Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series

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Background and Objectives: Buprenorphine/naloxone has been shown to be effective in the treatment of opioid use disorder. Due to its pharmacological properties, induction can be challenging, time-consuming, and result in sudden onset of withdrawal symptoms.

Methods: Retrospective case series (n = 2).

Results: Two patients with opioid use disorder were successfully started on buprenorphine/naloxone using a rapid micro-induction technique that did not cause precipitated withdrawal or require preceding cessation of other opioids.

Discussion and Conclusions: These cases provide an alternative method for starting buprenorphine/naloxone that offers unique benefits compared to protocols previously described in the literature. Scientific Significance: This method can be used to minimize barriers to opioid agonist therapy. (Am J Addict 2019;XX:1–4)

INTRODUCTION

Deaths caused by opioid overdose have been rising in both Canada and the United States.1,2 This increase has been observed in both illicit and prescription opioid users.3,4 Overprescribing practices and the availability of inexpensive high-potency synthetic opioids, such as fentanyl, have been implicated in this alarming change.5–7 Buprenorphine/naloxone has been shown to effectively treat opioid use disorder and has been recommended as first-line therapy.8–11 Buprenorphine, a partial mu-opioid receptor agonist, can also be used to provide analgesia while carrying a more favorable safety profile compared to full mu-opioid agonists.12,13 It is often combined with naloxone, a competitive opioid receptor antagonist with minimal oral and sublingual absorption, to discourage intravenous use.14 When administered at target doses, buprenorphine/naloxone has been shown to decrease binding of other opioids, thereby decreasing the likelihood of overdose.15 This is due to buprenorphine’s mu-opioid receptor binding affinity, which is significantly higher than other opioids.16 This high receptor binding affinity is also responsible for buprenorphine’s ability to displace other opioids and cause sudden onset of withdrawal symptoms, also known as precipitated withdrawal.15

In order to avoid this withdrawal effect, when buprenorphine/naloxone is first administered, patients are required to be in mild-to-moderate withdrawal from all other opioids.9,10 The recommended period of abstinence can range from 12 to 16 hours for short-acting opioids such as hydromorphone or diacetylmorphine (heroin) and upwards of 48 hours for longer-acting opioids such as methadone.11 Furthermore, traditional buprenorphine/naloxone induction involves the administration of small doses with an assessment of withdrawal symptoms after each dose.9,10 For these reasons, traditional induction can be time-consuming and difficult for patients to tolerate.8,17 A “micro-dosing” regimen which does not require prior withdrawal has been described in the literature in an outpatient setting.18 However, a limitation of this method is the significant length of time required to reach a therapeutic dose.

Here we present two cases in which inpatients were successfully started on buprenorphine/naloxone using a rapid micro-induction technique that did not require preceding...
withdrawal or cause precipitated withdrawal. Written consent was obtained from both patients.

**CASE 1**

A 33-year-old woman was brought to the emergency department at a tertiary care hospital in Vancouver, British Columbia after being struck by a vehicle. She was treated surgically for a subdural hematoma and a left proximal humerus fracture was managed conservatively. Her past medical history included severe opioid use disorder, severe alcohol use disorder, fetal alcohol spectrum disorder, hepatitis C virus, right brachial artery aneurysm, and remote left index finger amputation secondary to infection. Prior to admission, she was not taking prescription medications and reported using approximately .5 grams of intravenous heroin per day. During her admission, the patient experienced symptoms of opioid withdrawal and was receiving intravenous hydromorphone for treatment of withdrawal and pain. She also supplemented these medications with illicit intravenous heroin provided to her in hospital by friends. She was then seen by our complex pain and addiction consult team. Physical examination revealed extensive track marks on both of her upper extremities and neck. A urine drug screen (UDS) was positive for opiates and negative for fentanyl and methadone. She expressed interest in starting opioid agonist treatment (OAT) and was assessed to be a candidate for buprenorphine/naloxone.

At the time of induction, the patient was experiencing minimal withdrawal symptoms with a clinical opioid withdrawal score (COWS) of 2. While continuing to receive intravenous hydromorphone, she completed a rapid micro-induction. On Day 1, she received buprenorphine/naloxone 0.25 mg sublingual (SL) every four hours (q4h) for a total of five doses. This was doubled on the next day and consolidated into a single daily dose of 12 mg on Day 5. The full titration schedule is detailed in Table 1. Prior to induction, the patient had a COWS score of zero. He reported no symptoms suggestive of precipitated withdrawal and both his pain and withdrawal were well controlled after induction was completed. There were no further cravings for opioids and he was discharged to a residential treatment facility on a daily buprenorphine/naloxone dose of 12 mg.

**DISCUSSION**

Here we have described two cases in which inpatients with pre-existing opioid use disorder were started on

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<th>TABLE 1. Titration schedule for Case 1</th>
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<td>Buprenorphine/Naloxone*</td>
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<td><strong>Dosing</strong></td>
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*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.
buprenorphine/naloxone using a rapid micro-dosing induction protocol. Both required treatment for post-operative pain in addition to withdrawal symptoms. Each patient reached a therapeutic dose of buprenorphine/naloxone without requiring a period of opioid withdrawal prior to initiation. During this time, they continued to receive short-acting opioids without experiencing precipitated withdrawal symptoms. Following induction, both patients were maintained on buprenorphine/naloxone in hospital and did not experience withdrawal symptoms or cravings for illicit opioids.

The strength of this study is the demonstration of an alternative induction technique in a monitored setting that allowed for accurate assessment of therapeutic effect, as well as complications. In the first case, while there were no objective or subjective symptoms of precipitated withdrawal, there was an increase in hydromorphone use on the first day of induction. Initially this was concerning for perhaps masking withdrawal symptoms. However, review of the patient’s chart revealed that the majority of the hydromorphone (7 mg out of total daily dose of 11 mg) was received before buprenorphine/naloxone was administered. As well, the total daily dose on Days 1–3 was consistent with hydromorphone use prior to induction, with the minimal use on Day 0 being an anomaly.

To our knowledge, the only known existing micro-dosing protocol for buprenorphine in the literature is the “Bernese method” which has been described in a case series. This protocol utilized the administration of buprenorphine at “micro” doses either daily or twice daily in an effort to avoid precipitated withdrawal. The hypothesis was that small, successive doses of buprenorphine would slowly accumulate at the mu-opioid receptor. Our study postulated that doses could be administered more rapidly given buprenorphine’s time to peak plasma concentration of approximately 1 hour. The two patients in the Bernese method study took 10 days or greater to reach a therapeutic dose, whereas our two patients reached therapeutic doses in 3 to 5 days. While both patients in the previously described method started with a single dose of 0.2 mg on the first day, our patients received a higher starting dose that was dosed frequently. This allowed for the total dose on the first day of our method to be much higher. In contrast to the cases presented here, the Bernese method was demonstrated in an outpatient setting. Rapid induction is important in an inpatient setting where discharges are generally not delayed to complete buprenorphine/naloxone induction. The use of this protocol could increase the number of patients leaving hospital on a therapeutic dose.

In the cases presented, a traditional induction would have required the cessation of all opioids, which were serving a dual purpose of treating pain and withdrawal symptoms. It is unlikely that these patients would have been able to tolerate this required period of abstinence, effectively excluding them from this first-line treatment for their opioid use disorder. This can be extrapolated to an outpatient setting, where high-risk patients with opioid use disorder have difficulty initiating buprenorphine/naloxone due to the requirement of being in withdrawal. The complexity of the induction process has been seen as a barrier to buprenorphine/naloxone use among physicians. Eliminating the need for preceding withdrawal and simplifying the induction process could increase the availability of opioid agonist treatment. This protocol may also be applicable in patients with chronic pain who are receiving high doses of prescribed opioids. In addition to being an effective pain medication, buprenorphine/naloxone carries a better safety profile than other opioids. Thus, rapid micro-induction of buprenorphine/naloxone could be used to decrease risk of overdose in patients taking prescribed opioids and optimize long-term quality of life.

We would suggest that this protocol be tested in an inpatient setting for patients with opioid use disorder who meet existing criteria for buprenorphine/naloxone treatment. Given the strong evidence for buprenorphine/naloxone, it is imperative that research efforts are focused on eliminating barriers to its use. Micro-dosing is a possible solution to the requirement for preceding opioid withdrawal and risk of precipitated withdrawal that deters many patients from utilizing this therapy. Future research is needed to examine the safety and efficacy of micro-dosing inductions in diverse samples. This should be done for patients receiving short-acting opioids, such as in our cases, and also longer-acting opioid formulations such as methadone.

**Declaration of Interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.
REFERENCES


