# Using short-acting opioids to relieve opioid withdrawal in hospital

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A 35-year-old woman with opioid, methamphetamine, cocaine and alcohol use disorders presented to the hospital with suicidal ideation and severe opioid withdrawal. She had had 3 previous suicide attempts and multiple previous unintentional opioid overdoses, one of which occurred in her washroom during a hospital admission. Eight days before presenting, she stopped methadone 150 mg/d orally and slow-release oral morphine (SROM) 200 mg/d orally. She reported high use of intravenous fentanyl, both while taking and since discontinuing methadone and SROM. Her last alcohol consumption had been 7 days earlier. She had a history of seizures when stopping illicit fentanyl consumption. She also had a history of posttraumatic stress disorder, major depressive disorder, borderline personality disorder, attention-deficit/hyperactivity disorder and hypothyroidism.

On presentation she had a heart rate of 90 beats per minute and blood pressure of 144/93 mm Hg. She had severe joint or muscle aches, stomach cramps, restlessness, moderately dilated pupils, piloerection and anxiety. Her home medications of prazosin, levothyroxine, extended-release dextroamphetamine–amphetamine, propranolol, quetiapine, clonazepam and temazepam were restarted in the emergency department. Hydromorphone 8 mg orally every 2 hours was started on an as-needed basis for opioid withdrawal. On day 1, oral methadone 30 mg was started in the morning and she received 64 mg of hydromorphone over the day. She remained uncomfortable despite these doses. On day 2, we partially consolidated her previous total dose of short-acting opioids to SROM 200 mg/d orally, and we switched the as-needed medication for opioid withdrawal to morphine 40 mg orally every 4 hours as needed, with improvement in her withdrawal symptoms and comfort. We subsequently admitted her to the hospital for treatment of her concurrent psychiatric and substance use disorders, including up-titration of methadone and SROM.

The patient was discharged about 1.5 months later, a few days before she was to be admitted to a residential addiction treatment centre. At the time of discharge, she was taking methadone 70 mg/d orally and SROM 350 mg/d orally.

## Discussion

The case of this patient highlights some of the challenges that patients with opioid use disorder (OUD) face when presenting to hospital. There are no guidelines in Canada or the United States for the management of fentanyl withdrawal in hospital settings. Within inpatient settings, undertreated opioid and other withdrawal symptoms, pain and cravings are common for patients with OUD, who often face provider-level and system-level stigma and leave hospital before medically advised.[1–3]

### Key points

- Patients with opioid use disorder (OUD) often have undertreated opioid withdrawal, pain and opioid craving while in hospital.
- Methadone, buprenorphine and slow-release oral morphine are the main opioid agonist treatments (OAT) for OUD in Canada.
- Short-acting opioids can be used in hospital as OAT adjuncts to relieve patient suffering and enable patients with OUD to receive medically necessary care.
- Short-acting opioid doses must be tailored to a patient's opioid tolerance, comorbidities and coprescribed medications.
- Co-occurring withdrawal syndromes should be evaluated and addressed.

Our patient was at high risk for overdose, with multiple previous overdoses, polypharmacy with benzodiazepines and other sedating medications, recent discontinuation of methadone and SROM, comorbid substance use and psychiatric disorders, and co-occurring suicidal ideation. Suicidal ideation is common among people with OUD, and many drug overdoses have elements of suicidality.[4]

There are 3 main opioid agonist treatment (OAT) options for the treatment of OUD in Canada: buprenorphine, methadone and SROM. Buprenorphine is a partial agonist at the μ-opioid receptor with a half-life of 24–42 hours.[5] It has a ceiling effect on respiratory depression, which reduces its risk of causing an overdose, and is considered the preferred first-line treatment for OUD in Canada.[6] However, buprenorphine is not effective for all patients, and challenges with starting buprenorphine include the potential for precipitating withdrawal if started too soon after the last use of a full agonist opioid. Methadone is a full agonist opioid with a long and variable half-life (ranging from 8 to 59 h).[7] Guidelines recommend waiting several days between methadone dose increases; this means it may take weeks before patients reach doses therapeutic for opioid withdrawal and craving.[7,8] Methadone is an effective OUD treatment, but confers a higher risk of overdose, medication–medication

 

interactions and other adverse effects (e.g., QT prolongation and torsades de pointes) than buprenorphine.[6,7] Methadone is also more commonly prescribed with supervised dosing and daily dispensing from pharmacies, which is an important barrier for many patients.[8,9] Slow-release oral morphine is an off-label, third-line option (Table 1). In Ontario, a community of practice guideline based on expert opinion has endorsed co-prescribing a methadone and SROM, although there is limited evidence for this practice.[8] Short-acting opioids have been prescribed off label as a safer supply, although this approach has a lower level of evidence than other approaches.[10]

When a patient receiving methadone presents to hospital, the standard practice is to confirm the last dose with the dispensing pharmacy. Guidelines have traditionally recommended halving the methadone dose after 3 missed doses and restarting methadone at 30 mg after 4 missed doses,[8] although the Ontario community of practice guideline now advocates for longer periods before dose reductions and suggests that higher initiation doses in hospital settings may be considered.[8] The rationale for dose reductions after consecutive missed doses is that physiologic tolerance to methadone can be rapidly lost and that cross-tolerance between methadone and other opioids is incomplete.[7] This creates a potential for iatrogenic overdose if methadone is restarted at a high dose after a period without methadone use. Hospital pharmacists can provide important guidance about methadone initiation and titration, especially in patients with polypharmacy and potential for medication interactions.

As is commonly the case with patients using fentanyl, our patient had insufficient relief of withdrawal symptoms after receiving a starting dose of methadone 30 mg/d orally. If methadone is given more frequently or at higher doses to provide relief of withdrawal symptoms, there is a potential for "dose stacking." Dose stacking occurs when another dose of methadone is provided while previous doses remain unmetabolized; dose stacking may cause iatrogenic overdose. To avoid this while providing relief of withdrawal symptoms, we supplemented methadone with short-acting opioids.

Short-acting opioids can be provided off label, either alone or in a manner that facilitates the initiation of methadone or buprenorphine.[1,2] There are no uniformly accepted guidelines on how to dose short-acting opioids to relieve withdrawal symptoms, and dosing ranges must be tailored to local patterns of opioid use and individual patients' tolerance. We base initial dosing on a patient's withdrawal severity (including objective signs), opioid tolerance (based on quantity, frequency and route of unregulated opioid use, and previous documented tolerance to methadone, buprenorphine or short-acting opioids), medical comorbidities and co-prescribed sedating medications (especially benzodiazepines). We also typically provide lower initial doses, balancing the need for safe medication administration with the importance of relieving a patient's withdrawal symptoms.

For withdrawal from regular use of illicit fentanyl, we typically start with as-needed doses of between 4 and 6 mg hydromorphone orally every 3 hours, 20–30 mg of morphine orally every 3–4 hours, or oxycodone 15–20 mg orally every 4 hours in addition to methadone. We reassess patients frequently, especially after the initial dose, and adjust doses or switch to intravenous formulations if necessary. We hold doses if patients are sedated, have signs of intoxication or have respiratory depression. Lower doses should be considered if patients are suspected to have lower opioid tolerance, frailty, renal or hepatic impairment, or concurrent sedative-hypnotic use. Patients admitted to medical or surgical wards with co-prescribed medications or complex comorbidities that depress

**Table 1: Characteristics of opioid agonist treatments used in OUD treatment in Canada**

| Characteristic | Buprenorphine | Methadone | Slow-release oral morphine | Short-acting opioids |
|---|---|---|---|---|
| Effect at μ-opioid receptor | Partial agonist | Full agonist | Full agonist | Full agonist |
| Typical formulations used in OUD treatment | Sublingual, subcutaneous | Oral liquid | Oral capsule | Oral tablets<br>Intravenous or intramuscular solutions |
| Health Canada approval for OUD | Approved | Approved | Not approved | Injectable diacetylmorphine and high-concentration versions of injectable hydromorphone solutions are approved for administration under supervision;[13] all other uses of short-acting opioids for OUD are off label |
| Potential for precipitated withdrawal | Yes | No | No | No |
| Elimination half-life | 24–42 h[5] (for sublingual buprenorphine) | 8–59 h[7] | After absorption, half-life of morphine is 2–4 h[14] (long therapeutic effect is due to the slow-release mechanism) | Various |

Note: OUD = opioid use disorder.

respiratory drive (e.g., exacerbations of chronic obstructive pulmonary disease) may also benefit from lower doses and monitoring with continuous pulse oximetry. Higher starting doses or intravenous formulations can be cautiously considered for people with known high opioid tolerance; expert consultation can be helpful. As-needed dosing of short-acting opioids using this approach should be driven by patient reports of withdrawal symptoms, pain or craving and do not require specific thresholds on scales such as the Clinical Opiate Withdrawal Scale. The required doses are typically higher than those required for analgesia in opioid-naive patients, and some patients require substantially higher doses.

An important caveat regarding the use of short-acting opioids for opioid withdrawal is that little prospective evidence exists evaluating its safety and efficacy.[1] However, there are also no studies evaluating the safety or efficacy of applying approaches developed for heroin withdrawal to fentanyl withdrawal.[11] There are also no consensus best practices for managing the potential for concurrent benzodiazepine or xylazine withdrawal that may occur from a contaminated fentanyl supply. In emergency department and inpatient settings, we often offer at least 1 dose of a longer-acting benzodiazepine (e.g., diazepam 10 mg orally) to patients with daily fentanyl use when the local fentanyl supply has a high likelihood of benzodiazepine contamination.

Ordering short-acting opioids to treat opioid withdrawal in hospital extends the principles of OUD treatment from outpatient to inpatient settings. This may be discomfiting to some clinicians, given the efforts in recent years to reduce opioid analgesic prescribing. However, there are important differences between providing opioids to opioid-tolerant people with OUD and who use fentanyl regularly (for whom additional opioids received in hospital are unlikely to worsen their OUD) and opioid-naive people. There is evidence that injectable diacetylmorphine or hydromorphone, when provided under supervision as part of outpatient maintenance treatment for OUD, can improve outcomes for people with severe OUD and injection use of opioids who did not benefit from previous trials of OAT.[12,13] Both medications have Health Canada approval for this indication.[12,13] Hydromorphone tablets have also increasingly been prescribed through outpatient safer opioid supply programs to people with OUD to reduce the morbidity and mortality associated with exposure to a toxic, unregulated source of opioids.[10] Administering short-acting opioids to patients in hospital can attain many of the benefits of these approaches, while avoiding criticisms raised about safer supply programs, such as diversion-related risks.[10]

There is an urgent need for clinical studies to improve fentanyl withdrawal management within hospitals. In the meantime, short-acting opioids are an option that can be offered to patients experiencing fentanyl withdrawal in a shared decision-making model to relieve patient suffering and enable patients to receive needed inpatient care.

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