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Buprenorphine Induction Using Microdosing for the Management of Opioid Use Disorder in Pregnancy

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Abstract

Background Conventional buprenorphine inductions require patients to abstain from full agonist opioids until they experience mild-to-moderate opioid withdrawal. We described a successful buprenorphine induction case in a pregnant patient using microdosing, which avoided withdrawal symptoms.

Case Presentation The patient is a 29-year-old G2P1001 at 18 2/7 weeks of gestation, who desired a switch from methadone to buprenorphine to minimize neonatal opioid withdrawal syndrome (NOWS), which complicated her last pregnancy. She was given increasing microdoses of buprenorphine over a 7-day period, while continuing her daily dose of methadone. She discontinued the methadone on day 8. She did well during the week of buprenorphine microdosing, with no complaints of withdrawal or cravings. She was engaged in her prenatal care. Her dose of buprenorphine was increased to 8 mg twice daily in the third trimester for some withdrawal symptoms in the evening consisting of new onset nausea and vomiting.

The patient underwent an elective 39-week induction of labor and had a spontaneous vaginal delivery of an appropriately grown male fetus. Only nonpharmacologic interventions were used.

Conclusion Buprenorphine microdosing was well tolerated in this patient and avoided withdrawal symptoms in the mothers, and NOWS. A microdosing study in pregnancy is indicated

Keywords
- opioid use disorder pregnancy
- buprenorphine pregnancy
- buprenorphine microdosing pregnancy
- microdosing buprenorphine

For pregnant persons, medications for opioid use disorder (MOUD) are the recommended therapy and have been shown to improve pregnancy outcomes and save lives. Buprenorphine is a partial agonist at the μ opioid receptor with high-binding affinity and slow dissociation from the receptor. The partial agonist effect has significant safety benefits when compared with full agonist opioids such as methadone. Buprenorphine products are unlikely to cause respiratory arrest unless combined with other central nervous system depressants.

Because buprenorphine has a higher binding affinity for the μ receptor than full agonist opioids, immediately starting buprenorphine in a patient taking a full agonist will abruptly displace the full agonist from the μ receptor, leading to precipitated withdrawal. To avoid precipitated withdrawal during conventional buprenorphine inductions, patients abstain from full agonist opioids until they experience mild-to-moderate opioid withdrawal.

This is a case presentation of a successful buprenorphine induction of a pregnant patient on methadone maintenance,

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who desired induction onto buprenorphine to minimize the risk of neonatal opioid withdrawal syndrome (NOWS), which severely affected her prior child. Written consent to publish a report of the case has been obtained by the patient.

Case Presentation

The patient is a 29-year-old G2P1001 at 18 2/7 weeks of gestation, who desired a switch from methadone to buprenorphine to minimize NOWS in this pregnancy. The patient had a history of IV drug use from 17 to 25 years of age. This pregnancy was complicated by hepatitis C infection, a history of anxiety and depression, and tobacco use. Her medications included a daily Prenatal vitamin (PNV) and methadone 68 mg daily. Her prior pregnancy was 3 years earlier, a normal spontaneous vaginal delivery at 37 6/7 weeks of gestation of a female infant weighing 7 pounds 8 ounces, complicated by severe NOWS with a prolonged hospitalization.

She was counseled that buprenorphine maintenance can also be associated with NOWS, and that changes in neonatal treatment incorporating "eat, sleep, console" allow successful newborn transition and significantly decrease the experience of neonatal withdrawal symptoms and need for opioid medication.[1] She was also counseled regarding smoking cessation as a means to decrease the risk of NOWS.[2] Despite these recommendations, the patient slowly weaned herself from 68 mg of methadone, down to 30 mg daily, a decrease of 2 mg every other day. The methadone clinic instructed her to abstain from methadone for at least 48 hours, until she experienced moderate withdrawal symptoms before initiating the traditional buprenorphine induction.

The patient was counseled extensively regarding the possible risks and benefits of microdosing. She desired to proceed with microdosing instead of the traditional buprenorphine induction. The Prescription Monitoring Program was checked and the patient had no other prescriptions for opiates recorded.

She continued to take her daily dose of methadone 30 mg, while increasing her daily dose of buprenorphine according to the protocol used by Terasaki et al.[3] (►**Table 1**).

Table 1 Buprenorphine microdosing protocol

Day	Buprenorphine dosage	Methadone dose
1	0.5 mg[a] SL once/day	Full dose
2	0.5 mg SL twice/day	Full dose
3	1 mg SL twice/day	Full dose
4	2 mg SL twice/day	Full dose
5	4 mg SL twice/day	Full dose
6	8 mg SL once/day	Full dose
7	8 mg SL in am, and 4 mg SL in pm	Full dose
8	12 mg SL/day	Stop

Abbreviation: SL, sublingually.
[a]For our buprenorphine formulation, one-quarter of a 2 mg sublingual strip/film was used.

The patient did well during the week of buprenorphine microdosing, with no complaints of withdrawal or cravings. She continued to be engaged in her prenatal care. She had a normal fetal anatomy scan. Her dose of buprenorphine was increased to 8 mg twice daily in the third trimester for some withdrawal symptoms in the evening consisting of the new onset of nausea and vomiting. She had a normal follow-up growth ultrasound at 32 weeks. She was down to 2 cigarettes a day.

The patient underwent an induction of labor at 39 weeks and had a spontaneous vaginal delivery of a 3,340 gram male infant. Apgar scores were 8 and 9 after 1 and 5 minutes, respectively. The cord blood toxicology screen was positive for tetrahydrocannabinol (THC). The neonatal urine toxicology screen was positive for THC and buprenorphine. The Finnegan Neonatal Abstinence Score peaked at 5 days of life. Only nonpharmacologic interventions were used. He did not require any opioids for treatment. The patient continued her daily dose of buprenorphine intrapartum and postpartum. Her pain was adequately controlled with nonsteroidal anti-inflammatory drugs and Tylenol. She was referred to gastrointestinal postpartum for treatment of hepatitis C.

Discussion

Provisional data from Centers for Disease Control and Prevention National Center for Health Statistics indicate that there were an estimated 100,306 drug overdose deaths in the United States during the 12-month period ending in April 2021, with 75,673 due to opioids.[4] Overdose deaths from synthetic opioids, primarily fentanyl, also increased during that same time period. Opioid use in pregnancy has escalated dramatically, paralleling the epidemic observed in the general population.

The increase in synthetic opioids such as fentanyl in the illicit drug market has further complicated buprenorphine inductions.[5] Although fentanyl has a rapid onset and short duration of action, it is lipophilic, resulting in distribution to the peripheral tissues in a manner that is not dose dependent. Consequently, continuous and prolonged use of fentanyl can result in increased volume of distribution systemically with slow dissipation overall. Correspondingly, there appears to be an increased incidence of precipitated withdrawal during the induction process of buprenorphine with fentanyl use. This occurs despite patients objectively being in moderate-to-severe opioid withdrawal before starting the medication. This is a barrier to treatment for both patients and providers and has been associated with dissatisfaction and noncompliance.

Precipitated withdrawal occurs when there is a net decrease in opioid effect. Buprenorphine is a partial opioid agonist that has a high affinity for the μ-receptor, but less intrinsic opioid effect than a pure opioid agonist such as methadone or fentanyl. When buprenorphine is given to a patient with an opioid agonist on board, the partial agonist, buprenorphine, displaces the full agonist from the μ-receptor, and since it activates the receptor to a lesser degree than a full-agonist, this results in a net decrease in agonist effect, thereby precipitating withdrawal.[6]

Buprenorphine microdosing using the Bernese method, was first described by Hämmig et al in 2016[7] and involved repetitive, low-dose exposure to buprenorphine over several days, such that partial and full opioid agonists can be continued concurrently without precipitated withdrawal. Buprenorphine induction using microdosing can improve the care of patients with OUD by minimizing opioid withdrawal symptoms, reducing the dropout rate during induction, and decreasing the fear of withdrawal. It can safely be performed in the outpatient setting.[8]

MOUD is an approach to opioid use treatment that combines the use of U.S. Food and Drug Administration-approved drugs with counseling and behavioral therapies for people diagnosed with opioid use disorder (OUD). Both methadone and buprenorphine are medications used to treat OUD. It is generally recommended that if a pregnant person is already receiving therapy with methadone, she should not transition to buprenorphine because of the significant risk of precipitated withdrawal and destabilization. Staying on maintenance therapy has been shown to improve outcomes and saves lives.[9] Shared decision making and patient-centered care were instrumental in supporting this patient's decision to switch from methadone to buprenorphine. This allowed her to maintain MOUD throughout pregnancy and reduce her risk of relapse and overdose.

Buprenorphine acts on the same μ-opioid receptors as heroin and morphine, but functions as a partial rather than full agonist, making overdose less likely. Other advantages of buprenorphine over methadone include fewer drug interactions, the ability to be treated on an outpatient basis without the need for daily visits to an opioid treatment program, and evidence of less need for dosage adjustments throughout pregnancy. Lastly, several trials demonstrate evidence of less-severe NOWS.[10] Decreasing her nicotine use may have also contributed to a more favorable neonatal outcome.[2]

The patient slowly weaned herself down to a methadone dose of 30 mg in anticipation of a traditional buprenorphine induction where patients are requested to abstain from opiates until they are in mild-to-moderate withdrawal. However, higher doses of methadone such as 100 mg have been successfully transitioned to buprenorphine using a microdosing protocol.[11]

A growing body of literature supports microdosing of buprenorphine in nonpregnant persons.[2,4,5] Pregnancy is a window of opportunity to provide MOUD to persons with an opioid use disorder.[6] Given the safety profile of buprenorphine, its potential to be a lifesaving intervention, and the avoidance of withdrawal symptoms, a study of microdosing in pregnancy is indicated.

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Conflicts of Interest
None declared.

References

1 Grossman MR, Lipshaw MJ, Osborn RR, Berkwitt AK. A novel approach to assessing infants with neonatal abstinence syndrome. Hosp Pediatr 2018;8(01):1–6
2 Choo RE, Huestis MA, Schroeder JR, Shin AS, Jones HE. Neonatal abstinence syndrome in methadone-exposed infants is altered by level of prenatal tobacco exposure. Drug Alcohol Depend 2004;75 (03):253–260
3 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):1023–1029
4 Accessed November 17, 2021 at: https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm
5 Randhawa PA, Brar R, Nolan S. Buprenorphine-naloxone "microdosing": an alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. CMAJ 2020;192(03):E73
6 Medications for Opioid Use Disorder. Treatment Improvement Protocol. Tip 63. Updated 2021. SAMHSA. Substance Abuse and Mental Health Services Administration (SAMHSA). Accessed January 26, 2023 at: https://store.samhsa.gov/sites/default/files/SAMHSA_Digital_Download/PEP21-02-01-002.pdf
7 Hämmig R, Kemter A, Strasser J, 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
8 Robbins JL, Englander H, Gregg J. Buprenorphine microdose induction for the management of prescription opioid dependence. J Am Board Fam Med 2021;34(Suppl):S141–S146
9 Opioid use and opioid use disorder in pregnancy. Committee opinion No. 711. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e81–e94
10 Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev 2013;(12):CD006318
11 Anderson C, Cooley R, Patil D. Transitioning from high-dose methadone to buprenorphine using a microdosing approach: unique considerations at ASAM level 3 facilities. J Addict Med 2022;00:1–4