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Case Report: "Striving to Skip the Withdrawal" Using Buprenorphine–Naloxone Microdosing for Hospitalized Patients

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ABSTRACT

Opioid substitution therapy is a life-saving, first-line treatment for patients with opioid use disorder. It is a key intervention to prevent further mortality and morbidity during the opioid crisis that is claiming lives across Canada. Traditionally, patients must be experiencing at least moderate withdrawal in order to safely initiate buprenorphine–naloxone, which is recommended as first-line therapy for the treatment of opioid use disorder. Across Canada, physicians have been "microdosing" buprenorphine–naloxone in order to "skip the withdrawal" required for traditional inductions. However, the role of these protocols in acutely ill hospitalized patients has not been explored in the literature. We describe 2 cases where microdosing protocols were utilized in the management of hospitalized patients with both an acute medical issue and active opioid use disorder. This article explores special considerations when managing hospitalized patients with microdosing protocols, including case selection, timing, titration schedules, and the development of a therapeutic alliance.

Keywords: Buprenorphine–Naloxone, Hospitalized Patients, Opioid Substitution Therapy, Opioid Use Disorder

Le traitement de substitution aux opioïdes est un traitement de première ligne qui permet de sauver des vies chez les patients présentant un trouble de l'utilisation des opioïdes. Il s'agit d'une intervention clé pour prévenir davantage de mortalité et de morbidité durant la crise des opioïdes faisant de nombreuses victimes au Canada. Traditionnellement, les patients doivent subir un sevrage au moins modéré pour pouvoir prendre en toute sécurité de la buprénorphine-naloxone, recommandée en tant que traitement de première intervention du traitement du trouble de l'usage des opioïdes. Partout au Canada, les médecins utilisent le «microdosage» du buprénorphine-naloxone afin d'«éviter le sevrage» requis pour les inductions traditionnelles. Cependant, le rôle de ces protocoles chez les patients hospitalisés en phase aiguë n'a pas été exploré dans la littérature. Nous décrivons deux cas dans lesquels des protocoles de microdosage ont été utilisés dans la gestion de patients hospitalisés présentant à la fois un problème médical aigu et un trouble actif d'utilisation d'opioïdes. Cet article explore les considérations spéciales lors de la gestion des patients hospitalisés avec des protocoles de microdosage, y compris la sélection des cas, le choix du moment, les calendriers de titrage et le développement d'une coalition thérapeutique.

Mots clés: traitement de substitution aux opioïdes, buprénorphine-naloxone, trouble lié à l'utilisation d'opioïdes, patients hospitalisés

INTRODUCTION

The opioid crisis continues to claim unprecedented numbers of lives in Canada, with an estimated 3286 opioid-related deaths reported in 2018 alone.[1,2] People who inject drugs are at increased risk of infectious diseases and other sequelae of injection drug use (IDU) requiring intensive medical services.[3] These adverse outcomes continue to occur despite ongoing public health interventions to increase access to substance use treatment and harm reduction strategies, such as supervised injection sites.[4] Pharmacotherapy with opioid substitution therapy (OST), such as buprenorphine–naloxone and methadone, has been shown to reduce mortality in patients with opioid use disorder (OUD).[5]

Buprenorphine–naloxone has several attributes that make it preferable for the treatment of OUD: more rapid dose titration during induction, a superior safety profile, fewer side effects, and greater flexibility both in the provision of take-home doses and in the frequency of follow-up required. Furthermore, the Canadian Medical Association Journal has published a national clinical practice guideline in 2018 recommending buprenorphine–naloxone as first-line for the treatment of OUD.[6]

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Traditionally, it has been recommended that buprenorphine–naloxone be initiated when a patient is in a state of moderate-to-severe opioid withdrawal, in order to avoid precipitated withdrawal.[7] Buprenorphine is a partial μ-opioid receptor agonist with high binding affinity, but lower intrinsic agonist activity than other opioids.[8] Precipitated withdrawal occurs when there is rapid displacement of a full μ-agonist opioid, such as heroin or morphine, with the partial agonist activity of buprenorphine. Once the full μ-agonist opioid has been displaced, buprenorphine's lower intrinsic potency causes an intense and abrupt withdrawal. This is highly distressing and uncomfortable for patients. In clinical practice, the greatest limitation to starting individuals with OUD on buprenorphine–naloxone is the need for patients to be in adequate opioid withdrawal such that buprenorphine will provide relief of symptoms and not precipitate withdrawal. Opioid withdrawal is assessed using the clinical opioid withdrawal score (COWS), and initiation with buprenorphine generally requires a COWS score of at least 13, which is consistent with moderate opioid withdrawal.[9]

Achieving a moderate opioid withdrawal state can be challenging in the inpatient setting, where patients are often admitted for a condition that requires acute pain management. In an effort to eliminate this barrier, and avoid the discomfort of opioid withdrawal, Hämmig et al developed a protocol to administer "microdoses" of buprenorphine–naloxone while overlapping with a full opioid agonist, entitled "the Bernese method". Across Canada, microdosing schedules are being modified and implemented to adapt to available clinical resources and patient profiles. This is generally considered an off-label use of buprenorphine–naloxone, therefore informed consent from patients must be obtained after discussing the relative risks and benefits of a microdosing induction compared to a traditional induction protocol.

The purpose of this article is to review 2 cases where buprenorphine–naloxone microdosing protocols were employed or adapted in transitioning patients to buprenorphine maintenance therapy. We will explore differences between the cases to highlight challenges specific to the inpatient setting, and provide insight into appropriate case selection and transition protocols. The cases described below are an amalgamation of patients we have seen in the inpatient setting.

CASE 1: MICRODOSING FOR OUD AND MILD ACUTE PAIN

A 30-year-old patient, who will be referred to as AB, was admitted with bacteremia and septic pulmonary emboli as a complication of IDU. AB had previously trialed both methadone and buprenorphine–naloxone, and was contemplative about restarting buprenorphine–naloxone.

Table 1: Microdosing Schedule for Case 1 (AB)

	Buprenophine Dose (mg)*	HM
Day 1	0.5	2 mg IV q3h PRN = 6 mg total
Day 2	0.5	2 mg IV q3h PRN = 8 mg total
Day 3	1	2 mg IV q3h PRN = 12 mg total
Day 4	1.5	2 mg IV q3h PRN = 8 mg total
Day 5	2	2 mg IV q3h PRN = 8 mg total
Day 6	3	2 mg IV q3h PRN = 8 mg total
Day 7	4	2–4 mg PO q3h PRN = 20 mg total
Day 8	4	2–4 mg PO q3h PRN = 16 mg total
Day 9	4	2–4 mg PO q3h PRN = 12 mg total
Day 10	5	2–4 mg PO q3h PRN = 12 mg total
Day 12	6	2–4 mg PO q3h PRN = 8 mg total
Day 13	8	No HM
Day 14	10	No HM
Day 15	Discharged	

HM = hydromorphone, IV = intravenous; PO = per os.
* Dispensed as buprenorphine–naloxone.

However, AB was concerned that buprenorphine–naloxone would not help with their acute pain management. Furthermore, AB had received hydromorphone for acute pain upon admission, and was not interested in discontinuing the prescribed opioids in hospital in order to achieve the moderate withdrawal necessary for a traditional buprenorphine–naloxone induction. After discussion, AB was agreeable to proceed with the microdosing protocol, using hydromorphone for pain control in the interim (see Table 1). AB was aware that as the infection improved, the hydromorphone would be weaned and a hydromorphone prescription would not be provided on discharge. An agreement was made between AB and the addiction medicine physician to maintain the buprenorphine–naloxone at a low dose of 4 mg until the patient's hydromorphone requirements were minimal, at which time the buprenorphine–naloxone could be titrated up more rapidly. AB felt ready to wean the hydromorphone and increase the suboxone on day 9 of admission, and at that time the buprenorphine–naloxone titration was resumed. AB did not report any withdrawal symptoms throughout the entire hospitalization. AB was discharged home on day 15 of admission, on 10 mg of buprenorphine–naloxone. At the time of discharge, the patient reported that both withdrawal symptoms and pain were well controlled (Table 1).

CASE 2: MICRODOSING FOR OUD AND COMPLEX ACUTE PAIN

A 40-year-old patient, who will be referred to as CD, was admitted to hospital with frostbite in the setting of severe,

Table 2: Microdosing Schedule for CASE 2 (CD)		
	Buprenophine Dose*	HM
Day 1	0.5 mg	4 mg IV q3h
Day 2	0.5 mg	2 mg IV q2h then 4 mg
Day 3	1 mg	6 mg IV q3h
Day 4	1.5 mg	6 mg IV q3h
Day 5	2 mg	6 mg IV q3h
Day 6	3 mg	6 mg IV q3h
Day 7	4 + 2 + 2 mg	6 mg IV q3h
Day 8	4 mg BID + 2 mg	6 mg IV q3h
Day 9	4 mg TID	6 mg IV q3h
Day 10	4 mg TID	6 mg IV q3h
Day 12	8 mg BID	6 mg IV q3h
Day 14	12 mg BID	HM Contin 21 mg BID + PRN
Day 15	12 mg BID	Resumed 4 mg IV q3h
Day 16	24 mg daily	7 mg PO q3h routine
Day 17	Discharged	

HM = hydromorphone, IV = intravenous, PO = per os.
* Dispensed as buprenorphine–naloxone.

active OUD. Upon admission, the options of methadone maintenance therapy or buprenorphine–naloxone maintenance therapy were discussed with the patient. Given CD's fear of experiencing opioid withdrawal, the decision was made to attempt buprenorphine–naloxone microdosing. In the interim, CD was titrated up on subcutaneous hydromorphone for management of acute pain and withdrawal. By day 7 of the protocol, in an attempt to decrease CD's hydromorphone requirements, the buprenorphine–naloxone was up-titrated faster, no longer using the microdosing protocol (see Table 2). However, despite increases in buprenorphine–naloxone, the patient could not tolerate any decrease in the hydromorphone dose. No objective withdrawal symptoms were observed, thus a COWS was not tracked. This intolerance is perhaps explained by a combination of significant acute pain, anxiety, or failure of buprenorphine–naloxone to adequately control the patient's perceived withdrawal symptoms. It is also worth noting that hydromorphone was the patient's drug-of-choice in the community, which may have impacted the tolerability of the hydromorphone taper. By day 14, CD was on the Health Canada recommended maximum dose of buprenorphine–naloxone (24 mg) and still experiencing significant pain and withdrawal symptoms. CD was unable to tolerate transition to long-acting morphine or hydromorphone, thus was discharged on buprenorphine–naloxone 24 mg SL daily and hydromorphone 7 mg per os q3h routine. CD continues to engage in outpatient follow-up with one of our inpatient addictions medicine physicians who carries an outpatient practice. CD is currently on buprenorphine–naloxone 24 mg SL daily and slow-release oral morphine, actively participating in a scheduled taper as the pain improves.

DISCUSSION

These 2 cases highlight a unique opportunity in the inpatient setting to initiate microdosing protocols while providing a safe supply of opioid to minimize withdrawal symptoms. Given the frequency of dosing (every 3–4 hours), options for route of administration (oral/intravenous/subcutaneous), and frequent dose adjustments, these protocols may be more challenging to implement in the outpatient setting.

Case 1 highlights a relatively smooth transition from hydromorphone to buprenorphine–naloxone in a patient with OUD and mild acute pain. The rationale for using the above-defined doses, rather than those described by Hämmig et al is due to the available formulations of buprenorphine–naloxone. In Canada, the smallest sublingual tablet contains 2 mg of buprenorphine and 0.5 mg of naloxone. Thus, 1/4 of a tablet (0.5 mg of buprenorphine) is the lowest reasonable dose that can safely and conveniently provided by a pharmacy.

The traditional Bernese method, developed for use in outpatients without acute illness, describes a continuous daily up-titration of buprenorphine–naloxone.[10] Our experience with patients such as the one illustrated in Case 2 highlight unique challenges when attempting to transition inpatients to buprenorphine–naloxone using microdosing protocols in the setting of complex, acute pain, and severe OUD. There is evidence supporting the "occupancy theory" which suggests near maximal μ-opioid receptor binding at doses of buprenorphine–naloxone above 16 mg.[11,12] Although there remains clinical equipoise about how to best manage buprenorphine–naloxone in the perioperative setting, some of this literature can also be used to inform our management of acute pain in the hospitalized patient whom we are attempting to transition to buprenorphine–naloxone. However, we feel there is more to the art of transitioning to buprenorphine–naloxone in the inpatient setting than the pharmacology alone.

Initiating Opioid Substitution Therapy in the Setting of Acute Pain

Hospitalization for an acute infection or complication of IDU presents a chance to engage patients struggling with substance use disorder. Longer admissions provide an opportunity to titrate toward a therapeutic dose of methadone or buprenorphine–naloxone before discharge. However, there are clear challenges unique to the inpatient initiation of OST. In our experience, patients are often concurrently experiencing acute pain from

cellulitis, osteomyelitis, discitis, septic emboli, and a myriad of other presentations, similar to those patients described in the above cases. Many patients anecdotally describe a lack of efficacy of buprenorphine–naloxone in the setting of acute pain. As noted above, although the overall evidence is weak, this is well described in the literature around perioperative pain,[11] where some suggest considering a reduction in the dose of buprenorphine–naloxone in advance of the surgery, and recognize patients may require increased doses of high affinity, full μ-opioid agonist medications for acute pain control.[13,14]

The patient in Case 2 was experiencing severe pain due to frostbite, and the patient's top priority was achieving adequate pain control. Unlike Case 1, it was anticipated that this patient's pain would require ongoing management after discharge. Our priority was to provide adequate pain control, while also ensuring patient safety and providing an opportunity to initiate treatment for their OUD while in hospital. Balancing these agendas can be a challenge and decision-making must be shared between the physician and patient.

The patient in Case 2 clearly had higher baseline opioid requirements (total daily requirements 84 mg hydromorphone oral equivalent in comparison to 12–24 mg). This demonstrates that there will be variability in patients' baseline opioid requirements for both withdrawal and pain management, and may impact the relative ease of the transition to buprenorphine–naloxone.

Allow Patients to Experience the Symptomatic Benefit of Buprenorphine–Naloxone

As described above, a traditional buprenorphine–naloxone induction requires patients to experience moderate withdrawal before initiating the medication. This leads to an immediate and significant relief of their withdrawal symptoms and may generate a swift appreciation for the buprenorphine–naloxone. Alternatively, when microdosing, patients do not experience this early relief when starting the medication. It is thus possible for patients to slowly increase to a full therapeutic dose of buprenorphine–naloxone while still on other opioids, and not experience any noticeable relief of symptoms. Subsequent discontinuation of the full opioid agonist can then lead to significant anxiety, or the fear that pain will be inadequately managed (as seen in Case 2). In this case, one may consider maintaining the buprenorphine–naloxone at a low-to-moderate dose (e.g., 4–8 mg) until the patients expresses readiness to dose escalate. Once they feel more comfortable with the process, the patient can participate in titrating their dose upwards in order to optimize their comfort while maintaining some agency in their pain management.

Patient Engagement

Patient engagement to eventually discontinue the coprescribed opioid (e.g., morphine, hydromorphone) is essential to the success of the microdosing protocols. If the patient is engaged in this process, they can often guide the taper of the coprescribed opioid while the dose of buprenorphine–naloxone is gradually increased, as was described by Hämmig et al.[10] Although the hospitalized inpatient relinquishes some control over their opioid management to their prescribing physician, control can be shared with the patient through the use of as-needed hydromorphone. This is described in Case 1, where the patient was able to participate in the tapering of hydromorphone throughout the microdosing protocol. In contrast, the patient in Case 2 was unable to actively participate in the reduction of hydromorphone. The variation in outcomes may be explained by ongoing pain, underlying anxiety, severity of opioid use disorder, and perhaps a lack of confidence in the microdosing process.

In the outpatient setting, patients who access clinics for OST are generally in a contemplation, preparation, or action stage of change.[15] If they opt to start on a microdosing protocol in the outpatient setting and are successful, they have demonstrated motivation to attend the pharmacy daily, as well as regular follow-up appointments with their prescriber. In comparison, hospitalized patients are typically offered OST opportunistically by physicians and may opt to accept therapy at a time when they may not have otherwise sought treatment in an outpatient setting. Simply put, we may be initiating OST for patients in hospital at a premature stage of change. While there are certainly benefits of early introduction of OST for patients with OUD, these subtle differences in population characteristics may impact likelihood for success of microdosing inductions in hospital, and subsequent engagement in outpatient treatment after discharge. In both of the above cases, the patients expressed being in the action stage of change, but the patient in Case 2 became resistant when an attempt was made to lower the hydromorphone, which may reflect a misinterpretation of their readiness.

In these cases, the patients did not have a formal diagnosis of a concurrent disorder therefore we did not incorporate that into our analysis of the analysis of the case outcomes.

Therapeutic Alliance

It can be challenging to form an effective therapeutic alliance with patients over the short period available when providing an inpatient addiction medicine consultation. People who use drugs have often experienced

stigmatization in healthcare environments and may have previously experienced conflict in the administration of opioids (for pain or withdrawal) in these settings. These prior experiences can impact whether a patient will trust the addiction medicine physician during an inpatient hospital stay, particularly if we are modifying an opioid schedule that may have been in place for many years.

An additional challenge in the inpatient setting is the lack of continuity with the addiction medicine physician. For example, in our center the addiction medicine physician provides service coverage on a weekly basis, thus patients are introduced to a new provider each week. These transitions may have an impact on the resilience of the therapeutic alliance, particularly for patients who remain in hospital for a prolonged stay.

Ensuring Effective Transitions To Outpatient Care

It is of critical importance to ensure a safe and effective transition to outpatient care upon discharge from hospital. There are many challenges and barriers that impact this transition, and exploring it fully is beyond the scope of this particular paper. As highlighted above, patient engagement with the treatment plan and their stage of change at the time of OST initiation may impact compliance with outpatient follow-up. Given that microdosing buprenorphine–naloxone is a relatively new practice, it is important to ensure that the outpatient prescriber is comfortable continuing the management plan, particularly if the schedule is not complete before discharge.

CONCLUSION

In summary, we believe there are key factors that impact the success of transitioning patients onto buprenorphine–naloxone using microdosing protocols in the hospital setting. Specific challenges include reaching agreement with patients to discontinue their previous opioids, ensuring rapid and effective titration over a brief period of time, and managing acute pain on a background of OUD. In the inpatient setting, patients are provided access to an addiction specialist due to the medical complications of their substance use disorder, rather than a self-identified desire to change their substance use pattern. In this population, there is significant overlap between acute pain, "total pain,"[16] withdrawal and tolerance. The addiction provider must manage these complex elements in order to provide safe and effective care to patients with OUD in the hospital setting.

Despite these challenges, we feel it is important to explore the option of microdosing for hospitalized patients with OUD. In successful cases, patients can leave hospital with adequate control of withdrawal symptoms, and are provided an opportunity to remain on OST and connect with an outpatient provider upon discharge. In patients for whom microdosing buprenorphine–naloxone was ineffective or intolerable, many may have at least experienced compassionate, patient-centered substance use care while in hospital. This encounter may improve their willingness to engage in further care after leaving hospital, or to access treatment for their substance use disorder at a different time. Future research is required in order to further inform decision-making and best practices on the use of microdosing buprenorphine–naloxone for patients with substance use disorders in the inpatient setting.

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