mhc
MENTAL HEALTH CLINICIAN

CASE REPORT Open Access

Microdose induction of buprenorphine-naloxone in a patient using high dose methadone: A case report

Shannon Menard, PharmD[1]
Archana Jhawar, PharmD, BCPP[2]

How to cite: Menard S, Jhawar A. Microdose induction of buprenorphine-naloxone in a patient using high dose methadone: A case report. Ment Health Clin [Internet]. 2021;11(6):369-72. DOI: 10.9740/mhc.2021.11.369.

Submitted for Publication: May 3, 2021; **Accepted for Publication:** October 4, 2021

Abstract

Background: Buprenorphine is a partial mu-opioid receptor agonist approved for the treatment of opioid dependence. The risk of withdrawal symptoms and wait time required to safely initiate buprenorphine provides challenges to both patients and providers. Microdose induction is proposed as a possible solution to ease the transition to buprenorphine; however, little data has been published to date on patients stabilized on methadone doses greater than 100 mg.

Case Report: A 29-year-old patient stabilized on methadone 105 mg was successfully transitioned to sublingual buprenorphine-naloxone using a 7-day microdose protocol on an inpatient psychiatric service. During the transition, the patient reported only minimal symptoms.

Conclusion: This report adds to the growing literature supporting the use of a microdose induction to initiate buprenorphine-naloxone. Additionally, this approach may be significant for patients stabilized on high doses of methadone who may not be able to tolerate a traditional buprenorphine induction.

Keywords: buprenorphine, OUD, opioid use disorder, SUD, substance use disorder, methadone, microdose

[1] (Corresponding author) PGY-2 Psychiatry Pharmacy Resident, Department of Pharmacy Services, Jesse Brown Veterans Affairs Medical Center, Chicago, Illinois, shannon.menard@va.gov, ORCID: https://orcid.org/0000-0002-2735-9692; [2] Clinical Pharmacy Specialist, Department of Pharmacy Services, Jesse Brown Veterans Affairs Medical Center, Chicago, Illinois; Clinical Pharmacy Specialist, University of Illinois at Chicago, College of Pharmacy, Chicago, Illinois, ORCID: https://orcid.org/0000-0003-2317-5586

Disclosures: There are no conflicts of interest to disclose.

Background

Buprenorphine is a mu-opioid receptor partial agonist approved for treatment of opioid dependence. By only partially activating the receptor when bound, buprenorphine has a natural ceiling effect that can reduce the risk of potential overdose, making it an appealing option for patients and providers alike.[1,2] However, due to its strong affinity for the mu-opioid receptor, it can displace full mu-opioid agonists and precipitate acute opioid withdrawal. For this reason, buprenorphine treatment has historically been initiated only after a patient begins to exhibit objective signs and symptoms of opioid withdrawal. Clinicians and patients are challenged with 2 potential disadvantages of buprenorphine therapy. First, inability to tolerate the withdrawal symptoms required to initiate buprenorphine results in lower retention rates than methadone.[3-5] Second, the length of time required to metabolize full opioid agonists requires patients to wait hours to several days for metabolism and elimination prior to starting buprenorphine treatment.[1,3] When transitioning from methadone, this process can be further delayed as some providers recommend slowly tapering methadone to 30 mg.[1] Because of its long half-life, low methadone concentrations can persist, increasing the risk of withdrawal symptoms once buprenorphine is initiated.[1,6]

Clinicians have sought ways to minimize these barriers and increase patient retention during buprenorphine transitions. One proposed method involves initiating buprenorphine at low, subtherapeutic doses, referred to as microdoses, concurrently with a full mu-opioid agonist, such as heroin or methadone. It is hypothesized that introducing low doses of buprenorphine to slowly displace full opioid agonists allows the acclimatization of receptors and avoids withdrawal symptoms attributed to abrupt transition.[7] The first reports[7,8] of microdosing buprenorphine utilized the Bernese method and successfully transitioned 2 patients from full opioid agonists to buprenorphine. The Bernese method consists of initiating a low dose of 0.2 mg sublingual buprenorphine and slowly increasing the dose while continuing full opioid agonist therapy. Once buprenorphine has reached a sufficient dose, the full opioid agonist is discontinued without tapering. The first reported patient[7,8] was using 3 g of illicit heroin daily and unable to tolerate conventional buprenorphine induction. The patient successfully transitioned to buprenorphine over 9 days with minimal withdrawal symptoms and heroin cessation by day 6. The second patient[7] was transitioned to sublingual buprenorphine from methadone 40 mg and twice daily diacetylmorphine 400 mg over 29 days with minimal to no withdrawal symptoms. Another case series[9] reported 3 patients admitted to the hospital for endocarditis or osteomyelitis who were successfully transitioned from methadone (doses up to 100 mg) with or without concurrent opioids. These patients were transitioned to sublingual buprenorphine using a 7-day microdose protocol. On day 8, methadone was stopped, and buprenorphine was continued. Most recently, a case reported[10] a successful transition from methadone 160 mg to sublingual buprenorphine-naloxone over a period of 4 months using microdose induction.

To further contribute to the available literature supporting the use of microdosed buprenorphine to transition patients stabilized on methadone, this report describes a 7-day transition from high-dose methadone, 105 mg/d, to sublingual buprenorphine-naloxone utilizing the microdose induction approach.

Case Report

A 29-year-old male with a past psychiatric history significant for depression, cocaine and OUD, and PTSD presented to the emergency room with suicidal ideation and polysubstance use. The patient's documented working diagnoses were severe cocaine use disorder, heroin use disorder, and PTSD/substance-induced mood disorder. His urine drug screen on admission was positive for cocaine, opioids, and methadone, but blood alcohol was negative. He reported smoking 2 to 3 g of cocaine daily and using 2 g of heroin 2 days prior to admission. Blood counts and chemistries were within normal limits. The patient noted he was not taking any of his prescribed medications except for methadone prior to admission. He was accepted to a residential PTSD program that was unable to provide methadone, requiring a transition to buprenorphine-naloxone. There was significant concern from the patient, inpatient providers, and opioid treatment center providers that he would not tolerate the traditional transition method. They agreed to apply the Bernese method of micro-induction in this case of high-dose methadone.

During his admission, the patient continued to receive his outpatient methadone 105 mg dose and experienced minimal withdrawal symptoms that the team attributed to the restarting of divalproex as nausea was the only symptom. Nausea was managed with promethazine, trimethobenzamide, or diphenhydramine. On day 1 of induction, the team initiated a sublingual microdose buprenorphine-naloxone titration, starting with 0.5-0.125 mg once. The team explored starting buprenorphine 0.2 mg, but logistical concerns of splitting the available film dose, 2-0.5 mg, beyond fourths resulted in the higher dose of 0.5-0.125 mg. Concurrent full-dose methadone was continued for 6 days after initiation of buprenorphine-naloxone (Table). Each day, the patient was monitored for worsening of opiate withdrawal and a clinical opiate withdrawal scale (COWS) was administered and documented on days 1 and 6 through 8 with a score of 0 on all days.[11] Unfortunately, due to human error and limitations of charting, COWS was not obtained or documented on days 2 through 5. On day 7, methadone was discontinued, the patient was documented to be free from withdrawal symptoms, and depression and suicidal ideation had resolved. On day 8, the patient was discharged with sublingual buprenorphine-naloxone 12-3 mg daily and a plan to follow up at an opioid treatment center and then a residential treatment program.

Prior to and during the transition to buprenorphine-naloxone, the patient's main complaints consisted of minimal nausea and insomnia. The psychiatry team documented the symptoms as both mild and easily managed. These symptoms had also been of concern prior to initiating the microdose protocol. Overall, the team concluded the patient had tolerated the transition with minimal to no withdrawal symptoms while on the inpatient service and was successfully discharged with plans to follow up for continued management.

Discussion

This case report describes the transition from high-dose methadone to buprenorphine-naloxone utilizing a micro-

TABLE: Buprenorphine-naloxone microdose protocol from high-dose methadone

Day	Methadone, mg	Buprenorphine-Naloxone (Sublingual), mg	Clinical Opiate Withdrawal Scale
1	105 daily	0.5-0.125 once	0
2	105 daily	0.5-0.125 TID	. . .
3	105 daily	1-0.25 BID	. . .
4	105 daily	2-0.5 BID	. . .
5	105 daily	2-0.5 QID	. . .
6	105 daily	4-1 TID	0
7	0	12-3 daily	0
8	0	12-3 daily	0

BID = twice daily; QID - four times daily; TID = three times daily.

dose induction protocol in the inpatient setting. This protocol provided sublingual buprenorphine-naloxone in small, increasing doses with methadone 105 mg daily over a 7-day period with abrupt discontinuation of methadone on day 7. This is one of the few reports describing microdosed buprenorphine without first tapering high-dose methadone.

Similar to other published case reports[7-10] of microdosed buprenorphine overlapped with methadone, this patient reported minimal withdrawal symptoms during the induction period. He was transitioned from high-dose methadone 105 mg to sublingual buprenorphine-naloxone, and the minimal symptoms he experienced occurred prior to induction and were attributed to restarting home divalproex. The dose in this case report is slightly higher than the 100 mg described in another case report[9] that took 8 days to transition. Another case report[10] utilizing a microdose induction transitioned a patient from methadone 160 mg but took more than 4 months to complete, which is a significantly longer period of time than the 7-day conversion utilized in this report.

Microdosed buprenorphine with concurrent methadone is just 1 proposed approach to buprenorphine induction. There are other reports[12,13] of rapid induction utilizing buprenorphine transdermal patches initiated 3 or 12 hours after the last dose of methadone. The first case series[12] describes 11 patients on methadone doses up to 100 mg, who were administered a 35-mcg patch 12 hours after their last dose of methadone and then administered sublingual buprenorphine 48 hours postmethadone, which was titrated. At 24 to 48 hours postmethadone, only mild withdrawal symptoms were reported. This approach was then applied to a patient receiving methadone 70 mg twice daily.[13] For this patient, a 20-mcg patch was applied 3 hours after the last methadone dose, and sublingual buprenorphine-naloxone 1-0.25 mg was initiated on day 2. Although this was a faster transition with a lower dose, the patient did experience withdrawal symptoms on day 2 with a COWS of 16.[11,13] One advantage of this approach is that the rapid transition limits the potential duration of withdrawal symptoms. Conversely, the disadvantage is these patients did experience some withdrawal during the induction period compared with the minor symptoms experienced by the patient in this report that were likely due to other medications.

Another approach[14] uses oral naltrexone to precipitate withdrawal in patients stabilized on methadone 70 to 130 mg and initiate sublingual buprenorphine-naloxone once withdrawal symptoms occurred. On average, this induction took place over 7 days. COWS scores and actual withdrawal symptoms/severity of symptoms were not provided in this report, but the authors noted expected withdrawal symptoms were seen within 45 minutes. It is important to note that naltrexone-induced withdrawal can be distressing for the patient and include symptoms such as agitation, nausea/vomiting, hypertension, altered consciousness, and respiratory distress.[15,16] Although the amount of time to complete induction was comparable, the present report provides small doses of sublingual buprenorphine-naloxone along with methadone to avoid precipitated withdrawal and make the overall experience more tolerable for the patient.

Conclusion

This case report adds to the very limited existing literature by describing a successful transition from high-dose methadone to sublingual buprenorphine-naloxone utilizing the Bernese method of microdosing. Patients who are stabilized on higher doses of methadone may benefit from a microdose induction to diminish potential withdrawal symptoms, reduce the time burden associated with methadone tapering, and improve the overall induction experience. There are various microdose protocols proposed, and future research should evaluate which approach is best, what patient characteristics predict success, and long-term outcomes of a microdose approach compared with traditional approaches.

References

1. Jones HE. Practical consideration for the clinical use of buprenorphine. Sci Pract Perspect. 2004;2(2):4-20. DOI: 10.1151/spp04224. PubMed PMID: 18552728; PubMed Central PMCID: PMC2851017.
2. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55(5):569-80. DOI: 10.1038/clpt.1994.71. PubMed PMID: 8181201.
3. Fischer G, Gombas W, Eder H, Jagsch R, Peternell A, Stuhlinger G, et al. Buprenorphine versus methadone maintenance for the treatment of opioid dependence. Addiction. 2002;94(9):1337-47.

DOI: 10.1046/j.1360-0443.1999.94913376.x. PubMed PMID: 10615719.
4. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2: CD002207. DOI: 10.1002/14651858.CD002207.pub4. PubMed PMID: 24500948.
5. Hser Y-I, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, et al. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014;109(1):79-87. DOI: 10.1111/add.12333. PubMed PMID: 23961726.
6. Walsh SL, June HL, Schuh KJ, Preston KL, Bigelow GE, Stitzer ML. Effects of buprenorphine and methadone in methadone-maintained subjects. Psychopharmacology. 1995;119(3):268-76. DOI: 10.1007/BF02246290. PubMed PMID: 7675960.
7. Vogel M, Hämmig R, Kemter A, Strasser J, von Bardeleben U, Gugger B, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the "Bernese method". Subst Abuse Rehabil. 2016;7:99-105. DOI: 10.2147/SAR.S109919. PubMed PMID: 27499655; PubMed Central PMCID: PMC4959756.
8. Hämmig R. Einleitung einer Substitutionsbehandlung mit Buprenorphin unter vorübergehender Überlappung mit Heroinkonsum: ein neuer Ansatz ("Berner Methode"). [Induction of a buprenorphine substitution treatment with temporary overlap of heroin use: a new approach ("Bernese method").] Suchttherapie. 2010;11:129-32.
9. Terasaki D, Smith C, Calcaterra SL. Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. Pharmacotherapy. 2019;39(10):1023-9. DOI: 10.1002/phar.2313. PubMed PMID: 31348544.
10. Jafari S, Rafizadeh R. Successful transition from high-dose methadone to buprenorphine via microdosing in the outpatient setting: a case report. Can J Hosp Pharm. 2021;74(1):83-5. PMID: 33487660.
11. Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). J Psychoactive Drugs. 2003;35(2):253-9. DOI: 10.1080/02791072.2003.10400007. PubMed PMID: 12924748.
12. Hess M, Boesch L, Leisinger R, Stohler R. Transdermal buprenorphine to switch patients from higher dose methadone to buprenorphine without severe withdrawal symptoms. Am J Addict. 2011;20(5):480-1. DOI: 10.1111/j.1521-0391.2011.00159.x. PubMed PMID: 21838850.
13. Cortina S, Mihic T, Fennemore M, McLean M. Case report: high-dose methadone transition to buprenorphine/naloxone in an inpatient with a prolonged QT interval. Can J Addict. 2017;8(1): 25-8. DOI: 10.1097/02024458-201706000-00006.
14. Urban V, Sullivan R. Buprenorphine rescue from naltrexone-induced opioid withdrawal during relatively rapid detoxification from high-dose methadone: a novel approach. Psychiatry (Edgmont). 2008;5(4):56-8. PubMed PMID: 19727311.
15. Hassanian-Moghaddam H, Afzali S, Pooya A. Withdrawal syndrome caused by naltrexone in opioid abusers. Hum Exp Toxicol. 2014;33(6):561-7. DOI: 10.1177/0960327112450901. PubMed PMID: 23690227.
16. De Giacomo M, Gaspari R, Stefanelli A, Barelli A, Mannelli P. Emergency therapeutical approach simulating ultrarapid opioid detoxification in methadone withdrawal precipitated by erroneous administration of naltrexone. Eur J Emerg Med. 1999;6(2): 153-5. DOI: 10.1097/00063110-199906000-00013. PubMed PMID: 10461561.