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OPIOID-INDUCED HYPERALGESIA

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Charles Albutt may have been the first to recognize opioid-induced hyperalgesia (OIH), stating "*Does morphia tend to encourage the very pain it pretends to relieve*?"[1] More than 100 years later, interest in OIH grew upon documentation of enhanced sensitivity to pain secondary to opioid administration in animal studies. Since that time, opioid therapy has been discussed as a potential "double edged sword", resulting in paradoxical heightened pain states.[2]

In 1998, opioid use was prevalent in an estimated 1.2% of the US population. By 2005, this number had risen greater than 2-fold to 2.6%.[3] In any given week, over 10 million Americans take opioids and the national prevalence of regular opioid use (≥5 days/week for ≥4 weeks) is 2%, representing 4.3 million individuals.[3] With this increased prevalence, the number of adverse effects attributable to opioid therapy has likely increased as well. Although the impact of many of these adverse events, including gastrointestinal issues and opioid misuse, abuse and diversion, has been extensively studied in the literature, relatively little is known about OIH as an adverse effect of opioid use.[4] The paucity of data is due, in part, to the subjective nature of OIH which makes systemic analyses challenging. However, OIH is recognized as a growing issue and the 2008 American Society of Interventional Pain Physicians (ASIPP) recommend opioid contracts include informed consent regarding its risk.[5] This review discusses proposed mechanisms, evidence, and treatment options for OIH in light of its increasing recognition as a burden in pain management and the growing prevalence of opioid use nationwide.

Tolerance vs. OIH

OIH is defined as an enhanced pain response to a noxious stimulus.[6] Distinguishing OIH from other known opioid phenomenon, such as tolerance, can be challenging. For instance, tolerance represents a decreased therapeutic effect or need for a higher opioid dose to maintain analgesia and, like OIH, involves a reduction in response to a given dose after repeated administration.[7] However, the pain observed in OIH is often anatomically isolated and qualitatively different from the initial pain requiring opioid therapy, a hallmark finding which is not appreciated in tolerance.[2]

Proposed Mechanisms of OIH

Potential mediators of OIH include intracellular protein kinase C, toxic opioid metabolites, the central glutaminergic system, and spinal dynorphins. Activation of NMDA receptors has been observed after opioid exposure and this activation is thought to contribute to OIH through changes in neuronal development and plasticity.[9,10] Furthermore, increased dynorphin levels have been observed with continuous infusions of *mu*-receptor agonists, supporting the hy-

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Table 1 | Published data on OIH in surgical settings.

			Intraoperative High vs. Low Dose Group		Postoperative High vs. Low Dose Group	
Author (year)	Size	Design	Drug	Dose	Opioid Use	Pain Score
Guignard et al[13] (2000)	n = 49	DB, RCT	IV remifentanil	0.1 vs. 0.3 μg/kg/min	85% more*	50% higher*
Chiaa et al[14] (1999)	n = 60	DB, RCT	IV fentanyl	1 vs. 15 μg/kg	120% more*	30% higher*

*statistically significant change in low versus high-dose ($P < 0.05$)
DB = double blind; **IT** = intrathecal; **IV** = intravenous; **RCT** = randomized controlled trial; **vs.** = versus.

pothesis that OIH is a pro-nocioceptive process resulting from an increase in excitatory neuropeptide synthesis.[11,12] The increase in excitatory neuropeptides provides a physiological basis for amplified excitation to the spinal cord that may result in OIH.

Clinical Evidence of OIH

Hyperalgesia in Patients Undergoing Surgery

Hyperalgesia following intra-operative remifentanil was evaluated in 49 patients undergoing major abdominal surgery.[13] Patients were excluded from participation if they regularly took analgesics or had used opioids within 12 hours of surgery. Subjects were randomly assigned to receive a fixed desflurane concentration adjusted to age with remifentanil 0.25 μg/kg/min (increased stepwise by 0.05 μg/kg/min if insufficient anesthesia was suspected) or fentanyl 0.1 μg/kg/min with escalating desflurane doses to achieve anesthesia. Within 3 hours of extubation, patients were started on patient controlled analgesia (PCA) set to deliver 1 mg morphine bolus with lock-out interval of 5 minutes. The average time to first PCA use was shorter in the remifentanil group (3.5 hours) than the desflurane group (2.5 hours), but this difference was not statistically significant ($P > 0.05$; **Table 1**). However, the cumulative 24 hour post-operative morphine consumption was significantly higher in the remifentanil group (59 mg) versus the desflurane group (32 mg) ($P < 0.05$).[13] These finding suggest that large-dose intra-operative remifentanil doses may have a role in the development of OIH.

Similarly, the dose –response effect of fentanyl on hyperalgesia was assessed in patients undergoing hysterectomy.[14] Patients were randomly assigned to receive either IV 1 μg/kg (n = 30) or 15 μg/kg (n = 30) prior to induction of anesthesia. Halothane was used to maintain anesthesia in the low-dose group while the high-dose group received inhaled halothane plus 100 μg/hr IV fentanyl until the end of anesthesia. After extubation, PCA with an on demand bolus fentanyl dose of 15 μg and lockout of 5 minutes was started (4 hour max 300 μg). Patients in the high-dose group had higher visual analog scores at 4 hours (5.3 ± 1.1 vs. 3.8 ± 0.9; $P < 0.05$) and 8 hours (5.7 ± 1.5 vs. 3.9 ± 0.8; $P < 0.05$) post-operatively than the low-dose group. High-dose patients used 18-50% higher fentanyl doses during the 0-16 hour post-operative observation time than the low-dose group ($P < 0.05$). Specifically, the average 16 hour post-operative fentanyl use was 413.3 μg in the high-dose group and 189.8 μg in the low-dose group.[14]

Observations in Chronic Pain Patients

Studies addressing the development of OIH in the chronic pain population are scarce. However, a preliminary, observational study evaluated the development of tolerance and OIH in 6 patients suffering from chronic low back pain.[15] In this study, patients discontinued use of previous opioid therapy 12 hours prior to starting morphine as a washout period. Sustained-acting morphine was then titrated to a maximum of 120 mg/day over 5 days (median daily dose 75 mg). Hyperalgesia was measured by the change in experimental pain threshold and tolerance from baseline after 1 month of morphine therapy. Specifically, the cold pressor test was used to evaluate hyperalgesia and requires the patient to place his/her hand in an ice bath and indicate when pain is initially detected (threshold) and when pain can no longer be tolerated (tolerance). A series of 15-minute target remifentanil concentration were given prior to cold pressor tests (0 always given first, followed by 2 ng/mL and 4 ng/mL in random order) at baseline and again after one month of morphine therapy. The investigators report that all patients were hyperalgesic after prolonged morphine therapy since the average baseline cold pressor time at 2 ng/mL remifentanil fell from 45 seconds to 29 seconds after morphine treatment ($P < 0.01$). Likewise, the average baseline time at 4ng/mL

Table 2 | OIH studies in non-surgical settings.

Author (year)	Population	Size	Design	Drug	Results
Chu et al[15] (2006)	Chronic pain patients	n = 6	Prospective observational	SR morphine, remifentanil	All patients experienced hyperalgesia, precipitated by remifentanil, after one month of daily oral morphine therapy
Mercadante et al[16] (2003)	Cancer patients	n = 2	Case report	methadone, morphine	OIH resolved after discontinuation of opioid and initiation of bupivacaine

d = day; **SR** = sustained release.

remifentanil was 90 seconds and only 60 seconds after 1 month of morphine treatment ($P < 0.01$).[15]

The issue of OIH and barriers to its detection have been discussed in the setting of cancer pain and two case reports describe hyperalgesia and uncontrolled pain despite escalating opioid doses.[16] The first experienced uncontrolled pain accompanied by confusion, agitation, and "a state of hyperalgesia all over the body" despite 75 mg methadone and incremental dose escalation of IV morphine up to 200 mg daily. Opioid medications were discontinued and, upon administration of epidural bupivacaine (5ml of 0.25%), the patient experienced complete pain control without agitation. Similarly, the second patient experienced a diffuse state of hyperalgesia while taking 90 mg methadone and IV morphine bolus doses as needed. Relief occurred after placement of an infusion pump delivering 25 mg bupivacaine and 2 mg morphine daily at rate of 2ml/hr.[16]

Treatment Options

Opioid Dose Reduction

The role of opioid detoxification in mitigating OIH has been investigated based on the theory that the mechanisms for its development might reset after opioid abstinence or rehabilitation, resulting in pain reduction. One small study evaluated pain scores before and after opioid detoxification in 23 patients experiencing hyperalgesia.[17] Patients were on a variety of opioids prior to detoxification and were placed in two groups, ibuprofen-only (n = 7) and ibuprofen-buprenorphine (n = 16). All patients could take 200 mg ibuprofen as needed (up to six doses per day) during detoxification from respective opioid therapies, but the buprenorphine group was administered a scheduled sublingual (SL) loading dose of 4 mg every half hour for the first 3 doses then 4 mg SL TID. Buprenorphine was then tapered to discontinuation over a maximum of 180 days. All but two patients experienced (both in the ibuprofen group) significant reductions in pain scores (0 to 10 scale) following opioid tapering. The average pain score for all patients was 8.3 prior to detoxification and 3.3 after detoxification ($P < 0.001$; **Table 2**). Furthermore, a 47% reduction in pain scores was reported in the ibuprofen group and 63% in the buprenorphine group. Despite the apparent difference between the groups, final levels of pain relief achieved were not statistically significantly different ($P > 0.05$). The authors concluded that detoxification from opioid therapy in patients with uncontrolled chronic non-malignant pain may aid in pain control.[17]

While detoxification from opioid therapy may alleviate OIH, even dose reduction of opioids without discontinuation might mitigate OIH.[18] One published report described a patient with uncontrolled pain despite IV hydromorphone PCA with basal rate of 80 mg/hr and on demand 40 mg every 15 minutes. The patient experienced increasing pain and, subsequently, intrathecal morphine 8 ml/hr (1150 mg/day) and fentanyl 75 µg/hr were added to his regimen.[19] Hyperalgesia was considered after the patient's regimen was titrated to the oral morphine equivalent of 200,000 mg per day. Following careful tapering of hydromorphone and fentanyl to discontinuation and reduction of the morphine dosage by 100 fold, the patient experienced excellent analgesia.[20] The authors note that OIH occurred distinct from tolerance as evidenced by adequate analgesia at much lower dosages.

Non-Opioid Adjuvant Therapy

Additional literature suggests that using opioid-sparing approaches to pain therapy may help prevent the development of OIH.[21] Concomitant use of non-opioid medications may help minimize the dose of opioid therapy and therefore OIH. This theory was investigated in former opioid addicts experiencing hyperalgesia.[22] Specifically, the effect of adjuvant gabapentin, titrated to 2400 mg/day, on pain threshold scores in 10 patients were compared to pain threshold scores in 16 patients receiving only methadone. The study included a convenience sample recruited from a single methadone clinic and enrolled patients were between the ages of 18 and 55, in good physical and psychological health, compliant in methadone treat-

ment, and on stable methadone doses for at least 6 weeks. Here, pain threshold (measured in seconds using cold pressor tests) was significantly improved at both peak (7.54s vs. 10.49s) and trough (7.61s vs. 9.90s) methadone levels for the gabapentin-methadone group (P<0.05). In the methadone only group, cold pressor times worsened from baseline at both peak (15.82s vs. 12.33s) and trough (14.23s vs. 13.78s) methadone levels. Despite a small sample size, this study may provide support for gabapentin as adjuvant therapy to reduce hyperalgesia associated with opioid therapy.

Cyclooxygenase (COX) inhibitors may also mitigate OIH since prostaglandins (specifically prostaglandin E2) can stimulate glutamate release and antagonize the NMDA receptor.[21,22] This hypothesis was studied in the surgical setting in 66 children (aged 3-11 years) randomly assigned to receive either placebo (n = 32) or rofecoxib 1 mg/kg plus IV fentanyl 2 µg/kg (n = 34).[23] Post-operative pain scores (range 0 to 6) were evaluated using Wong and Baker faces by a blinded nurse observer. Both 2 and 24 hour post-operative scores were significantly lower in the rofecoxib group as compared to placebo (2h: 2.0 vs. 1.3; 24h: 2.5 vs. 1.3; P<0.05).[23] The authors suggest prostaglandin inhibition may block OIH by a mechanism beyond synergistic analgesia.

Specific NMDA Receptor Antagonists

Ketamine, an NMDA receptor antagonist with intrinsic analgesic properties, is used as adjuvant therapy for both chronic pain and OIH. One cross over study enrolled 13 healthy volunteers and used 6 separate treatment trials (separated by ≥1 week) to investigate ketamine's role in attenuating OIH.[24] Specifically, electrical stimulation was used to induce acute pain and areas of hyperalgesia on the forearm in subjects receiving hidden IV infusions of remifentanil 0.1 µg/kg/min, S-ketamine 5 µg/kg/min, or a combination of the two. The hyperalgesic area was measured before, during, and after a 90 minute infusion. Co-administration of S-ketamine and remifentanil resulted in the smallest areas of hyperalgesia at 30, 45, and 60 minutes (24 cm^2, 9 cm^2, 10 cm^2) compared to administration of either remifentanil alone (40 cm^2, 30 cm^2, 29 cm^2) or S-ketamine alone (40 cm^2, 38 cm^2, 29 cm^2) (P<0.05).[24] A similar reduction in hyperalgesic area was identified with co-administration of S-ketamine during a 90 minute infusion of fentanyl in 10 healthy volunteers (**Table 3**).[25]

Opioid Class Rotation

A large proportion of the data regarding opioid class rotation centers on switching to treatment with

Table 3 | Literature supporting dose reduction and non-opioid adjuvant therapy for OIH treatment.

Author (year)	Population, size	Design	Drug	Route	Dose	Intervention
Baron et al[17] (2006)	Chronic pain patients, n = 23	Cohort	Varied*	PO	Varied*	Detoxification from opioids, initiation of buprenorphine and/or ibuprofen
Wilson et al[19] (2003)	Cancer pain, n = 1	CR	mor, HM, F	IT	Ultra-high^	Discontinued hydromorphone & fentanyl, ↓ morphine concentration 100 fold
Compton et al[20] (2010)	MM ex-addicts, n =26	PC, RC	meth	PO	Stable MM dose x 6 w	+ 2400 mg gabapentin/day
Joshi et al[23] (2003)	Surgery, n = 66	RC	F	IV	2 µg/kg	+ 1 mg/kg rofecoxib
Troster et al[21] (2006)	Post-operative, n = 15	R, DB, PC, CO	RF	IV	0.1 µg/kg/min	+ 40 mg parecoxib
Koppert et al[24] (2003)	Healthy volunteers, n = 13	R, DB, PC, CO	RF	IV	0.1 µg/kg/min	+ S-ketamine
Angst et al[25] (2003)	Healthy volunteers, n = 10	R, DB, PC, CO	RF	IV	0.1 µg/kg/min	+ S-ketamine

*Pre-detoxification opioid therapy differed – morphine (n=8), fentanyl (n=6), extended release oxycodone (n=5), hydrocodone (n=2), methadone (n=2).
^Patient was titrated to the equivalent of 200,000 mg oral morphine per day.
+ = added to regimen with no reduction in previous opioid dosage; **APAP** = acetaminophen; **CO** = cross over; **CP** = cold pressor; **CR** = case report; **DB** = double blind; **F** = fentanyl; **HM** = hydromorphone; **IT** = intrathecal; **IV** = intravenous; **meth** = methadone; **MM**= methadone maintained; **mor** = morphine; **PC** = placebo controlled; **PO** = oral; **RF** = remifentanil; **w** = weeks.

Table 4 | Evidence for class rotation as OIH treatment.

Author (year)	Sample Size	Design	Drug	Dose	Route	Results
Mercadante et al[26] (2005)	Cancer, n = 1	CR	F, mor	TD PO	12 mg/day 120 mg prn	Switched to 75 mg methadone/day; resolution of OIH
Zimmerman et al[27] (2005)	Cancer, n = 1	CR	HM	PCA	150 mg/h, 100 mg TID	Switched to 60 mg methadone TID + 75 mg QHS; resolution of OIH
Vorobeychik et al[28] (2008)	Cancer, n = 1	CR	HM	PCA	27 mg/h + 13 mg q10 min	43% dose reduction of hydromorphone + methadone 10 mg BID; resolution of OIH
Koppert et al[29] (2005)	Healthy volunteers, n = 15	R, DB, PC, CO	*	ID	Electric current	SL and IV buprenorphine resulted in less hyperalgesia and greater analgesia than fentanyl
Okon et al[31] (2008)	Cancer, n = 1	CR	F	PCA	60 µg/h basal, 40 µg q 10 min	Switched to tramadol, hydrocodone/APAP 5/500 mg, & ibuprofen; resolution of OIH

*0.15 mg IV buprenorphine and placebo sublingual (SL) pill, 0.2 mg SL buprenorphine and IV saline 0.9%, or IV saline 0.9% and SL placebo pill as a control.
APAP = acetaminophen; **CO** = cross over, **CR** = case report; **DB** = double blind; **F** = fentanyl; **HM** = hydromorphone; **ID** = intradermal; **IV** = intravenous; **Mor** = morphine; **PC** = placebo controlled; **PCA** = patient controlled analgesia; **PO** = oral; prn = as needed; **QHS** = at bedtime; **R** = randomized; **SL** = sublingual; **TD** = transdermal.

methadone (**Table 4**). Interestingly, methadone's d-isomer is an NMDA receptor antagonist which may prevent or reduce OIH. This theory was discussed in a case report of a patient with hyperalgesia despite 12,000 µg/day of transdermal fentanyl and morphine 120 mg as needed.[26] A switch to 240 mg methadone per day was planned based on an initial fentanyl:methadone ratio of 20:1 and administration of methadone was to be divided into three doses. However, the patient achieved analgesia after only 80 mg of methadone.[26] A similar report described metastatic cancer in a patient with uncontrolled pain despite hydromorphone SC infusion at 1.5 mg/h and gabapentin 600 mg every 8 hours. The hydromorphone dose was

Table 5 | Comparison of opioid analgesics.

Generic	Brand	Activity	Approximate Equianalgesic Dose		Duration
			Oral	Parenteral	
morphine SA	MS Contin, Kadian, Avinza, Oramorph	µ, δ, κ agonist	30 mg	-	8-12 h
morphine IR	Roxanol	µ, δ, κ agonist	30 mg	10 mg	3-4 h
oxycodone SA	OxyContin	µ, δ, κ agonist	20 mg	-	4-6 h
oxycodone IR	Oxy IR, Roxicodone	µ, δ, κ agonist	20 mg	-	3-4 h
hydrocodone	Lortab, Vicodin, Norco	µ, δ, κ agonist	30 mg	-	3-4 h
hydromorphone	Dilaudid	µ, δ, κ agonist	7.5 mg	1.5 mg	3-4 h
meperidine	Demerol	µ, δ, κ agonist	300 mg	100 mg	3-4 h
methadone	Dolophine	µ, δ, κ agonist, d-isomer = NMDA antagonist	See Table 6	See Table 6	8-12 h
fentanyl 25 µg/h	Duragesic	µ, δ, κ agonist	45 mg mor/d	15 mg mor/d	72 h
buprenorphine	Buprenex, Subutex	Partial µ agonist full κ antagonist	0.4 mg SL	0.3 mg	6-9 h
tramadol	Ultram	Partial µ agonist, inhibits 5HT & NE	120 mg	80 mg	4-6h

*Various brands names for hydrocodone combined with acetaminophen.
d = day; **mor** = morphine; **NMDA** = N-Methyl-D-aspartic acid; **SL** = sublingual, **SA** = sustained action; **IR** = immediate release; **h** = hour; **5-HT** = serotonin; **NE** = norepinephrine.
Adapted from pain management tables, including VA National Pain Management Strategy Coordinating Committee Pharmacy Workgroup, VA National Formulary and the International Association for Hospice and Palliative Care.

Table 6 | Methadone dosing based on Morphine Equivalent Daily Dose (MEDD).

Oral MEDD (mg/d)	Initial Dose Ratio (morphine:methadone)
<100	3:1
101-300	5:1
301-600	10:1
601-800	12:1
801-1000	15:1
>1001	20:1*

*Often only a portion of the total converted dose is given initially.
Adapted from pain management tables, including VA National Pain Management Strategy Coordinating Committee Pharmacy Workgroup, VA National Formulary and the International Association for Hospice and Palliative Care

then increased to 14 mg/hr over the course of 7 days. Similar to the previous report,[26] a methadone switch was planned at 20 mg every 8 hours with tapering of the hydromorphone. However, five days after starting methadone, the patient's pain was adequately controlled on only 7 mg every 8 hours without adjuvant hydromorphone.[27]

While the case reports previously mentioned employ a complete switch to methadone, anecdotal reports exist for successful treatment of OIH through reduction in the current opioid dose and addition of low-dose methadone. One study described intractable cancer pain inadequately controlled on the hydromorphone PCA with basal rate of 27 mg/h and demand dose of 13 mg every 10 minutes, the equivalent of 50,000 mg oral morphine.[28] Reduction of the hydromorphone by 43% to a basal rate of 20 mg/h with 10 mg every 10 min on demand and addition of methadone 10 mg twice daily resulted in decreased pain intensity.

Like methadone, buprenorphine has distinct pharmacologic properties that may mitigate OIH. **Tables 5** and 6 provide a comparison of various opioid properties and equianalgesic dosages. As mentioned previously, spinal dynorphin may increase during opioid administration, acting as a *kappa*-receptor agonist. Therefore, buprenorphine, a partial opioid agonist with *kappa* antagonistic properties, may have a role in treatment of OIH. In fact, buprenorphine was shown to treat experimental hyperalgesia better than IV fentanyl in volunteers.[29] Specifically, hyperalgesic areas (induced by electrical stimulation) were measured before and up to 150 minutes after administration of 0.15 mg buprenorphine IV plus placebo SL pill, 0.2 mg SL buprenorphine plus IV saline, or IV saline plus placebo SL pill. All 15 patients received the 3 regimens described and sessions were separated by 2 week washout periods. Hyperalgesic areas were reduced by 66% (95% C.I. 57 -75%) from baseline for IV buprenorphine and 43% (95% C.I. 33-53%) for SL buprenorphine. However, there was no statistical difference in reduction between groups ($P > 0.05$). The investigators reanalyzed previously published data for comparison,[30] reporting that fentanyl reduced hyperalgesic areas by only 8% and even increased hyperalgesic areas in some patients (95% C.I. -11% to 27%).

Emerging Therapy: Low-dose Opioid Antagonists

The addition of an ultra-low dose opioid antagonist to opioid therapy is an emerging concept for treatment and/or prevention of OIH. While the largest, well-constructed studies investigate the use of these agents for pain reduction rather than OIH mitigation, the results offer insight into the potential role of low-dose opioid antagonists in treating OIH. One study reported improved pain relief in patients with low-back pain given a combination of oxycodone and low-dose naltrexone when compared to oxycodone alone (**Table 7**).[32] In this study, 719 patients were randomly assigned to receive placebo, oxycodone 4 times daily, oxycodone twice daily (BID) with 1 µg naltrexone BID, or oxycodone four times daily (QID) with 1 µg naltrex-

Table 7 | Studies assessing addition of low-dose opioid antagonist for management of OIH.

Author (year)	Population, size	Design	Groups & Dose	Results
Webster et al[32] (2006)	Low back pain, n = 719	DB, PC, RCT	1. OXY 4x daily 2. OXY + 1 µg NTX 4x daily 3. OXY + 1 µg NTX BID 4. Placebo	12% lower OXY dose required in OXY + NTX groups
Chindalore et al[33] (2005)	Osteoarthritis, n = 360	DB, PC, RCT	1. OXY 10 mg 4x daily 2. OXY 10 mg + 1 µg NTX 4x daily 3. OXY 20 mg + 1 µg NTX BID 4. Placebo	OXY + NTX BID decreased pain 39%

DB = double blind; **OXY** = oxycodone; **PC** = placebo controlled; **Pop** = population studied; **RCT** = randomized controlled trial; **NTX** = naltrexone; **BID** = twice daily.

one QID.[33] After a washout period, patients were dose-escalated weekly from 10 to a maximum of 80 mg oxycodone/day until adequate pain relief was achieved (defined as pain score ≤ 2 on 0 to 10 scale). At the end of the 12 week treatment period, the percentage reductions in pain scores from baseline were not different among active treatment groups, but the total average daily dose was 12% lower for both oxycodone plus naltrexone BID (34.5 mg) and QID (34.7 mg) groups than patients only receiving oxycodone (39 mg) (P = 0.03 for both comparisons).[32] Similar results were found in a randomized, double-blind, placebo controlled trial of patients with osteoarthritis in which pain intensity significantly decreased in patients receiving oxycodone and 1 µg naltrexone BID compared to oxycodone alone and oxycodone with 1 mcg naltrexone QID daily despite equivalent oxycodone dosages.

Summary

Opioids may lead to a paradoxical increase in pain through mechanisms involving the central glutaminergic system as well as increases in spinal dynorphin. Importantly, clinical evidence suggests hyperalgesia may occur subsequent to both acute and chronic opioid exposure. Therefore, opioid-induced hyperalgesia should be considered in patients with increasing pain unresponsive to increasing opioid dosages.

Based on mechanisms derived from preclinical and clinical evidence, several strategies are available for managing suspected OIH cases. Literature supports keeping opioid doses as low as clinically effective in an effort to reduce the likelihood of OIH. Furthermore, simple opioid dose reduction has been successful, especially in cases where ultra-high doses are being employed, such as OIH in the palliative setting. Providing non-opioid adjuvant therapy, such as gabapentin or non-steroidal anti-inflammatory medications, may allow for an opioid dose reduction; evidence supports this approach for OIH even when not reducing opioid doses. Moreover, opioid class rotation may be beneficial in cases of OIH, with several case reports supporting switching to lower-than-expected doses of methadone. While adjuvant ultra-low dose naltrexone is an emerging concept and animal studies regarding its use in mitigating OIH are available,[34] more clinical evidence is needed before the addition of opioid antagonists can be recommended for the prevention or treatment of OIH.

References

1. Albutt C. On the abuse of hypodermic injections of morphia. *Practitioner* 1870;3:327-330.
2. Ossipov MH, Lai J, King T, et al. Underlying mechanisms of pronociceptive consequences of prolonged morphine exposure. *Biopolymers* 2005;80:319-324.
3. Kelly JP, Cook SF, Kaufman DW. Prevalence and characteristics of opioid use in the US adult population. *Pain* 2008;138L507-513.
4. Strassels SA. Econcomic burden of prescription opioid misuse and abuse. *JMCP* 2009;15:556-562.
5. Trescot AM, Helm S, Hansen H, et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) guidelines. *Pain Physician* 2008;11:S5-S62.
6. Angst MS, Clark JD. Opioid-induced hyperalgesia, a qualitative systemic review. *Anesthesiology* 2006;104:570-587.
7. Bekhit MH. Opioid-induced hyperalgesia and tolerance. *Am J Ther* 2010;17: 498-510.
8. Mao J, Sung B, Ji RR, et al. Chronic morphine induces downregulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. *J Neurosci* 2002;22:8312-8323.
9. Trujillo, KA, Akil H. Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801. *Science* 1991;251:85-87.
10. Marek P, Ben Eliyahu S, Gold M, et al. Excitatory amino acid antagonists (kynurenic acid and MK-801) attenuate the development of morphine tolerance in the rat. *Brain Research* 1991;547:77-81.
11. Gardell LR, Wang R, Burgess SE, et al. Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release form primary afferent fibers. *J Neurosci* 2002;22:6747-6755.
12. Mao J, Price D, Mayer D. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. *Pain* 1995;62:259-274.
13. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 2000;93:409-417.
14. Chiaa YY, Liu K, Wang JJ, et al. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. *Can J Anaesth* 1999;46:872-877.
15. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. *J Pain* 2006;7:43-48.

16. Mercadante S, Ferrera P, Villari P, et al. Hyperalgesia: an emerging iatrogenic syndrome. *J Pain Symptom Manage* 2003;26:769-775.
17. Baron MJ, McDonald PW. Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. *J Opioid Manag* 2006;2:277-282.
18. Wilson GR, Reisfield GM. Morphine hyperalgesia: a case report. *Am J Hosp Palliat Care* 2003;20:459-461.
19. Cohen SP, Christo PJ, Wang S, et al. The effect of opioid dose and treatment duration on the perception of a painful standardized clinical stimulus. *Reg Anesth Pain Med* 2008;33:199-206.
20. Compton P, Kehoe P, Sinha K, et al. Gabapentin improves cold-pressor pain responses in methadone-maintained patients. *Drug Alcohol Depend* 2010;109:213-219.
21. Troster A, Sittl R, Singler B, et al. Modulation of remifentanil induced analgesia and postinfusion hyperalgesia by parecoxib in humans. *Anesthesiology* 2006; 105:1016-23.
22. Baba H, Kohno T, Moore KA, et al. Direct activation of rat spinal dorsal horn neurons by prostaglandin E2. *J Neuro* 2001;21:1750-1756.
23. Joshi W, Connelly NR, Reuben SS, et al. An evaluation of the safety and efficacy of administering rofecoxib for posteroperative pain management. *Anesth Analg* 2003;97:35-38.
24. Koppert W, Sittl R, Scheuber K, et al. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. *Anesthesiology* 2003;99:152-159.
25. Angst MS, Koppert W, Pahl I, et al. Short term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. *Pain* 2003;106:810-815.
26. Mercadante S, Acrcuri E. Hyperalgesia and opioid switching. *Am J Hosp Palliat Care* 2005;22:291-294.
27. Zimmermann C, Seccareccia D, Booth C, et al. Rotation to methadone after dose escalation of hydromorphone: how should individulalized dosing occur? *J Pain Palliat Care Pharmacother* 2005;19(2):25-31.
28. Vorobeychik Y, Chen L, Bush MC, et al. Improved opioid analgesic effect following opioid dose reduction. *Pain Med* 2008;9:724-727.
29. Koppert W, Ihmsen H, Korber N, et al. Different profiles of buprenorphine induced analgesia and antihyperalgesia in a human pain model. *Pain* 2005;118:15-22.
30. Koppert W, Dern SK, Sittl R, et al. A new model of electrically evoked pain and hyperalgesia in human skin: the effects of intravenious alfentanil, S (+)-ketamine, and lidocaine. *Anesthesiology* 2001;95:395-402.
31. Okon TR, George ML. Fentanyl induced neurotoxicity and paradoxic pain. *J Pain Symptom Manage* 2008;35:327-333.
32. Webster LR, Butera PG, Moran LV, et al. Oxytrex minimizes physical dependence while providing effective analgesia: a randomized controlled trial in low back pain. *J Pain* 2006;7:937-946.
33. Chindalore VL, Craven RA, Yu KP, et al. Adding ultralow-dose naltrexone to oxycodone enhances and prolongs analgesia: a randomized, controlled trial of Oxytrex. *J Pain* 2005;6:392-399.
34. Terner JM, Barrett AC, Lomas LM, et al. Influence of low doses of naltrexone on morphine antinociception and morphine tolerance in male and female rats of four strains. *Pain* 2006;122(1-2):90-101.

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