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Case Report

Ketamine as a Vehicle for Change in Chronic Pain and Comorbid Addiction

Siddharth S. Arora, DO, MS[1], Adrian Darryll Sulindro, MD[2], and George C. Chang Chien, DO[3]

Chronic pain is a disease that affects hundreds of millions of Americans and costs the United States billions of dollars a year. It is a disease that has both physical and psychological effects, posing a difficult therapeutic challenge. Innovations in interventional treatments continue to improve, but our pharmacological options have yet to catch up, with opioids remaining as one of the more effective treatments still available. Unfortunately, its rapid onset of pain relief coupled with its highly addictive potential has directly contributed to our current opioid crisis. One way to curb the epidemic is the use of a well-established opioid replacement treatment, buprenorphine, which has a high degree of efficacy in chronic pain and minimal risk of intoxication and overdose. A major limitation to its use is the initial induction stage, whereby the patient experiences severe withdrawal, cravings, and worsening pain. A novel solution in treating chronic pain patients with comorbid addiction may be the use of a low dose series of sub-anesthetic intravenous ketamine infusions as a bridge to buprenorphine therapy during the induction phase. There is emerging evidence that subanesthetic doses of ketamine may be a better option in treating these complex patients, as it has been shown to display robust analgesic activity, favorable effects on mood, reductions in relapse rates, and minimal side effects. Here we review the currently available literature supporting this. Given the current opioid crisis and the lack of safe and effective alternative pharmacological treatments, developing a better pain management strategy would be of great clinical and societal value.

Key words: Ketamine, opioid withdrawal, chronic pain, opioid addiction, buprenorphine, opioid epidemic

Chronic pain, loosely defined as any pain lasting beyond 3 months, affects at least 100 million people in the United States and has an annual incremental health care cost of over $600 billion, with additional estimated productivity losses of $60 billion a year (1). Treatment for chronic pain has lagged behind in advancement compared to other chronic diseases such as diabetes, heart disease, and cancer. This is driven, in part, by the multidimensional nature of pain, individual variances in the human experience of pain, and poorly understood pathophysiological underpinnings. Additionally, comorbid psychiatric and substance use disorders complicate treatment. The primary pharmacological therapies have remained the same; nonsteroidal anti-inflammatory drugs, gabapentinoids, antidepressants, and opioids. Despite the drawbacks of opioids, they target almost all levels of the pain neurocircuitry and remain one of the more effective treatments available (2). The rapid onset of pain relief coupled with its addictive properties has directly contributed to the current opioid epidemic. Tolerance for opioids rapidly develops, necessitating higher doses for adequate pain management,

From : [1]Department of Pain Medicine, Nova Southeastern University/Larkin Hospital, South Miami, FL; [2]Department of Rehabilitation, Icahn School of Medicine at Mt. Sinai, New York, NY; [3]Medical Director of Pain Management, Ventura County Medical Center, Ventura, CA

Author for correspondence: Siddarth Singh Arora, DO, MS
Department of Pain Medicine, Nova Southeastern University/Larkin Hospital, 7031 SW 62nd Ave,, South Miami, FL 33143
E-mail: siddsarora@gmail.com

potentially worsening the current opioid crisis (3). Since 1999, the number of opioid prescriptions has quadrupled (4), yet there has been no overall change in pain perception by most patients (5,6). Opioids' addictive properties have led to alarming rates of abuse, overdoses, and deaths in our communities. Indeed, up to 30% of opioids prescribed for pain are misused, and up to 10% are abused (7). Physicians are faced with the challenge of balancing pain control while attempting to minimize addiction. Developing a better pain management strategy would be of great clinical and societal value.

Opioid replacement treatment (ORT) is a well-established modality utilized to treat opioid dependence and abuse (8). Opioid maintenance therapy utilizing buprenorphine, a partial mu-agonist, has been one of the more effective solutions for opioid addiction since the 1980s (9-11), with documented use in pain management dating back to the 1970s (12). Furthermore, its high degree of efficacy has been validated in pain patients with comorbid addiction (13). Buprenorphine's potent analgesic activity may be due to its ability to prevent and reverse opioid-induced hypersensitivity (14), defined as an abnormally heightened state of pain brought on by continued opioid use. Buprenorphine has a significantly lower risk of intoxication and overdose compared to other opioids, especially when combined in sublingual form with naloxone (15,16). An unfortunate limitation of buprenorphine induction is the occurrence of up to 3 days of severe withdrawal, punctuated by worsening pain and depression, when traditional opioids are discontinued. Addressing this challenge with an effective yet comfortable transition to buprenorphine is crucial to enabling broader use of this therapy. Of note, ORT is not without controversy, as some critics cite it as replacement of one addictive substance with another (17). Nonetheless, the goal of ORT is to minimize risk utilizing medications that adequately treat withdrawal symptoms while reducing the overall risk for morbidity and mortality (18).

There is emerging evidence for the use of subanesthetic intravenous ketamine as a bridge to buprenorphine therapy during the induction phase of ORT. Ketamine, an N-methyl-D-aspartate receptor (NMDA) antagonist, is classified as a dissociative anesthetic and is commonly used for analgesia in adults and for procedural sedation in children. Opioid tolerance and dependence has been shown to be mediated by NMDA receptors (19). Specifically, in the treatment of opioid dependence, ketamine has been shown to attenuate the signs of opioid withdrawal and reverse existing opioid tolerance (20-23) by preventing significant rises in respiratory, cardiovascular, and neuroendocrine responses during opioid withdrawal (24,25). Ketamine's positive impact on opioid withdrawal is also seen in the pediatric population, while still maintaining a strong degree of safety (26).

Here, we will review the literature investigating the role of ketamine in the treatment of opioid dependence and its implications for managing chronic pain patients with comorbid opioid addiction; this is summarized in Table 1. Taken together, the data suggest that ketamine use during opioid withdrawal is effective, has a favorable safety profile, and may provide pain relief beyond the pharmacodynamics of ketamine itself (Table 1).

DISCUSSION

Subanesthetic doses of ketamine have been investigated for the use of withdrawal of medically prescribed opioids in people with chronic pain, opioid tolerance, and hyperalgesia (27). Emerging evidence suggests that this therapy may increase the successful outcomes in ORT utilizing buprenorphine and may provide more effective and lasting pain relief due to its opioid-sparing effects and ability to abolish opioid-induced hyperalgesia (23,28). In fact, several observational studies reported on the use of subanesthetic intravenous doses of ketamine resulting in sustained benefits up to 6 months post-treatment (27,29,30). Interestingly, a recent abstract described a patient presenting with severe withdrawal after his intrathecal pump, containing a daily regimen of 21,044 oral morphine equivalents, had suddenly failed (31). The patient subsequently underwent a trial of low-dose ketamine infusions. Remarkably, after the first infusion, all withdrawal symptoms were controlled. Following 2 more sequential infusions, the patient remained pain- and symptom-free for 6 months, demonstrating ketamine's lasting analgesic effect. This effect is particularly important, as worsening pain is often a trigger for relapse (32).

In addition to its impact on the physical dependence of opioids, ketamine also addresses the psychological factors of addiction. Ketamine's influence on the

Table 1. Ketamine use in opioid withdrawal.

Authors	Year	Study Design	Patients	Treatment Arms	Outcome Measures	Follow-Up	Adverse Effects of Ketamine	Results
Jovaisa et al (25)	2006	Randomized, placebo-controlled, double-blind study	58 patients	Ketamine group (n = 22); Normal saline control group (n = 28)	SOWS, OOWS	4 mos	None	Ketamine group: fewer withdrawal symptoms. No differences in opioid usages at 4 mos
Koppert et al (28)	2003	Double-blinded placebo study	13 volunteers	Group (n = 13) received RF+ketamine, RF+clonidine, RF+saline in separate treatments	Numerical 11-point pain rating	30 mins	Hyperacusis and moderate sedation	Opioid-induced, post-infusion hyperalgesia abolished by ketamine
Quinlan et al (27)	2012	Case study	15 patients	Group (n = 15) Opioid-dependent patients with tolerance and hyperalgesia	Questionnaire	Post-infusion, 2 mos, and 6 mos	Hypomania, delerium	Initial response to ketamine's anesthetic effect reduced over time, patients felt better initially, 8/11 felt better at 2 mos, 3/11 felt better at 6 mos with no opioid
Freye et al (38)	2006	Case study	31 patients	Group (n = 31) compared opioid withdrawal symptoms before and after ketamine	EEG and median nerve-evoked somatosensory potentials	60 mins after infusion	Dreaming and hallucination	Ketamine reduced EEG and SSEP change brought on by acute opioid withdrawals
Freye et al (24)	2005	Case study	36 patients	Group (n = 36) compared opioid withdrawal symptoms before and after ketamine	Beta, alpha, theta, and delta bands measured with EEG	2 hrs after infusion	None	Ketamine reversed acute abstinence-related EEG changes
Lalanne et al (30)	2016	Case report	One female	Opioid-dependent patient (n = 1)	COWS	Inpatient opioid taper	None	Reduction in opioid amount, without opioid withdrawal symptoms with ketamine
Ito et al (26)	2006	Case report	One child	Failed opioid taper patient (n = 1)	Opioid withdrawal symptoms	Hospital discharge	None	Ketamine was used to facilitate opioid withdrawal in a child without withdrawal symptoms

COWS = clinical opiate withdrawal scale; RF = remifentanil; SOWS = subjective opiate withdrawal scale; OOWS = objective opiate withdrawal scale; EEG = electroencephalography; SSEP = somatosensory evoked potential

dopaminergic and serotonergic systems enables rapid onset of antidepressant properties (33), allowing for a smooth transition from traditional opioids to buprenorphine. This is particularly important, since relapse is often triggered by dysphoric symptoms associated with withdrawal or pain (34). Other data suggest that ketamine may affect the reward center of the brain, the nucleus accumbens, during opioid withdrawal suppression (20). Ketamine has also been used in combination with psychotherapy for heroin addiction and has been shown to increase the rate of abstinence, reduce heroin cravings, and

trigger positive changes in nonverbal emotional attitudes (35).

The use of ketamine as a bridge to buprenorphine therapy must be undertaken with caution, as it carries increased risks of sympathetic stimulation to the cardiovascular system, cognitive impairment, and cystitis (36). When administered at subanesthetic doses for chronic pain and depression, benign dissociative and psychotomimetic effects (23) including auditory and visual hallucinations have been reported (28). Other effects, including hypomania, sedation, and delirium, have also been reported (27,28). Given these findings, it is imperative to carefully monitor patients, even during administration of subanesthetic doses. With repeated use, one should also be vigilant about assessing for the potential for abuse (9,16). In a recent 2017 consensus review of ketamine use for mood disorders, Sanacora et al (37) provide suggestions for clinicians to ensure safe, off-label therapeutic use of ketamine.

When appropriately used and safely monitored in chronic pain patients with comorbid addiction, ketamine has the potential to save lives, particularly when combined with buprenorphine therapy. Ketamine's robust analgesic effects on chronic pain, ability to eliminate opioid-induced hyperalgesia, low side-effect profile at subanesthetic doses, ability to suppress opioid withdrawal, favorable effects on mood, and ability to decrease relapses underscores its vast potential in pain management, especially given the lack of currently available options in treating chronic pain and comorbid opioid addiction. Utilizing ketamine as a bridging agent to buprenorphine may bring us one step closer to overcoming the opioid epidemic in the chronic pain population.

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