

Successful Management Of Refractory Precipitated Opioid Withdrawal Syndrome Following Buprenorphine Intake Using Ketamine: A Case Report

Iman Attackpour Torik

imanatk1998@gmail.com

Golestan University of Medical Sciences

Mohammad Moeini

Golestan University of Medical Sciences

Shahram Moghaddam

Golestan University of Medical Sciences

Seyede Almas Fahim Yegane

Golestan University of Medical Sciences

Case Report

Keywords: Precipitated Withdrawal Syndrome, Opioid Withdrawal Syndrome, Emergency Interventions, Sedatives, Ketamine Infusions, Refractory Cases

Posted Date: September 3rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10429635/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Introduction:

Precipitated withdrawal syndrome (POW) occurs when agonist-antagonist opioids are administered to individuals dependent on full agonist opioids. This class of drugs exerts strong antagonistic effects, is associated with mu-opioid receptor depletion, and induces severe withdrawal symptoms in affected patients. Standard management typically involves supportive care and high-dose buprenorphine. This report describes a complex case of refractory case to multiple lines of therapy, and withdrawal symptoms were ultimately controlled with sedative doses of ketamine.

Case Presentation

: A 50-year-old man with a 10-year history of opioid use presented to the emergency department in severe distress. He had angiography and stenting, hypertension, and sleep disturbances. The patient ingested three 8-mg buprenorphine tablets following 30 mg of methadone syrup, resulting in severe withdrawal symptoms, body aches, and agitation. On admission, his Glasgow Coma Scale (GCS) was 15/15, but he was extremely agitated and unresponsive to questions. Blood pressure was 163/105 mmHg, and heart rate was 112 beats per minute. Initial management included 500 mL of normal saline, clonidine tablets, 10 mg of midazolam, and 250 µg of fentanyl. Due to persistent pain and agitation, 80 mg of propofol was administered. A single dose of 5 mg morphine and 400 mg ibuprofen was also given, but severe pain persisted. After no improvement with 0.5 mg intramuscular haloperidol, ketamine therapy was initiated at 30 mg (0.5 mg/kg), followed by an infusion at 30 mg/hour for 24 hours. After 24 hours, the infusion was discontinued, and intermittent 30 mg doses were administered as needed. The patient was sedated at the initiation of ketamine, and his vital signs stabilized and normalized. He remained calm and alert during hospitalization and was discharged after 48 hours without pain or new drug dependence.

Conclusion

This case demonstrates that sedative doses of ketamine may serve as a rapid, effective, and safe therapeutic intervention for patients with withdrawal syndrome resistant to first-line therapies. By targeting alternative pain neurotransmitter pathways, such as NMDA receptors, ketamine offers a potential option when standard therapies and mu-opioid receptor agonists are ineffective.

Background

Opioid use disorders are a major global health crisis. Although medications such as buprenorphine and methadone are used to manage this problem, switching between these two drugs carries risks. Buprenorphine is a mu receptor agonist-antagonist with high receptor affinity but less efficacy than full

agonists such as methadone. If buprenorphine is used rapidly by a person taking methadone, it decreases activated receptors and causes severe withdrawal symptoms called Precipitated Opioid Withdrawal (POW).[1–3]

This type of withdrawal syndrome is usually more severe and rapid than withdrawal syndromes that occur due to the lack of opioid use.[4] These patients often experience severe psychomotor agitation, restlessness, and autonomic instability. Although most cases can be managed with supportive care and additional buprenorphine administration, there is a high risk for these patients if they become resistant.[5] These patients may become aggressive, uncooperative, and develop dangerous cardiovascular problems.[6] Adjusting the buprenorphine dose also carries a high risk since it is a long-acting drug that can cause respiratory depression.

Ketamine is an NMDA receptor agonist and can produce analgesia through a different mechanism than opioids.[7] It reduces hyperalgesia, reduces central pain perception, and re-regulates the adrenergic cascade through a different pathway than mu receptor agonists.[8] In practice, it can be used in sedative doses to manage patients presenting with POW syndrome in the emergency department.[1, 9, 10]

Case Presentation

GENERAL PRESENTATION:

A 50-year-old middle-aged man presented to the emergency department with sudden, severe generalized pain and uncontrollable agitation. The patient had a 10-year history of opioid use and was currently on methadone. His past medical history included:

- Ischemic heart disease (IHD), which had undergone angiography and stent placement. He was currently being treated with aspirin 80 mg daily.
- Hypertension, which was being treated with propranolol 10 mg PRN and losartan 50 mg twice daily.
- Sleep Disorder, which was being treated with alprazolam 0.5 mg every night before bed.

CLINICAL FINDINGS:

Approximately two hours before admission, the patient had taken 30 mg of methadone. He then self-administered three 8 mg sublingual buprenorphine tablets (total of 24 mg). Less than an hour after administration, the patient experienced severe pain throughout the body, uncontrollable agitation, and aggression.

Upon arrival at the emergency department, the patient was conscious but in severe pain and was screaming for help. Initial assessment was a GCS of 15. Due to the patient's severe pain and agitation, he dismissed his IV line three times, making stabilization of the patient challenging.

LABORATORY EVALUATION:

Initial assessment of vital signs revealed severe autonomic stimulation. The patient's blood pressure was 163/105, heart rate was 112–130, and respiratory rate was 24 breaths per minute. The patient's arterial blood results were as follows, which were acceptable:

PH: 7.42 PCO2: 38.6 PO2: 34 HCO3: 24.4

Initial blood and biochemical tests were sent for the patient, all of which were reported to be within the physiological range.

INTERVENTIONS:

Given the possibility of a POW diagnosis, standard treatment based on sedation and analgesics was initiated. Although the patient received high doses across multiple treatment lines in the first hour, no improvement in his clinical symptoms was observed. His medications included the following:

1. Midazolam 2 mg intravenously, repeated every 5 minutes for up to 5 times for sedation (total 10 mg)
2. Fentanyl 50 micrograms intravenously, repeated every 5 minutes for up to 5 times for analgesia (total 250 micrograms)
3. Propofol 40 mg intravenously, repeated every 5 minutes for up to 2 times for sedation (total 80 mg)
4. One 100 mg clonidine tablet was prescribed for sedation and central sympathetic system suppression
5. One 400 mg ibuprofen tablet was prescribed for analgesia and sedation
6. Morphine 5 micrograms was prescribed for the patient, followed by fentanyl for further analgesia
7. Finally, by order of the psychiatric service, 0.5 mg haloperidol was given intramuscularly to the patient

Despite the above-mentioned drug therapy, the patient remained the same, the patient's vital signs had increased, and the patient's pain remained unchanged. Given the resistance of the case to standard drug therapies, in consultation with the anesthesia service, the patient was started on a 30 mg bolus dose of ketamine (0.5 mg per kg of body weight).

MAINTENANCE & PATIENT FOLLOW UP:

The patient was placed under full cardiovascular monitoring. Immediately following the bolus dose, the patient fell asleep. The patient's blood pressure was 124/78, and his heart rate decreased from 75 to 82. Ketamine infusion was started for the patient to continue treatment, and the patient remained stable for the next 24 hours without any cardiovascular events. After 24 hours, the infusion was stopped, and the dosage was changed to a 30 mg bolus in case of pain or withdrawal symptoms.

Fortunately, the patient did not require further analgesia during the next 24 hours of hospitalization. The patient was conscious, breathing spontaneously, and oriented to time, place, and person. The patient was discharged from the hospital after 48 hours of hospitalization without any signs of withdrawal syndrome.

Discussion

Precipitated Opioid Withdrawal Syndrome (POWS) following agonist-antagonist use poses complex and acute clinical challenges for emergency medical personnel. The mechanism of this symptom is related to its pharmacokinetics: buprenorphine binds to mu opioid receptors due to its higher receptor affinity, but because it is much less potent than full agonists, it can cause acute withdrawal effects in patients dependent on opioid agonist drugs.

When a patient presents to the emergency department with severe, treatment-resistant agitation, traditional treatments are usually ineffective. As we saw in the case presented, despite the administration of high doses of full agonist drugs (morphine and fentanyl), mu receptors remained occupied by buprenorphine and remained ineffective. Also, high doses of benzodiazepines (midazolam) and antipsychotics (haloperidol) are ineffective due to the severe hyperalgesia in patients who receive central administration, especially since, at high doses, the risks of using these drugs, such as apnea and hypoxia, remain.

What makes this case a complex, challenging one is his past history of cardiovascular disease, making him a medical ticking bomb prone to MI or cardiac arrest.

In this acute, complex, and treatment-resistant condition, ketamine can be a good solution. In patients with chronic opioid use, NMDA receptors are up-regulated within the central nervous system.[11] Ketamine suppresses sensitized glutamatergic pathways in the central nervous system by using these receptors. Also, by interfering with sympathetic nerve pathways, it can suppress the excessive neurotransmitter release associated with the withdrawal syndrome and reduce the cardiovascular stress burden on the patient.

Recent studies have shown that a sedative dose of ketamine (0.1–0.3 mg/kg/hour) can provide adequate analgesia and suppress withdrawal responses in patients. Fortunately, severe side effects such as decreased consciousness, delirium, and respiratory depression are not seen at this dose. Given the patient's history of cardiovascular disease and high blood pressure, controlling and managing the patient's autonomic response using ketamine could be beneficial. Ketamine also provides better safety for use in these patients due to its rapid onset of action and less interaction with other intravenous and sedative drugs.

Conclusion

POW withdrawal syndromes result in severe agitation in patients and are challenging scenarios for medical staff, often resistant to standard sedation and analgesia. In this case, it was observed that even sedative doses of ketamine can lead to rapid resolution of withdrawal and agitation symptoms in the patient. The drug is safe, provides adequate analgesia, and also leads to central suppression of the sympathetic system. Therefore, it is recommended that ketamine could be a safe, rapid, and effective option for management in the emergency department for future treatment-resistant cases.

Declarations

Ethics and consent to participate

This study was conducted in accordance with the ethical principles outlined in the guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Consent to Publish

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Competing interests

The authors declare that there is no conflict of interest or competing interests regarding the publication of this article.

Funding:

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution

I.A.T. and M.M. conceived and supervised the study, contributed to the clinical management of the patient, and critically revised the manuscript for important intellectual content. A.Y. and S.M. collected and analyzed the clinical data, performed the literature review, drafted the initial manuscript, and participated in the revision and editing of the article. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Acknowledgments:

The authors would like to express their sincere gratitude to the patient and her family for their cooperation and for providing consent for publication of this case report. The authors also acknowledge the medical and nursing staff involved in the patient's care whose dedication contributed to the successful management of this case.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. No additional datasets were generated or made available.

References

1. Christian, N.J., et al., *Precipitated Opioid Withdrawal Treated With Ketamine in a Hospitalized Patient: A Case Report*. J Addict Med, 2023. 17(4): p. 488–490.
2. Jafari, S. and R. Rafizadeh, *Successful Transition from High-Dose Methadone to Buprenorphine via Microdosing in the Outpatient Setting: A Case Report*. Can J Hosp Pharm, 2021. 74(1): p. 83–85.
3. Spadaro, A., et al., *Precipitated opioid withdrawal after buprenorphine administration in patients presenting to the emergency department: A case series*. J Am Coll Emerg Physicians Open, 2023. 4(1): p. e12880.
4. Gowing, L., R. Ali, and J.M. White, *Buprenorphine for the management of opioid withdrawal*. Cochrane Database of Systematic Reviews, 2009(3).
5. Modesto-Lowe, V., et al., *Use and misuse of opioid agonists in opioid addiction*. Cleveland Clinic Journal of Medicine, 2017. 84(5): p. 377–384.
6. Wang, L., et al., *Cardiac and mortality outcome differences between methadone, buprenorphine and naltrexone prescriptions in patients with an opioid use disorder*. Journal of Clinical Psychology, 2023. 79(12): p. 2869–2883.
7. Steven, B.R., et al., *Ketamine*. 2024.
8. Induru, R.R. and M.P. Davis, *Buprenorphine for Neuropathic Pain—Targeting Hyperalgesia*. 2009.
9. Gbujie, E., L. Vercollone, and J. Suzuki, *Ketamine treatment for buprenorphine-precipitated opioid withdrawal: a case report*. Frontiers in Psychiatry, 2025. Volume 16–2025.
10. Roberts, E., N. Kalk, and J. Strang, *Pharmacological treatment strategies to manage precipitated withdrawal following the administration of buprenorphine in opioid use disorder: A systematic review*. Addiction, 2026. 121(5): p. 1083–1099.
11. Pan, H.-L., et al., *$\alpha 2\delta$ -1-Bound N -Methyl- d -aspartate Receptors Mediate Morphine-induced Hyperalgesia and Analgesic Tolerance by Potentiating Glutamatergic Input in Rodents*. Anesthesiology, 2019. 130(5): p. 804–819.