Opioids Make Pain Worse?

CURRENT COMMENTS

Commentary Author: **Peggy Compton, RN, PhD**

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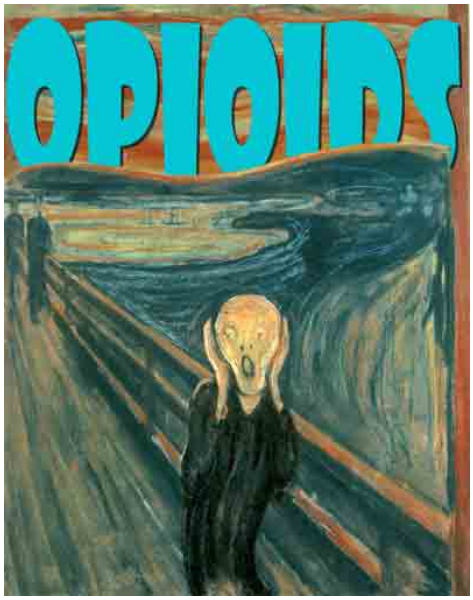
Practice Pointers Summary

- In certain cases, opioid administration not only induces analgesia but also may paradoxically cause diminished tolerance for pain (that is, opioid-induced hyperalgesia or OIH).
- OIH appears to be the result of changes to the nervous system incurred by opioid exposure that essentially up-regulate pain-processing mechanisms.
- OIH has been well-characterized in pain-free animal models, but its presence and clinical implications in patients with pain are only beginning to be described.
- There appears to be a genetic propensity for certain strains of animals to develop OIH, which also may explain why it occurs in some patients but not others.
- In assessing the possible presence of OIH, practitioners need to rule out other sources of opioid-analgesia failure, including worsening pain pathology, opioid tolerance, physical withdrawal, pseudoaddiction, and addiction.
- Several strategies have the potential to minimize the development of OIH, or resolve OIH if it does occur.



With new understandings that opioids may produce hyperalgesic as well as analgesic responses, clinicians are increasingly wondering if ongoing opioid therapy for chronic pain might actually worsen the pain experience for some patients.

Understanding OIH

In an early essay describing his clinical observations of patients injecting morphine on a daily basis, physician/author Clifford Albutt [1870] wondered, *"Does morphia tend to encourage the very pain it pretends to relieve?"*

He continued, *"I have much reason to suspect that a reliance upon hypodermic morphia only ended in a curious state of perpetuated pain"* [p. 329]. Although this was essentially ignored in subsequent clinical research at that time, questions about the pain responses of opioid-dependent patients again arose with the advent of methadone maintenance treatment for addiction in the 1960s [Ho & Dole 1979; Martin & Inglis 1965], and culminated in current understandings of what is described as

opioid-induced hyperalgesia (OIH) — that is, diminished tolerance for pain following opioid administration [see reviews Angst and Clark 2006; Mao 2002; Ossipov et al. 2005].

The implications of this altered pain state have become of interest to researchers, as well as to clinicians involved in the prescription of opioid analgesics for chronic pain [Chang et al. 2007; Koppert & Schmelz 2007; Mercandante et al. 2003; Wilder-Smith & Arendt-Nielsen 2006]. Appreciating that opioids appear to impart hyperalgesic as well as analgesic responses, clinicians are increasingly asking if ongoing opioid analgesic therapy for the treatment of chronic pain might actually worsen the pain experience for certain patients.

Convergent lines of preclinical (laboratory) and clinical evidence indicate that opioid administration not only provides rapid and powerful pain-relieving effects, but may concurrently set into motion certain paradoxical anti-analgesic or hyperalgesic processes. These can be observed during both opioid analgesia and opioid withdrawal [Angst et al. 2003; Ballantyne 2007; Ballantyne & Shin 2008; Chu et al. 2008; Li et al. 2001; Simonnet 2005; Vanderah et al. 2001].

Further examination of the neural mechanisms underlying the development of this hyperalgesic effect has provided evidence that it develops concurrently with tolerance to opioid analgesia [Mao et al. 1995; Xie et al. 2005]. This suggests to some researchers that opioid tolerance encountered in clinical settings may actually reflect hyperalgesic changes [Colpaert 1996; Gardell et al. 2006; Laulin et al. 1999; Mao 2006].

Animal/Preclinical Models of OIH

Hypothesized mechanisms underlying the development of OIH have been attributed to various opioid-induced changes within pain processing structures of both the spinal cord and the brainstem. Pain is the most finely-tuned of the senses, with modulation of a painful stimulus occurring in the spinal cord as transmission of the pain ascends to the brain. There also are descending controls on the pain experience from the brainstem and higher cortical centers of the brain. Although they often dampen or decrease the perception of pain, these modulatory processes can also facilitate pain or make it "feel worse." It is these latter effects that have been implicated in the development of OIH.

From a molecular perspective, the best studied OIH mechanism occurs in cells of the ascending dorsal horn tracts of the spinal cord where opioids may induce the upregulation of excitatory N-methyl-D-aspartate (NMDA) receptors [Mao et al. 1994; Mayer et al. 1999], which results in the increased transmission of nociceptive signals. Other spinal neuropeptides possibly involved in the development of OIH include the anti-opioid neuropeptides FF [DeVillers et al. 1995], NK-1 [Vera-Portocarrero et al. 2007], and lumbar dynorphin, a kappa opioid agonist with pain facilitating activity [Gardell et al. 2002; Vanderah et al. 2000].

Pain modulating processes descending from the brain to the spinal cord also have been implicated in the development of OIH. Good preclinical evidence has shown that opioids binding to receptors in the brainstem can result in increased release of a pro-nociceptive peptide, cholecystokinin (CCK), in the medulla. Interestingly, recent work suggests a role for the im-

Brief Definitions of Terms

- **Opioid Tolerance** – a reduction in response to a given dose of drug after repeated administration.
- **Physical Dependence** – a state resulting from habitual use of a drug in which negative physical withdrawal symptoms arise following discontinuation.
- **Opioid Dependence (Addiction)** – a psychiatric diagnosis (from DSM-IVR) characterized by loss of control over opioid use and continued use despite negative consequences.
- **Pseudoaddiction** – a syndrome that may be created by the undertreatment of pain, and is characterized by drug-seeking behaviors that can be mistaken for addiction.
- **Opioid Withdrawal** – a clinical syndrome produced by sudden abstinence from an opioid drug in a physically-dependent individual, including symptoms of restlessness, lacrimation, rhinorrhea, piloerection, muscle spasms, abdominal cramps, insomnia, nausea, vomiting, and/or diarrhea.
- **Analgesia** - deadening or absence of the sense of pain without loss of consciousness.
- **Hyperalgesia** – increased sensitivity to pain.
- **Allodynia** – pain from stimuli that are not normally painful.
- **Nociception** – activation of afferent pain receptors by stimuli that have the potential to damage tissue.

mune system in the production of OIH [DeLeo et al. 2004; Hutchinson et al. 2008; Liang et al. 2008; Ossipov et al, 2005; Watkins & Maier 2000]. For example, opioids have been shown to bind to μ-opioid receptors located on astrocytes of the blood-brain barrier, resulting in the subsequent expression and release of pro-inflammatory chemokines and cytokines that activate nociceptors and increase the severity of the pain experience.

Genetic factors are also implicated in the development of OIH, as well as opioid responses in general — some patients may be more susceptible to OIH than others. Preclinical evidence suggests that there are certain strains of animals who, by nature, are relatively intolerant of pain, do not receive good analgesia from opioids, and are likely to find opioids highly rewarding. Not only do these data suggest a positive relationship between pain sensitivity and a propensity for addiction to opioids [see Elmer et al. 1998; Mogil et al. 1999], but that other inherited differences in opioid responses (eg, tolerance, physical dependence) [Kest et al.,2002a, 2002b, 2004] may exist.

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Individual variation in opioid response is evident in the development of OIH as well. In a recent examination of 16 different strains of inbred mice, significant differences in the development of OIH following 4 days of morphine treatment were found, with an increase in pain sensitivity ranging from 4% to 36% by strain. One strain known to be relatively intolerant of pain also developed a notable degree of hyperalgesia (24%) following chronic morphine administration [Liang et al., 2006]. In humans, this suggests that patients who are, by nature, pain sensitive might also be more likely to develop hyperalgesia with opioid therapy.

Clinical Evidence for OIH

Since evidence for the existence of OIH and its characteristics have been principally established in animal models, it is challenging to extrapolate preclinical findings to everyday clinical experience with patients having chronic pain. Not only is pain a much more highly modulated and emotional experience in humans, but it is not entirely clear how the pain tolerance in humans (eg, the point of subjective intolerance to pain, possibly as an indicator of hyperalgesia) compares with the pain threshold in animals (eg, the point at which an animal withdraws its tail, jumps on a hotplate, etc. in response to a painful stimulus). Furthermore, the development of OIH has been better characterized in animals either without pain or with acute pain, thus its effects and relevance in the setting of clinically chronic pain remain incomplete.

Although recent work confirms that opioid administration induces hyperalgesia to experimental pain in healthy human subjects [Angst et al. 2003; Celerier et al. 2001; Koppert et al. 2003], accounts in the literature of its emergence in patients with pre-existing chronic pain are relatively uncommon and often limited to case reports. It is likely that, due to shared characteristics or a somewhat indistinguishable presentation in the patient (eg, increased pain and/or need for more opioid), clinical instances of OIH may have been mistakenly considered as analgesic tolerance, thus limiting empirical insights into the actual prevalence of OIH.

Due to shared characteristics or vague presentation in patients, clinical instances of OIH may have been mistakenly considered as analgesic tolerance.

Probably the best described evidence for OIH was in postoperative patients who had received opioids intraoperatively, and it seemed to develop in a dose-dependent manner [Chia et al. 1999; Cooper et al. 1997; Hansen et al. 2005; Guignard et al. 2000]. Investigators showed that, in patients undergoing various abdominal surgeries, postoperative reports of pain severity and/or opioid consumption were significantly higher in patients

receiving intrathecal or intravenous short-acting opioids (fentanyl and remifentanil) during surgery, in comparison with those receiving placebo [Cooper et al. 1997; Hansen et al. 2005] or low dose opioids [Chia et al. 1999; Guignard et al. 2000]. It is theorized that the increased opioid exposure during surgery induced hyperalgesic changes producing increased pain perception and opioid need during the postoperative period.

As noted above, reports of OIH in patients with histories of chronic pain have been much less common, and these have been primarily limited to individuals with malignant, cancer-related pain. Across a number of case studies, the emergence of hyperalgesia or allodynia has been reported in cancer patients prescribed large or rapidly escalating doses of morphine or fentanyl [Ali 1986; Mercandante et al. 2003; Mercadante & Arcuri 2005; Sjogren et al. 1993]. These effects were resolved by rotation to a weak opioid (tramadol) [Okon & George 2008; Zylicz & Twycross 2007].

In a number of cases hyperalgesia was reported in cancer patients prescribed large or rapidly escalating doses of morphine or fentanyl.

A similar pattern of OIH incurred by intrathecal sufentanil and clearing with opioid discontinuation was described in a single case report of a woman with chronic non-malignant low back pain (failed back syndrome) [DeVulder, 1997]. This suggests that, regardless of the etiology of chronic pain (malignant versus non-malignant), OIH may become evident in certain individuals within the context of high-dose opioid therapy.

A single study by Chu and colleagues [2006] seems of most relevance to the clinical situation of chronic non-malignant pain (CNMP) and ongoing opioid therapy. These researchers demonstrated the development of OIH in a small sample of patients (n=6) with chronic non-malignant low back pain following 1 month of oral sustained-release morphine treatment (median dose 75 mg/day). Thirty days of morphine at therapeutic doses not only resulted in analgesic tolerance to challenge doses of remifentanil but also diminished cold-pressor pain tolerance by almost 25% from baseline. Despite the fact that some analgesic effect was achieved, the increased sensitivity to experimental pain in these patients suggests the presence of hyperalgesic changes.

Indirect evidence of OIH may be reflected in the large number of CNMP patients who do not respond to and/or ultimately discontinue ongoing opioid therapy. According to recent meta-analyses of existing clinical trial data, the benefits of opioid therapy beyond 6-8 weeks for CNMP have yet to be demonstrated [Chou & Huffman 2007; Deshpande et al. 2007; Eisenberg et al. 2006; Furlan et al. 2006]. Therefore, potential long-term consequences of opioid therapy, such as OIH, have not been fully evaluated. High rates of drop-outs (approximately 30%) are reported in short-term trials [Fields 2007], with up to 56% of subjects dropping out of longer-term follow-up studies (7 to 24 months) [Kalso et al. 2004]. The drop-out rates are most commonly attributed to opioid side effects or a perceived lack of analgesic efficacy; however, the degree to which the development of OIH contributes to poor outcomes in these patients is unclear.

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Interestingly, and in agreement with the study by Chu and colleagues [2006], findings of increased pain following opioid titration have been noted [Caldwell et al. 1999; Moulin et al. 1996, 2005], and several investigators have observed patient improvement with opioid detoxification [Baron & McDonald 2006; Saper & Lake 2008]. Commenting on a large cross-sectional study by Eriksen and colleagues [2006] — which showed that patients on opioid therapy for the treatment of CNMP were less likely to achieve key outcomes (pain relief, quality of life, functionality) than those not on opioid therapy — Ballantyne [2006, p. 4] warned that "not all patients benefit, and a cautious, structured and selective approach is the best way to preserve opioid therapy for those that do."

Differential Assessment of OIH

Although the precise mechanisms underlying OIH are complex and continue to be elucidated, clinical approaches to the patient prescribed chronic opioid therapy can be garnered from the research literature. Overarching these suggested recommendations is the tenet that chronic opioid use requires careful oversight on the part of the prescribing clinician for both therapeutic response to opioids and for the emergence of opioid responses that counter analgesic effects. In addition to OIH, pain increasing in the presence of opioid therapy can indicate not only worsening pain-generating pathology but several other opioid-related phenomena, including tolerance, withdrawal, addiction, or pseudo-addiction [Compton 2008; Singla et al. 2007; Tzabazis & Koppert 2007].

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Each of these conditions should be considered in the differential assessment of the patient. The following ***Table*** summarizes some of the factors that may help to distinguish one condition from another.

Differential Assessment of OIH vs Other Conditions

Condition	Nature of Pain	Presentation or Onset of Pain	Response to Opioid Administration
Opioid-Induced Hyperalgesia (OIH)	Increased sensitivity to pain; diffuse pain, extending beyond the distribution of pre-existing pain; allodynia may be present.	Abrupt onset with rapid opioid escalation or high-dose opioid administration.	Pain worsens.
Worsening Pain Pathology	Localized to site of pre-existing pain or new site of pathology.	Variable, depending on source of pain.	Pain improves.
Opioid Tolerance	Localized to site of pre-existing pain.	Gradual onset.	Pain improves.
Opioid Withdrawal	Increased sensitivity to pain; diffuse, extending beyond the distribution of pre-existing pain.	Abrupt with short-acting opioids or antagonist administration; gradual with long-acting opioids.	Pain improves.
Opioid Addictive Disease	Increased sensitivity to pain; diffuse, may extend beyond the distribution of pre-existing pain.	Gradual onset.	Pain may improve but functionality may worsen.
Pseudoaddiction	Localized to site of pre-existing pain.	Variable, depending on source of pain.	Pain improves.

Table adapted in part from Mitra 2008.

Additionally, several general principles should be kept in mind when considering the differential diagnosis of possible OIH…

1. The presence of worsening pathology or psychological influences on the experience of pain must be ruled out. These are unrelated to opioid administration and each can contribute to increased complaints of pain; therefore, they should be carefully evaluated.
2. Tolerance, withdrawal-related symptoms, pseudoaddiction, or addiction can be differentiated from OIH by a trial of increasing the opioid dose and/or frequency. Doing so will either

satisfy the increased opioid need (due to tolerance or pseudoaddiction), treat opioid deficit (reflected by withdrawal), or allow for possible signs of substance dependence (addiction) to emerge (difficulty controlling use, preoccupation with use, etc.).

3. If complaints of pain increase with upward opioid titration, OIH should be considered. If OIH is present, a careful neurological examination could reveal characteristic qualities of the pain. Specifically, pain that presents as being diffuse, difficult to describe, and/or beyond the distribution of the original pain source is likely to be indicative of OIH.

Treatment Strategies

Although well-designed clinical trials are lacking, certain strategies can be recommended to help avoid or minimize the development of OIH in the patient with chronic pain. For one thing, the research literature suggests using opioid-sparing approaches to the degree possible; OIH is demonstrated to increase with opioid dose and length of exposure [Cohen et al. 2008], thus it can help to keep the opioid dose as low as is clinically effective.

Strategies for Minimizing or Resolving OIH

- Keep opioids doses as low as is clinically effective.
- Provide adjuvant medications to enhance opioid sparing.
- Use long-acting opioids.
- Use opioid rotation.
- Consider low-dose opioid antagonists.

Another approach for opioid sparing in chronic pain patients is the use of adjuvant medications. The best studied agent in this regard is the relatively weak NMDA-antagonist dextromethorphan; although, evidence for its efficacy to offset OIH in patients with pain has been mixed. Acute dextromethorphan administration has been shown to decrease the opioid-analgesic requirement (possibly due to emerging OIH) in postoperative patients [Helmy & Bali 2001; Weinbroum et al. 2000] and to reduce OIH in cancer patients, but it appears less effective in consistently doing so for patients with chronic nonmalignant pain [Dudgeon et al. 2007; Galer et al. 2005; Haugan et al. 2008; Heiskanen et al. 2002]. These conflicting data suggest that a trial of dextromethorphan may be attempted and helpful in certain patients, but the clinician should prescribe with the understanding that it may not be effective.

Other adjuvants that have been identified as being potentially helpful include:

- propofol, due to it's gabaminergic activity [Singler et al. 2007],
- COX-2 inhibitors (eg, parecoxib, rofecoxib) for their ability to inhibit prostaglandin synthesis [Joshi et al., 2003; Troster et al., 2006],
- CCK antagonists (eg, proglumide) to block descending pain facilitatory processes [Bernstein et .al., 1998, McCleane, 2003; 2004],
- α2-receptor agonists (eg, clonidine), which appeared to attenuate OIH in a small sample of healthy human subjects [Koppert et al. 2003].

Next, as is standard for chronic pain treatment in general, the use of long-acting versus short-acting opioids is preferred. Long-acting agents have a more gradual onset and offset of action, and provide relatively constant coverage of analgesic effects. This helps avoid rapid escalations in opioid plasma levels that have been related to the development of OIH in clinical and preclinical settings. Additionally, investigators have shown that intermittent opioid dosing or repeated episodes of opioid withdrawal worsen OIH, thus the relatively stable plasma levels of drug afforded by long-acting opioids may help to minimize the emergence of OIH [Hood, 2003; Sweitzer et al. 2004].

Opioid rotation is another suggested strategy to mitigate OIH. Incomplete cross-tolerance between opioids often provides comparable analgesia but at a lower equianalgesic opioid dose

[DuPen et al. 2007]. Methadone appears to be particularly useful for rotation, which is theorized as being due to its NMDA-antagonist properties in reducing neuronal excitability.

Of increasing interest in the literature is the use of low-dose opioid antagonists in conjunction with opioid agonists to counteract the development of OIH [Carroll et al. 2004; Cepeda et al. 2004; Terner 2006; Wang et al. 2005; Webster 2007]. In two recent randomized clinical trials enrolling patients with osteoarthritis [Chindalore et al., 2005] and low back pain [Webster et al., 2006], investigators reported significant benefits for pain relief over time and diminished physical withdrawal with the combination of oxycodone-plus-low-dose naltrexone (2-4 mcg/day) versus oxycodone alone. It is theorized that the efficacy of low-dose opioid antagonists in preventing OIH is related to the suppression of G-protein switching in the presence of opioid agonist. (For a review of this subject, see Sloan and Harmann [2006].)

Remaining Questions

Many questions remain about the development and treatment of OIH in pain patients prescribed ongoing opioid therapy. In that many chronic pain syndromes include a significant neuropathic component, it is conceivable that any hyperalgesia induced by opioid therapy might contribute to this neuropathy, thereby worsening the experience of pain. Related to this, the development of OIH in the presence of acute nociceptive (ie, post-operative) pain as opposed to chronic neuropathic pain (or experimental pain, for that matter) requires further research [Kupers 1995; Liang et al. 2006].

The time-course of OIH development also is unclear. Opioid withdrawal-related hyperalgesia can be elicited within hours of opioid exposure [Angst et el. 2003; Compton et al. 2003a; 2003b; Koppert et al. 2003], and OIH appears to develop after relatively short courses of intraoperative opioid administration [Chia et al. 1999; Cooper et al. 1997; Guignard et al. 2000]. Further, limited evidence from this author's laboratory indicates that the development of OIH may vary between different opioid medications, especially those that differ in intrinsic activity (eg, methadone vs. buprenorphine) [Compton et al. 2001]. Therefore, which opioids are more or less likely to induce OIH, and at what point following opioid exposure, are important but still unanswered questions.

Conclusion: A Challenging Problem

Centuries of use have shown that opioids are highly effective for the treatment of acute and chronic cancer pain and, for certain individuals, chronic nonmalignant pain. Opioid-induced hyperalgesia does not appear to complicate the management of pain for the vast majority of patients; thus, fears of inducing OIH should not limit the prescribing of opioids when clinically necessary.

Opioid-induced hyperalgesia does not appear to complicate pain management in the majority of patients. Yet, when OIH does arise, it can pose a clinically challenging problem.

Yet the development of OIH has been consistently demonstrated following opioid administration in animal models, and increasingly in humans with and without pain. Theorized factors underlying the individual development of OIH range from genetically-influenced responses to opioids to the quality and source of the pain. These factors continue to be elucidated.

What is clearly evident from the literature is that when OIH does arise, it can be challenging for the clinician to manage. Interventions aimed at limiting the patient's total exposure to opioid agonists appear to be useful approaches for minimizing the development of these problematic opioid responses that counter analgesic effects. Decreasing the opioid dose, using opioid-sparing adjuvants, prescribing long-acting opioids, and opioid rotation are suggested approaches for either avoiding or treating OIH.

Probably most important is careful monitoring of the patient's response to opioid therapy to begin with. Several opioid-related responses other than OIH – including tolerance, withdrawal, pseudoaddiction, or addiction – can lessen opioid-analgesic effectiveness in the clinical setting, so it is incumbent upon the clinician to identify and differentiate between these conditions.

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About the Author:

Peggy Compton, RN, PhD, FAAN, is Associate Professor of Nursing at the University of California Los Angeles School of Nursing, Los Angeles, CA. She received her PhD in nursing science at New York University and completed postdoctoral training at the UCLA Drug Abuse Research Center. Dr. Compton serves as principal investigator for NIH-supported grants focusing on pain and opioid addiction from clinical perspectives and with a specific interest in how the presence of one affects the expression of the other. She has been systematically studying the pain responses of opioid-addicted individuals and is a clinical expert in detecting opioid abuse and addiction in patients with chronic pain. Additionally, she consults, lectures to various groups, and has authored numerous publications on opioid-induced hyperalgesia, addiction in the patient with chronic pain, and pain management for the patient with co-occurring addictive disease.

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