

Caring for patients with opioid use disorder in the hospital

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Opioid use disorder refers to a problematic pattern of opioid use leading to clinically significant impairment or distress, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).¹ The term “opioid” refers to any substance that acts at opioid receptors, including prescription medications, such as morphine, and illicit drugs, such as heroin. All practitioners, regardless of specialty, will care for patients with this prevalent, chronic medical condition, including during acute hospital admissions.

Patients with substance use disorders are among the highest users of health care, incurring disproportionately high health care costs and frequently requiring readmission to hospital.^{2–4} Nonetheless, a recent retrospective study concluded that addiction-specific interventions remain underused, both during acute hospital admissions and at the time of discharge.⁵

In this review, we consider issues unique to adult patients with opioid use disorder during acute hospital admissions. We use current guidelines, systematic reviews and current studies to familiarize readers with the use of opioid agonist therapy (Box 1),^{6–14} management of opioid withdrawal and overdose, acute pain management and safe discharge practices for hospital inpatients with opioid use disorder (Box 2).

How can patients with opioid use disorder be identified in hospital?

Substance use disorders are common in the hospital setting. In two studies conducted in urban hospitals in the United States, substance use not related to alcohol or tobacco among hospital inpatients was about 11%, not including patients stabilized on opioid agonist therapy.^{15,16} In practice, either inpatients will have a previous diagnosis of opioid use disorder or providers will become concerned about this condition in patients who exhibit certain “red flag” behaviours. These behaviours may be evident only after discussions with primary care providers and upon review of data from prior hospital admissions and prescription monitoring programs. They include injecting oral formulations of pain medications, using other illicit drugs concurrently, having multiple opioid prescribers, being inflexible with pain management plans and having recurrent admissions for pain without identifiable cause.¹⁷ Once opioid use disorder is suspected, the DSM-5 criteria¹ can be used to establish a diagnosis and determine severity.

How is opioid withdrawal managed?

Opioid withdrawal may occur if opioids are stopped abruptly or the dose is substantially reduced. For patients taking short-acting opioids, withdrawal symptoms (Table 1)¹⁸ may begin 6–12 hours after the last dose, peak in 36–72 hours and last for 7–10 days. With longer-acting opioids, symptoms may begin 24–48 hours after the last dose, peak at 72–96 hours and last for up to several weeks.^{18,19} The severity of opioid withdrawal can be graded with validated instruments such as the Clinical Opioid Withdrawal Scale, the Subjective Opioid Withdrawal Scale and the Objective Opioid Withdrawal Scale.^{18–20} Withdrawal from other

KEY POINTS

- Physicians from many specialties may care for patients with opioid use disorder in the inpatient setting.
- An acute hospital admission is an opportunity to engage patients with this common chronic condition in addiction treatment and to affect the course of their illness.
- Acute pain can be frustrating for patients with opioid use disorder and their health care providers, although an informed approach can improve outcomes.
- Before discharge from hospital, providers should discuss long-term addiction treatment options and harm reduction strategies, screen for infectious diseases and immunization status, and prescribe opioid medications, in limited amounts, when indicated for pain.

substances, particularly alcohol and benzodiazepines, can be life-threatening, and vigilance for detecting such withdrawal is therefore important.

The goals of treating withdrawal are to alleviate unnecessary distress, maintain the therapeutic alliance between patient and provider, facilitate treatment of the primary reason for admission and increase the patient's engagement in long-term addiction management. According to a 2010 systematic review,²¹ there was no statistically significant difference in completion of opioid detoxification between the opioid agonists buprenorphine and methadone (odds ratio 1.64, 95% confidence interval [CI] 0.68–3.79). As such, choosing between them should take into account the patient's preference and commitment to long-term addiction treatment, comorbid medical conditions, potential adverse effects (e.g., QTc prolongation), medication interactions (e.g., with some antiretroviral medications) and availability of outpatient providers able to continue the opioid agonist therapy.²¹ Methadone initiated at 10–

30 mg daily and slowly titrated to a total daily dose of 20–40 mg is usually sufficient to treat withdrawal symptoms.^{18,20} Alternatively, buprenorphine may be initiated, according to standard protocols, once moderate opioid withdrawal is evident (Figure 1).²² Buprenorphine initiated too early can precipitate withdrawal.

Continuation of opioid agonist therapy after discharge, for long-term management of opioid use disorder, is preferred. However, if such therapy will not be continued beyond the hospital stay (because of patient preference or lack of available outpatient providers), consensus guidelines recommend tapering off over three to five days, with a daily dose reduction of 5–10 mg (methadone) or 2 mg (buprenorphine), although longer tapering schedules are preferred when possible.^{18,22}

According to a 2016 Cochrane review,²³ α_2 adrenergic agonists (clonidine and lofexidine) are more effective than placebo for prevention of severe withdrawal (relative risk [RR] 0.32, 95% CI 0.18–0.57) and for completion of

Box 1: Management of opioid use disorder

Opioid agonist therapy

Therapy with opioid agonists, including methadone, buprenorphine and diacetylmorphine, can be used for long-term treatment of opioid use disorder and for acute management of withdrawal symptoms.

Methadone is a synthetic opioid agonist with a variable half-life, averaging 24–36 hours at steady state.⁶ This characteristic makes once-daily dosing effective for treating opioid use disorder and withdrawal, but it also increases the risk of overdose if the dose is escalated too quickly, because of accumulation of drug in the serum. It is available as a liquid or tablet, although when used for addiction the liquid formulation is preferred. Among inpatients, relevant adverse effects may include constipation, drowsiness and QT interval prolongation.⁷

Buprenorphine is a semisynthetic partial agonist with very high affinity at the opioid μ receptor. Its partial agonist property confers a ceiling effect on analgesia and respiratory depression, although 2 autopsy studies highlighted the risk of overdose when other respiratory depressants are used concomitantly.^{8,9} For the treatment of opioid use disorder, the most commonly used formulation of buprenorphine is the combination product, buprenorphine–naloxone, available as a dissolvable sublingual tablet or film. Buprenorphine without naloxone is available in the United States; in Canada, it can be prescribed in specific clinical situations, such as pregnancy, through Health Canada's Special Access Programme. Naloxone is clinically active only if injected, and it is therefore added to the combination product as a deterrent to intravenous administration of the oral formulation. Common adverse effects relevant to hospital inpatients include constipation and headache, and transaminases may become elevated in patients with chronic hepatitis C or alcohol use.¹⁰

Both methadone and buprenorphine are considered safe for patients with renal disease, although dose reductions may be needed in those with glomerular filtration rate below 10 mL/min.¹¹ Likewise, both are primarily metabolized in the liver, so administration to patients with severe liver impairment requires close monitoring. In Canada, the prescription of methadone for the treatment of opioid use disorder requires an exemption under section 56 of the Controlled Drugs and Substances Act, although a temporary exemption can be obtained when caring for a patient with opioid use disorder during an acute hospital admission.¹² Restrictions regarding buprenorphine prescribing vary by province, and providers should refer to local regulations.¹³

Diacetylmorphine (the active ingredient in heroin) is a short-acting, semisynthetic injectable opioid agonist that has received increasing attention for treatment of severe opioid use disorder in patients with failure of more traditional approaches involving oral agonists.¹⁴ This drug is not available for the treatment of opioid use disorder in the US, and it has not yet been studied as a medication for inpatients with opioid use disorder.

Opioid antagonist therapy

Treatment options for opioid use disorder in the outpatient setting also include the opioid antagonist naltrexone. With its high binding affinity and long half-life, naltrexone prevents the analgesic and euphoric effects of opioid agonists, thereby leading to a reduction in the use of all opioids.¹⁰ Importantly, if a patient takes the first dose of naltrexone while there are still active opioids in the circulation, the naltrexone may abruptly precipitate withdrawal. Naltrexone is available in 2 formulations: oral (50 mg taken once daily) and intramuscular (380 mg monthly). Common adverse effects of both forms include nausea, which typically resolves after a few days of use, and hepatotoxicity, which is rare; in addition, with the intramuscular form, an idiosyncratic injection site reaction may occur, lasting for several weeks. Patients receiving maintenance naltrexone therapy who are admitted with acute pain may require very high doses of opioids to override the blocking effects of naltrexone, depending upon the timing of the most recent dose.¹⁰

treatment (RR 1.95, 95% CI 1.34–2.84). Of note, although α_2 adrenergic agonists improve withdrawal symptoms, they do not address craving. Other adjunct medications targeting withdrawal symptoms are listed in Table 1.

How is opioid overdose managed?

Opioid overdose in the inpatient setting may occur when opioid tolerance is overestimated (i.e., following a period of abstinence), when opioids are aggressively dosed or administered to patients with new renal or hepatic impairment, when medications that influence opioid metabolism or potentiate respiratory depression are coadministered and when patients undertake self-administration of opioids.²⁴ Overdose should be suspected in patients with any combination of depressed mental status, decreased respiratory rate or chest wall rise, and miotic pupils.²⁵

Assessment begins with basic life support and includes a review of all administered medications. A focused examination includes inspection of the skin for transdermal opioid patches. Patients who are protecting their airway and who have good oxygen saturation levels, a respiratory rate greater than 10–12 breaths/min and no evidence of hypercarbia by blood gas or capnography can simply be observed in a monitored setting.²⁵

For patients with apnea, bag-valve mask ventilation should be performed and naloxone administered by the intravenous route.²⁵ Naloxone can also be administered intramuscularly, intranasally or via endotracheal tube, depending on the clinical scenario. The effects of naloxone last 20–90 minutes; therefore, suspected overdoses involving long-acting opioids may require repeat dosing or intravenous infusion. If the air-

way is difficult to maintain or the respiratory rate does not improve after escalating doses of naloxone, orotracheal intubation should be performed. Patients with recurrent apnea and those who require a naloxone infusion or intubation should be transferred to an intensive care unit.²⁵

How should acute pain be managed in opioid use disorder?

Acute pain is common among hospital inpatients, and early recognition and management alleviates the patient’s discomfort while facilitating management of other medical issues.^{26,27} In

Box 2: Evidence used in this review

For each clinical question included in this review, a National Center for Biotechnology Information “PubMed” and “Books” database search was performed, with search terms depending on the clinical question. For example, for the section “How is opioid withdrawal managed?” the search terms were “opioid withdrawal,” “methadone,” “buprenorphine” and “alpha adrenergic.” Searches were limited to full-text English-language articles published after the year 2000. Additionally, we reviewed reference lists from guideline statements and seminal review articles. We chose the most relevant and recent articles presenting results from randomized controlled trials, case-control and cohort studies, meta-analyses, guideline statements and reviews. We included some case series when the available literature was limited. We reviewed 186 citations, of which 56 contributed to the data included in this review. The lead author (J.H.D.) reviewed all of the articles, and the coauthors (S.R.H. and J.M.T.) reviewed selected articles.

Table 1: Signs and symptoms of opioid withdrawal and targeted management¹⁸

Sign or symptom*	Pharmacologic management
Tachycardia, hypertension, hyperthermia, diaphoresis, lacrimation, rhinorrhea, piloerection, mydriasis, yawning	α_2 agonist (clonidine, lofexidine)*
Anxiety, insomnia	Antihistamine (e.g., diphenhydramine, hydroxyzine), sedating antidepressant (e.g., trazodone)
Myalgia, bone pain	Acetaminophen, nonsteroidal anti-inflammatory drugs (e.g., ibuprofen)
Abdominal cramps	Antispasmodic (e.g., dicyclomine)
Nausea and vomiting	Antiemetic (e.g., prochlorperazine, promethazine, ondansetron)
Diarrhea	Antidiarrheal (e.g., loperamide)
Hyperreflexia	No specific therapy

*Clonidine is initiated at 0.1–0.2 mg orally every 4–6 h, with a daily maximum of 1.2 mg on day 1 and 2.0 mg afterward. Lofexidine (not available in the United States) is initiated at 0.8 mg/day in divided doses and can be titrated to a maximum of 2.4 mg/day. Both require tapering before discontinuation.

addition, studies have identified associations between the undertreatment of pain in individuals with opioid use disorder and illicit opioid use by inpatients and discharges against medical advice.^{28,29}

Basic pain management principles apply, including assessing the pain with standardized assessment tools, addressing the underlying

cause, maximizing the use of physical measures (ice, heat, massage, bracing) and administering non-opioid medications (nonsteroidal anti-inflammatory drugs, acetaminophen, nerve blocks).^{26,30} When opioid analgesics are needed, prescription drug monitoring programs should be consulted where available.³¹ Because intermittent intravenous administration of opioids is

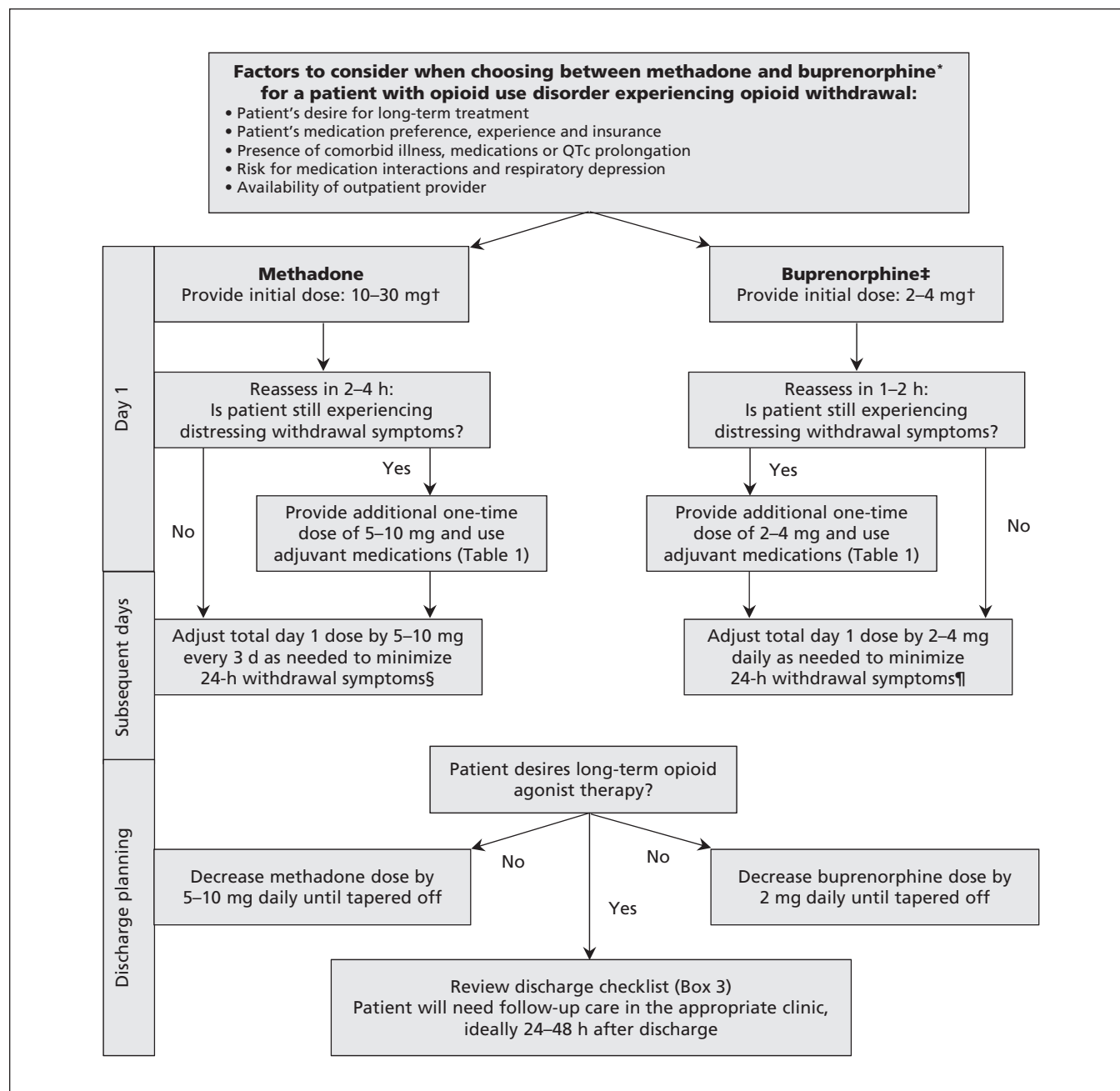


Figure 1: Initiation of methadone or buprenorphine for the treatment of withdrawal in the inpatient setting.^{18,22} *Long-term opioid agonist therapy is preferred and should be encouraged. Methadone should be used with caution in patients with QTc prolongation. †Consider the lower end of the dose range for older adults, adolescents, patients who are using other central nervous system depressants, those otherwise at higher risk for respiratory depression and those whose opioid use is infrequent. Higher initial doses may be needed for patients with higher daily opioid use. ‡Buprenorphine may be administered once a patient is in moderate withdrawal (Clinical Opioid Withdrawal Scale > 12). A combination buprenorphine–naloxone product is available in Canada, and buprenorphine alone can be obtained through Health Canada's Special Access Programme if necessary. §Methadone doses above 40 mg are rarely needed to treat withdrawal. ¶It is recommended to not exceed buprenorphine 8 mg on day 1 and 16 mg on day 2.

unnecessarily reinforcing, a transition from intravenous to oral opioids should occur once the patient can tolerate oral medications and the pain is reasonably controlled, typically within 24 hours after admission.³² When possible, medications that are currently or were formerly problematic for the patient should be avoided.³³ Aspects of acute pain management unique to patients with opioid use disorder are reviewed in the following sections.

Provider and patient biases

Interviews with providers have commonly identified concerns about deception and manipulation on the part of patients with opioid use disorder who report pain.^{34,35} At the same time, patients with opioid use disorder fear that they will be labelled as “drug seekers,” that their pain will go undertreated, that the underlying condition will go undiagnosed or that their opioid agonist therapy will be discontinued.^{34,36} Elements of an effective initial pain encounter include reviewing both patient and provider expectations regarding pain management, acknowledging prior difficult interactions, reassuring the patient that the pain will be addressed and that opioid agonist therapy will be continued or substituted if necessary, and reviewing the medication schedule. Involving the patient in decisions about pain management is particularly relevant for those with opioid use disorder and may prevent some of the stressful doctor–patient interactions related to opioids that both parties dislike.^{26,27,37}

Patients actively abusing opioids

In light of the well-established phenomena of tolerance and opioid-induced hyperalgesia among chronic, active opioid users, patients with opioid use disorder will likely require higher doses of opioid than will non-opioid-dependent patients.^{26,30,38} In patients with moderate to severe acute pain who currently use illicit opioids, the aim of management is to provide adequate analgesia and prevent opioid withdrawal.³⁰

One strategy is to initiate methadone as outlined above and to prescribe additional short-acting opioids titrated to pain.³⁹ This approach has the advantage of treating both the opioid use disorder and the pain. Alternatively, short-acting opioids can be used alone; however, physicians should be aware of the potential for withdrawal symptoms to occur between intermittent doses of short-acting agents if given too infrequently. The administration frequency of short-acting opioids generally should be scheduled, rather than on an “as needed basis,” with hold parameters if the patient appears oversedated.^{26,27,30,37,38}

Patients receiving opioid agonist therapy

Patients experiencing acute pain who are already receiving methadone maintenance therapy should continue to receive their usual dose, once confirmed by the outpatient treatment centre. The analgesic effects of methadone are much shorter than its effects on withdrawal and cravings.^{26,37} As such, if non-opioid modalities fail to provide sufficient relief, short-acting opioids should be added to methadone maintenance therapy to treat moderate to severe acute pain. It is difficult to predict the effect of the additional analgesics, and frequent re-evaluation and dose titration are necessary.^{26,30} In the setting of acute pain, the physician could consider splitting the patient’s daily methadone dose into two or three times daily dosing, given the shorter analgesic effect of methadone; however, there is scant literature to support this approach.⁴⁰

The analgesic effect of buprenorphine is also shorter than its effects on withdrawal and craving. Given its high affinity for the opioid μ receptor, buprenorphine effectively blocks the actions of most other opioids, thereby complicating acute pain management.⁴¹ Several strategies have been described to overcome this problem, predominantly based in expert opinion. The first is to continue daily buprenorphine and add short-acting opioids titrated to pain control. High-dose opioids, and possibly patient-controlled analgesia, will likely be needed.^{26,39,41–43} A second strategy uses the inherent analgesic properties of buprenorphine by giving the total daily dose divided three or four times daily.^{26,42} Doses of 4–8 mg every six to eight hours have been used to treat moderate to severe pain.^{41,43} A third strategy is to discontinue buprenorphine and use short-acting opioids to treat the acute pain. The blocking effects of buprenorphine wear off over 24–72 hours, so the patient must be carefully monitored for signs of overdose, given that the initial opioid dose will be much higher than ultimately needed.²² After the need for acute pain management has resolved, buprenorphine can be re-introduced.

Is there benefit to inpatient initiation of opioid agonist therapy?

Initiation of opioid agonist therapy during an acute hospital admission can facilitate management of other medical issues by relieving symptoms associated with withdrawal, reducing the rates of discharge against medical advice and

increasing the likelihood that patients with opioid use disorder will transition to long-term outpatient addiction treatment. This approach, in turn, has been shown to reduce illicit opioid use, increase retention in addiction treatment, lower the risk of opioid-associated health problems such as HIV infection, decrease hospital utilization, improve psychosocial functioning and improve management of other comorbid medical and psychologic conditions.^{10,44}

Several retrospective studies have identified patients with substance use disorders as having a high risk of discharge against medical advice, which is associated with increases in hospital readmissions and health care costs, as well as in the risk of death, highlighting the importance of prevention.⁴⁵⁻⁴⁸ Qualitative research and one systematic review found that opioid withdrawal, inadequate pain management, younger age, daily heroin injection and unstable employment were factors contributing to discharges against medical advice among patients with substance use disorders.^{29,49,50}

Available evidence suggests that opioid agonist therapy, when paired with referral to outpatient addiction services, may reduce discharge against medical advice and increase

engagement in postdischarge addiction treatment.⁵¹⁻⁵⁵ One observational study of inpatients with opioid use disorder showed that initiation of methadone during the hospital stay, coupled with linkage to an outpatient addiction program, led to a high rate (82%) of post-discharge follow-up.⁵⁴ A randomized controlled trial showed that inpatient initiation of buprenorphine and referral to an outpatient addiction provider led to significantly better rates of long-term treatment for opioid use disorder than inpatient detoxification alone (16.7% v. 3%, $p = 0.007$, at 6 months after the hospital stay).⁵³

What factors should be considered before discharge from hospital?

Discharging patients with opioid use disorder requires advance planning, and providers should refer to the discharge checklist provided in Box 3. According to expert opinion, physicians should discuss overdose prevention with all patients who have opioid use disorder and should consider prescribing naloxone rescue medication. Patients should be reminded that after a period of

Box 3: Discharge checklist*

- Screened for associated infectious diseases during this hospital admission or previously?
 - HIV
 - Hepatitis B, hepatitis C
- Screened for other substance use disorders?
- Addressed psychosocial comorbidities such as homelessness, depression, post-traumatic stress disorder?
- Immunizations up to date?
 - Tetanus
 - Hepatitis A, hepatitis B
 - Influenza
 - Pneumococcus
- Considered education and/or referral for harm reduction strategies?
 - Needle exchange programs and supervised injection facilities (where available)
 - Safe injecting practices
 - Opioid overdose education and prescription of naloxone rescue doses
 - Safe opioid storage, particularly if children living in the home
- Considered long-term treatment for opioid use disorder?
 - Discussed initiation of opioid agonist therapy
 - Referral to specialized addiction treatment centre
 - Referral to pain specialist if indicated
 - Referral for counselling interventions (i.e., self-help, mutual help, one-to-one counselling)
 - Established primary care physician
- Thoughtful prescribing of new medications?
 - Consideration of medication interactions if taking opioid agonist treatment
 - If needed, short-term opioid analgesia with close follow-up after discharge

*Checklist developed by the authors.

abstinence, such as a hospital stay, the risk of overdose is high because of loss of tolerance.

When patients with opioid use disorder have acute pain needs extending beyond the period of the admission, careful attention must be given to the duration of treatment and the frequency of administration of opioids, because of the risk of addiction relapse.⁵⁶ In accordance with the guidelines for prescribing opioid treatment for chronic noncancer pain published recently by the US Centers for Disease Control and Prevention, physicians should prescribe the lowest effective dose and limit the quantity of opioids prescribed to the expected duration of severe acute pain, usually less than one week.³¹ Increased frequency of follow-up appointments to assess ongoing need for pain medication may be necessary, particularly when severe pain continues for longer than initially expected.³¹

Conclusion

The inpatient care of patients with opioid use disorder can be medically and psychosocially complex. In this review, we have highlighted the unique aspects of caring for this population during an acute hospital admission. Future studies should focus on strategies to reduce discharges against medical advice, to manage acute pain (particularly for patients receiving buprenorphine) and to increase engagement in long-term outpatient care (Box 4). When possible, we recommend seeking consultation from an addiction specialist or an inpatient addiction consult service, although this review provides a framework for other physicians to improve their care of inpatients with opioid use disorder.

At the core is the concept that addiction is a chronic disease, and thoughtful consideration of the underlying opioid use disorder should be part of the patient's daily care plan. Failure to engage with patients on their opioid use, offer appropriate treatments and create a thoughtful discharge plan represent a missed opportunity to affect the

course of this common chronic condition and to prevent related morbidity and mortality.

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Box 4: Unanswered questions

- What are the optimal strategies for successful transition of hospital inpatients with opioid use disorder into long-term outpatient treatment programs?
- What are optimal non-opioid strategies for managing pain in patients with opioid use disorder?
- What is the optimal strategy for managing acute, moderate to severe pain for patients who are receiving buprenorphine?
- What are the best strategies to mitigate against discharges against medical advice among patients with opioid use disorder?

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