Successful Treatment of Opioid-Induced Hyperalgesia with Buprenorphine: A Case Report

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ABSTRACT

Introduction: Opioid-induced hyperalgesia (OIH) is a paradoxical increase in pain sensitivity in patients receiving chronic opioid therapy. Many patients with OIH may be labeled incorrectly as drug-seeking or addicted. Common management strategies include opioid rotation, dose reduction, and use of N-methyl-D-aspartate receptor antagonists and/or nonsteroidal anti-inflammatory drug. However, evidence supporting these interventions is limited.

Case presentation: We report the case of a 57-year-old woman with metastatic endometrial cancer, previously treated with hysterectomy, chemotherapy, and pelvic radiation, who was receiving hospice care. Despite escalating opioid doses (240 morphine milligram equivalents daily), her pain worsened. She was discharged from hospice for opioid overuse and referred to our addiction clinic. OIH, rather than opioid use disorder, was suspected as the primary barrier to pain relief. Using a microdosing strategy, we transitioned her to buprenorphine, resulting in significant pain reduction and improved quality of life.

Discussion: Buprenorphine is an opioid widely used for the treatment of opioid use disorder, and emerging evidence supports its role in chronic pain management. However, its ability to treat OIH has not been well described. This case suggests that buprenorphine may be effective for patients with opioid tolerance and hyperalgesia and underscores the importance of considering alternative diagnoses in those who are diagnosed with opioid use disorder.

Conclusions: Buprenorphine may offer a safe and effective option for managing OIH in patients with chronic pain and high-dose opioid exposure. Further research is needed to clarify its role in treating OIH and to guide clinical practice.

INTRODUCTION

Opioid-induced hyperalgesia (OIH) is a paradoxical increase in pain sensitivity in patients receiving chronic opioid therapy, which can make managing chronic pain difficult. A hallmark feature of OIH is pain that extends beyond the original site. OIH may also include allodynia, defined as pain evoked by non-noxious stimuli.[1]

The pathophysiology of OIH is complex and not completely understood, with current evidence pointing to multiple contributing factors.[2] Chronic stimulation of μ-opioid receptors is believed to activate the central glutaminergic system and the release of pro-nociceptive spinal dynorphins, both of which enhance nociception.[3,4] The most widely researched theory of OIH is the neuroexcitatory model, which suggests that certain opioids and their metabolites activate the N-methyl-D-aspartate (NMDA) receptor. This activation leads to calcium influx, increasing neuronal excitability and facilitating pain transmission. Evidence supporting this model includes the observation that OIH is not relieved by opioid antagonists such as naloxone, which may worsen pain in patients receiving high-dose opioids by blocking μ-receptor activation while leaving hyperalgesia unopposed.[5] Multiple genetic variants encoding catechol-O-methyltransferase also appear to influence central sensitization by decreasing catecholamine breakdown.[2] This mechanism may partially explain the benefits of NMDA receptor antagonists in treating OIH.

Management of OIH can be challenging. Current pharmacological approaches include opioid, rotation, dose reduction, and use of NMDA receptor antagonists or nonsteroidal anti-inflammatory drugs (NSAIDs).[2] Studies show that OIH is more strongly associated with opioids from the phenanthrene class, such as codeine, hydromorphone, and morphine (opioid classes are listed in Table 1). Codeine is metabolized to morphine via CYP2D6,

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and morphine is primarily converted to morphine-3-glucuronide (M3G) through glucuronidation. M3G, an NMDA agonist with minimal μ-receptor affinity, is produced at a higher rate than other metabolites, contributing to neuroexcitatory effects. Switching to or initiating therapy with a structurally different opioid, such as buprenorphine, can avoid NMDA-activating metabolites and help resolve or prevent OIH.[5]

Buprenorphine is a semisynthetic opioid known for its analgesic properties and well-established role in the treating opioid use disorder (OUD). It has complex, incompletely understood effects at multiple receptors: it acts as a partial agonist at the μ-opioid receptor, antagonizes κ- and δ-opioid receptors with high affinity, and binds to the opioid receptor-like (ORL1) receptor.[6] Its ability to attenuate κ-receptor activity may reduce spinal dynorphins, which contribute to OIH pathogenesis.[7] It is theorized that buprenorphine's ORL1 activity may also reduce the risk of opioid tolerance and sensitization to painful stimuli compared with morphine.[8,9] Additionaly, buprenorphine belongs to the nonphenanthrene class of opioids, making it less likely to act as an NMDA agonist.[5]

CASE PRESENTATION

We present the case of a 57-year-old woman with endometrial cancer treated with hysterectomy, chemotherapy, and pelvic radiation in 2015, after which she developed chronic rectal and pelvic pain. When her cancer returned in 2017, she was treated at a tertiary care hospital 2.5 hours by car from her residence. Due to worsening pain, she was unable to travel this distance despite taking 240 morphine milligram equivalents (MME) daily, including fentanyl and oxycodone. Local pain management services treated her with hypogastric plexus blocks and multiple opioid pain regimens, including oxycodone, methadone, and oral hydromorphone. Her pain control was inadequate or short-lived despite several opioid rotations and high doses. She became progressively walker-dependent and exhibited significant weight loss, from 157 pounds to 98 pounds (body mass index [BMI], 15). During this period, she was hospitalized multiple times for pain control and severe opioid-induced constipation. Her pain also spread beyond the primary pelvic site including painful swallowing, headaches, generalized abdominal and back pain, and pain with defecation. Because of widespread symptoms and inability to tolerate cancer treatment, she was referred to hospice care.

While in hospice, she received long- and short-acting morphine with ketamine and diazepam. Initially, pain control was adequate; however, she began exhausting her weekly morphine supply within a few days due to escalating pain. After multiple hospitalizations for pain control and severe opioid-induced constipation, she was switched to oral morphine extended-release (MS Contin) 90 mg 3 times daily, hydromorphone 4 mg every 4 hours, and oral ketamine, which provided only temporary relief. Over 2 weeks, she again depleted her weekly supply within a few days.

Table 1. Classes of Opioids[10]

Phenanthrene Opioids	Nonphenanthrene Opioids
Codeine	Piperidine derivatives:
Hydrocodone	Fentanyl
Hydromorphine	Meperidine
Morphine	Sufentanil
Oxycodone	Other:
Oxymorphone	Buprenorphine
	Methadone
	Tramadol

Her pain worsened and spread—particularly painful swallowing and defecation—and she reported overuse of medications due to uncontrolled pain. After 6 weeks in hospice, staff determined they could no longer safely manage her pain and began tapering opioids in preparation for discharge. Her pain complaints were new and not related to cancer, and OUD was diagnosed by the hospice team. Our addiction service was consulted for pain and addiction management.

The patient reported initial relief from opioids but required progressively higher doses, eventually experiencing worsening pain regardless of dose. Pain spread to include upper abdominal pain, painful swallowing, and constant headaches. Based on these symptoms, OIH was suspected. She met fewer than 2 Diagnostic and Statistical Manual of Mental Disorders criteria for OUD. Following a microdosing strategy, we initiated a 5 mcg/hour buprenorphine patch for 7 days and escalating doses of oral buprenorphine without discontinuing long-acting morphine or hydromorphone. A patch was chosen to simplify titration; we believed she could not manage cutting films or following a complex regimen. After approximately 2 weeks of titration, a maintenance dose was achieved with a 20 mcg/hour buprenorphine patch for 7 days and 8 mg oral buprenorphine 3 times daily. We recommended continuing full opioid agonists for later tapering, but she overused them and ran out after the first week. She denied withdrawal symptoms, and her pain improved after discontinuation. After her induction, she remained on buprenorphine only, with pain controlled at approximately 3 of 10 on the pain scale. She gained 20 pounds over the next 3 months (weight, 118 pounds; BMI, 19). In the 3 months before buprenorphine induction, she was hospitalized 3 times for pain and constipation; in the 3 months after buprenorphine initiation, she was hospitalized only once for unrelated issues.

With improved pain control and overall health, she was discharged from hospice and resumed her cancer treatment. Three years after starting buprenorphine, she is in remission, weighs 130 pounds, and has not been hospitalized for pain. Pain control has remained stable on a 20 mcg/hour patch every 7 days and 8mg oral buprenorphine 3 times daily. She continues to rate pain 1 to 3 out of 10 since induction. On prior regimens, her pain never decreased below 5 and consistently worsened over time.

DISCUSSION

OIH should be considered when opioid tolerance develops and pain extends beyond the original site. Increasing opioid doses generally exacerbates pain, whereas dose reduction may improve symptoms. There are no commonly available tests to confirm the diagnosis. Patients with tolerance but without OIH typically do not improve with decreased MMEs and do not experience spreading or worsening pain with increasing dosages. An opioid rotation and/or reduction in total MME is commonly attempted to diagnose or manage OIH. This approach involves tapering the current opioid and transitioning to a different opioid with distinct pharmacokinetics and receptor activity. Case reports describe success with changing from morphine to methadone.[11]

Table 2. A Review of Evidence for Pain Control With Buprenorphine

Article	Brief Summary
Khanna et al[9]	Buprenorphine is safe and effective for chronic pain. It has a superior safety profile when compared to full opioid agonists. It can be combined with other opioids when breakthrough pain control is needed. This review covers evidence, pharmacology, and safety of buprenophine for both acute and chronic pain.
Powell et al[12]	A systematic review of 22 small studies and case reports indicates that rotating opioids to buprenorphine from other regimens maintains or improves chronic pain. The risk of precipitated withdrawal was low. The quality of evidence in this meta-analysis was limited, suggesting the need for more research on the topic.
Spreen et al[10]	Microdosing strategies for buprenorphine are safe and effective for the induction of buprenor-phine. Article reviews the evidence for buprenorphine and catalogues dosing protocols.

A 2021 systematic review examined buprenorphine rotation for patients with chronic pain and long-term opioid use. The review found opioid rotation to buprenorphine to be safe and effective without precipitating withdrawal. Patients were transitioned to buprenorphine for multiple indications, including inadequate pain control, intolerable adverse effects, risky opioid regimens, and aberrant opioid use.[12] Evidence supporting buprenorphine for pain management is summarized in Table 2.

To our knowledge, this case report is the first described example of buprenorphine treatment correlating clinically with a reduction in OIH. Our literature review identified few studies examining buprenorphine's antihyperalgesic effects. In 2005, a randomized, double-blind crossover study involving 15 patients demonstrated a greater reduction in transcutaneous stimulation-induced hyperalgesia in patients given buprenorphine compared with fentanyl.[13] No studies to date have examined buprenorphine's potential ability to attenuate hyperalgesia specifically induced by opioid therapy.

CONCLUSIONS

We present a case of a 57-year-old woman whose opioid-induced hyperalgesia was effectively treated with buprenorphine therapy. She experienced improvements in pain, ability to perform activities of daily living, and nutritional status. This case highlights the need for further clinical investigation into the relationship between buprenorphine and OIH. Given the stigma, anchoring bias, and implications of an OUD diagnosis, our case emphasizes the importance of maintaining an open mind and comprehensive differential when diagnosing and treating patients with suspected OUD.

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