



Published in final edited form as:

Ann Intern Med. 2006 January 17; 144(2): 127–134.

## Acute Pain Management for Patients Receiving Maintenance Methadone or Buprenorphine Therapy

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### Abstract

More patients with opioid addiction are receiving opioid agonist therapy (OAT) with methadone and buprenorphine. As a result, physicians will more frequently encounter patients receiving OAT who develop acutely painful conditions, requiring effective treatment strategies. Undertreatment of acute pain is suboptimal medical treatment, and patients receiving long-term OAT are at particular risk. This paper acknowledges the complex interplay among addictive disease, OAT, and acute pain management and describes 4 common misconceptions resulting in suboptimal treatment of acute pain. Clinical recommendations for providing analgesia for patients with acute pain who are receiving OAT are presented. Although challenging, acute pain in patients receiving this type of therapy can effectively be managed.

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The treatment of opioid dependence, both on heroin and prescription narcotics, with opioid agonist therapy (OAT) (that is, methadone or buprenorphine) is effective: It decreases opioid and other drug abuse, increases treatment retention, decreases criminal activity, improves individual functioning, and decreases HIV seroconversion (1–5). Because of the increasing use of these medications for prolonged periods in primary care, a practice called *office-based opioid treatment*, nonaddiction specialists will be treating more of these affected patients in clinical practice, including those with episodes of acute pain (6–11).

Adequate treatment of acute painful conditions is an essential dimension of quality medical care (12–17). Inadequate treatment is common among a wide spectrum of patients (18–23). Nonopioid analgesics (for example, non-steroidal anti-inflammatory drugs and acetaminophen) are recommended for treating acute pain; however, moderate to severe acute pain will often require opioid analgesics (24). Physicians may not prescribe effective opioid analgesia across all patient populations because of fears of cognitive, respiratory, and psychomotor side effects; iatrogenic drug addiction; and prescription drug diversion (25,26). This tendency of health care professionals to undermedicate patients with opioid analgesics has been termed *opiophobia* (27). Such fears are exaggerated when treating patients with a known history of a substance use disorder. The provision of opioid analgesics to a patient with opioid dependence receiving OAT can be particularly challenging (28,29).

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**Potential Financial Conflicts of Interest:** None disclosed.

See also: **Web-Only.** CME quiz, Conversion of tables into slides

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**Grant Support:** Drs. Alford and Samet were supported by a grant from the National Institute on Drug Abuse (R25-DA-13582).

We highlight the issues associated with the management of acute pain in patients receiving OAT and describe theoretical and empirical findings that suggest unique requirements for opioid analgesia for such patients. In addition, we identify common misconceptions of health care providers that underlie inadequate pain management and provide practical recommendations for the analgesic management of acute pain in this special clinical population. To help illustrate these issues, we present the following clinical vignette from our experience.

A 29-year-old woman reported severe right arm pain after fracturing her olecranon process. She had a history of injection heroin use and received methadone, 90 mg/d, in a methadone maintenance program. In the emergency department, she seemed uncomfortable and received one 2-mg dose of intramuscular morphine sulfate over 6 hours. While hospitalized, she continued to report severe pain despite receiving her daily methadone dose and intramuscular ketorolac. She was told that her usual methadone dose should help control her pain. She was labeled as “drug-seeking” because of her constant requests for additional pain medications.

## Pain and Opioid Dependence

The clinical conditions of pain and opioid dependence are not unrelated phenomena (30–32). Forty-one years ago, Martin and Inglis (33) observed that opioid-addicted patients abuse opioids to treat “an abnormally low tolerance for painful stimuli.” Opioids, whether administered with analgesic or addictive intent, activate opiate receptors in the locus coeruleus and amygdala, which provide both analgesia and reward (34,35).

The presence of one condition seems to influence the expression of the other. Clinical examples of this include how the presence of acute pain seems to decrease the euphorogenic (pleasurable) qualities of the opioid (36) and how the presence of addictive disease seems to worsen the experience of pain. With respect to the latter, Savage and Schofferman (37) found a decade ago that persons with addiction and pain have a “syndrome of pain facilitation.” Their pain experience is worsened by subtle withdrawal syndromes, intoxication, withdrawal-related sympathetic nervous system arousal, sleep disturbances, and affective changes, all consequences of addictive disease (37). Supporting a negative effect of addiction on pain tolerance, patients who abuse stimulants and those who abuse opioids have been shown to be less tolerant of pain than their peers in remission (38,39).

The clinical approach is complicated by the confusing and often misunderstood terminology used in pain management and addiction medicine (40–43). As detailed in Table 1, physical dependence and tolerance are typical and predictable physiologic consequences of opioid exposure. These terms in and of themselves do not indicate maladaptive behaviors and do not meet the diagnostic criteria of substance dependence (41) outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revision, without, for example, loss of control or continued use despite harm. *Drug-seeking* is another commonly ill-defined term that may indicate the presence of addiction but, as will be described, can also reflect *pain relief-seeking* because of unrelieved pain or anxiety about pain management (44).

## Common Misconceptions

Four common misconceptions of health providers result in the undertreatment of acute pain in patients receiving OAT: 1) The maintenance opioid agonist (methadone or buprenorphine) provides analgesia; 2) use of opioids for analgesia may result in addiction relapse; 3) the additive effects of opioid analgesics and OAT may cause respiratory and central nervous system (CNS) depression; and 4) the pain complaint may be a manipulation to obtain opioid medications, or drug-seeking, because of opioid addiction.

### Misconception 1: The Maintenance Opioid Agonist (Methadone or Buprenorphine) Provides Analgesia

There are pharmacokinetic and pharmacodynamic explanations for why patients do not receive adequate analgesia from maintenance opioids prescribed for addiction treatment. Not only do the analgesic and addiction treatment profiles of these opioids differ, but the neuroplastic changes associated with long-term opioid exposure (that is, tolerance and hyperalgesia) may effectively diminish their analgesic effectiveness (45).

**Analgesic Properties of Maintenance Opioids**—Patients receiving maintenance therapy with opioids for addiction treatment do not derive sustained analgesia from it. Methadone and buprenorphine, potent analgesics, have a duration of action for analgesia (4 to 8 hours) that is substantially shorter than their suppression of opioid withdrawal (24 to 48 hours) (46–50). Because most patients receiving OAT are given a dose every 24 to 48 hours, the period of even partial pain relief with these medications is small.

**Opioid Tolerance**—Tolerance is one factor that explains why these patients derive little pain relief from maintenance opioids. Tolerance, the need for increasing doses of a medication to achieve its initial effects, develops with continuous opioid use but differentially affects specific opioid properties. For example, tolerance readily develops to the respiratory and CNS depressive effects of opioids but not to their constipating effects (51,52). Analgesic tolerance develops for different medications within the opioid class, a phenomenon called *cross-tolerance* (53,54). Doverty and colleagues (55) found that patients receiving maintenance methadone therapy were cross-tolerant to the analgesic effects of morphine and that pain relief, when obtained, did not last as long as expected. Therefore, cross-tolerance between the opioids used for maintenance therapy and other opioids used for analgesia may explain why patients receiving OAT often require higher and more frequent doses of opioid analgesics to achieve adequate pain control.

**Opioid-Induced Hyperalgesia**—An alternative explanation for the lack of analgesia derived from maintenance opioids may be the presence of opioid-induced hyperalgesia. This is the result of neuro-plastic changes in pain perception that yield an increase in pain sensitivity. The outcome is that opioids have less potent analgesic effects (45,56–58). Empirical evidence supports increased sensitivity to experimental pain in patients receiving OAT (33,38,55,59–62), such that patients receiving maintenance methadone therapy tolerate cold-pressor pain only half as long as do matched controls (55,59). Accumulating evidence suggests that maintenance with buprenorphine therapy has similar and statistically significant effects on pain tolerance, although to a lesser degree than methadone (63). The pain intolerance of patients receiving methadone and buprenorphine maintenance therapy can be conceptualized as a latent hyperalgesia secondary to long-term opioid exposure.

The presence of hyperalgesia with ongoing opioid use has resulted in reexamination of the previously described phenomenon of opioid analgesic tolerance. Both hyperalgesia and opioid tolerance involve neuroplastic changes associated with excitatory amino acid (*N*-methyl-D-aspartate) and opioid receptors (64–70). The hyperalgesic processes precipitated by opioid administration serve to counteract opioid analgesia (56,71–73); thus, it is possible that what seems to be opioid analgesic tolerance may in fact be an expression of an opioid-induced increased sensitivity to pain.

Therefore, despite the benefits of OAT for the opioid-dependent person, the accompanying hyperalgesia (or analgesic tolerance) counteracts the analgesic effects of opioids and complicates pain management. At clinically effective doses for the treatment of opioid dependence, patients do not experience analgesia to experimental pain but demonstrate the

hyperalgesic effects of OAT. Thus, from a theoretical and experimental basis, it is clear that the perception of pain is not decreased in OAT patients.

### **Misconception 2: Use of Opioids for Analgesia May Result in Addiction Relapse**

A common concern of physicians is that the use of opioids for analgesia in patients receiving OAT May result in relapse to active drug use. However, there is no evidence that exposure to opioid analgesics in the presence of acute pain increases rates of relapse in such patients. A small retrospective study (74) of patients enrolled in maintenance methadone programs who received opioid analgesics after surgery did not find a difference in relapse indicators compared with matched patients receiving maintenance methadone therapy. Similarly, no evidence of relapse was seen in 6 patients receiving methadone maintenance therapy who were treated with opioid analgesics for cancer-related pain (75). In fact, relapse prevention theories would suggest that the stress associated with unrelieved pain is more likely to be a trigger for relapse than adequate analgesia. In a study by Karasz and colleagues (76), patients receiving methadone maintenance therapy stated that pain played a substantial role in their initiating and continuing drug use.

### **Misconception 3: The Additive Effects of Opioid Analgesics and OAT May Cause Respiratory and CNS Depression**

Physicians' concerns that opioid analgesics will cause severe respiratory or CNS depression in patients receiving OAT is a theoretical risk, which has never been clinically demonstrated. As previously noted, tolerance to the respiratory and CNS depressant effects of opioids occurs rapidly and reliably (50–52). Similarly, patients with worsening cancer-related pain who require dose escalations typically do not exhibit respiratory and CNS depressant effects when additional opioids are administered (75,77–79). It has been suggested that acute pain serves as a natural antagonist to opioid-associated respiratory and CNS depression (15,43). This purported effect is supported by the observation that a patient with chronic pain who was treated with opioids developed signs of respiratory depression after a successful nerve block procedure (80). Therefore, the concern about severe drug toxicity with analgesic opioid treatment is not supported by clinical or empirical experience.

### **Misconception 4: Reporting Pain May Be a Manipulation To Obtain Opioid Medications, or Drug-Seeking, because of Opioid Addiction**

Physicians' concerns about being manipulated by drug-seeking patients is substantial, difficult to quantify, and emotion-laden. It is a powerful motive underlying physicians' reservations about prescribing opioid analgesia for acute pain to patients receiving OAT for opioid dependence. Pain is always subjective, making assessment of its presence and severity difficult. A careful clinical assessment for objective evidence of pain will decrease the chance of being manipulated by a drug-seeking patient and will support the use of opioid analgesics in patients with a history of opioid dependence. Reports of acute pain with objective findings are less likely to be manipulative gestures than are reports of chronic pain with vague presentations. Furthermore, patients receiving OAT typically receive treatment doses that block most euphoric effects of coadministered opioids, theoretically decreasing the likelihood of opioid analgesic abuse (81,82).

Not uncommonly, patients dependent on opioids are perceived by health care providers to be demanding when hospitalized with acute pain. This scenario develops in part because of the patients' distrust of the medical community, concern about being stigmatized, and fears that their pain will be undertreated or that their OAT may be altered or discontinued (76,83). Patient anxiety related to these concerns, which can be profound and well-founded, can complicate provision of adequate pain relief.

Requests for opioid analgesia from patients receiving OAT may be labeled as drug-seeking behaviors, which are defined as concerted efforts on the part of the patient to obtain opioid medication, including engaging in illegal activities (44). It is important to keep in mind that there may be appropriate reasons for a patient to seek medication. The distinction between appropriate drug-seeking and addiction is harder to discern when the patient requests a drug with known abuse potential, such as opioid analgesics, regardless of the apparent validity of the complaint. In the case of unrelieved pain, drug-seeking behaviors arise when a patient cannot obtain tolerable relief with the prescribed dose of analgesic and seeks alternate sources or increased doses, a phenomenon referred to as *pseudoaddiction* (84). Alternately, patients receiving good pain relief may exhibit drug-seeking behaviors because they fear not only the reemergence of pain but perhaps also the emergence of withdrawal symptoms. Rather than indicating addictive disease, such behaviors, termed *therapeutic dependence* (85), are actually efforts to maintain a tolerable level of comfort. Other patients with adequate pain control may continue to report persistent severe pain to prevent reduction in current effective doses of opioid analgesics, a behavior termed *pseudo-opioid resistance* (86).

## Recommendations for Treating Acute Pain

### General Recommendations

The appropriate treatment of acute pain in patients receiving OAT includes uninterrupted therapy to address the patient's baseline opioid requirement for their addiction treatment and aggressive pain management (Table 2). As with all patients who have acute pain, nonpharmacologic and nonopioid analgesic pain-relieving interventions should be aggressively implemented. However, patients with moderate to severe acute pain will often require opioid analgesics (24). The literature suggests that undertreating acute pain may lead to decreased responsiveness to opioid analgesics, thus making subsequent pain control more difficult (54, 87). To decrease the total amount of opioid provided to these patients, multimodal analgesia (for example, nonsteroidal anti-inflammatory drugs and acetaminophen) (88) and adjuvant analgesics that enhance opioid effects (for example, tricyclic antidepressants) (89) may be coadministered (90). Continuing the usual dose of OAT, after the important step of verification with the patient's provider or program, avoids worsening pain symptoms due to the increased pain sensitivity associated with opioid withdrawal (77,91,92). Thus, daily opioid treatment requirements must be met before attempting to achieve analgesia. To decrease anxiety, patients should be reassured that the treatment for their opioid addiction will continue and that their pain will be aggressively treated. When the increased pain sensitivity and cross-tolerance with OAT are considered, adequate pain control will generally necessitate higher doses of opioid analgesic administered at shorter intervals. Analgesic dosing should be continuous or scheduled, rather than as needed. Allowing pain to reemerge before administering the next dose causes unnecessary suffering and anxiety and increases tension between the patient and the treatment team.

Empirical data on the use of patient-controlled analgesia in patients with substance dependence are limited. Paige and colleagues (93) reported that although women receiving maintenance therapy with methadone had higher pain scores after cesarean section surgery, there was no statistically significant difference in use of opioid analgesics compared with controls. Boyle (94) reported on the successful use of postoperative patient-controlled analgesia in a patient who actively used heroin. Clinical experience supports consideration of patient-controlled analgesia in patients receiving OAT; increased control over analgesia minimizes patient anxiety about pain management.

The pharmacologic properties of opioids must be considered when selecting an opioid analgesic for the patient receiving OAT. Although opioids bind to multiple subtypes of opioid receptors in the CNS, binding to the  $\mu$  receptor subtype is primarily responsible for the analgesic

effect (95). Mixed agonist and antagonist opioid analgesics, such as pentazocine (Talwin, Sanofi-Synthelabo Inc., New York, New York), nalbuphine (Nubain, Bristol-Myers Squibb Holdings Pharma, Ltd., Manati, Puerto Rico), and butorphanol (Stadol, Bristol-Myers Squibb Co., Princeton, New Jersey), must be avoided because they probably will displace the maintenance opioid from the  $\mu$  receptor, thus precipitating acute opioid withdrawal in these patients (28). Combination products of opioid analgesics containing fixed doses of acetaminophen and an opioid (for example, Percocet, Wilmington Laboratories, L.L.C., Wilmington, Delaware, and Vicodin, Knoll Pharmaceuticals, Mount Olive, New Jersey) should be limited to patients not requiring large doses to avoid acetaminophen-induced hepatic toxicity. Alternatively, each medication could be prescribed individually at appropriate doses to achieve the desired analgesic effect and to avoid hepatic damage.

### **Recommendations for Patients Receiving Maintenance Methadone Therapy**

Acute pain management for the patient receiving maintenance methadone therapy should follow the aforementioned general recommendations, which include using opioid analgesics, when indicated, in addition to the patient's daily methadone maintenance dose (Table 2). If the patient is hospitalized, in addition to dose verification, the methadone maintenance program should be notified at the time of hospital admission and discharge, in part to make program clinical staff aware of any controlled substances that were given to the patient and may be detectable by drug testing. If the patient is not receiving oral intake, the methadone dose can be given parenterally. Intramuscular or subcutaneous methadone dosing should be given as half to two thirds the maintenance dose divided into 2 to 4 equal doses (48,96,97).

### **Recommendations for Patients Receiving Maintenance Buprenorphine Therapy**

Clinical experience treating acute pain in patients receiving maintenance therapy with buprenorphine is limited. Pain treatment with opioids is complicated by the high affinity of buprenorphine for the  $\mu$  receptor. This high affinity risks displacement of, or competition with, full opioid agonist analgesics when buprenorphine is administered concurrently or sequentially. There are several possible approaches for treating acute pain that requires opioid analgesia in the patient receiving buprenorphine therapy (Table 2). With such limited clinical experience, the following treatment approaches are based on available literature, pharmacologic principles, and published recommendations. The most effective approach will be elucidated with increased clinical experience. In all cases, because of highly variable rates of buprenorphine dissociation from the  $\mu$  receptor, naloxone should be available and level of consciousness and respiration should be frequently monitored. Treatment options are as follows.

1. Continue buprenorphine maintenance therapy and titrate a short-acting opioid analgesic to effect (90,98). Because higher doses of full opioid agonist analgesics may be required to compete with buprenorphine at the  $\mu$  receptor, caution should be taken if the patient's buprenorphine therapy is abruptly discontinued. Increased sensitivity to the full agonist with respect to sedation and respiratory depression could occur.
2. Divide the daily dose of buprenorphine and administer it every 6 to 8 hours to take advantage of its analgesic properties. For example, for buprenorphine at 32 mg daily, the split dose would be 8 mg every 6 hours. The available literature suggests that acute pain can be effectively managed with as little as 0.4 mg of buprenorphine given sublingually every 8 hours in patients who are opioid naive (47,99,100). However, these low doses may not provide effective analgesia in patients with opioid tolerance who are receiving OAT. Therefore, in addition to divided dosing of buprenorphine, effective analgesia may require the use of additional opioid agonist analgesics (for example, morphine).

3. Discontinue buprenorphine therapy and treat the patient with full scheduled opioid agonist analgesics by titrating to effect to avoid withdrawal and then to achieve analgesia (for example, sustained-release and immediate-release morphine) (90,98, 101). With resolution of the acute pain, discontinue the full opioid agonist analgesic and resume maintenance therapy with buprenorphine, using an induction protocol (98,102).
4. If the patient is hospitalized with acute pain, his or her baseline opioid requirement can be managed and opioid withdrawal can be prevented by converting buprenorphine to methadone at 30 to 40 mg/d. At this dose, methadone will prevent acute withdrawal in most patients (97) and, unlike buprenorphine, binds less tightly to the  $\mu$  receptor. Thus, responses to additional opioid agonist analgesics will be as expected (that is, increasing dose will provide increasing analgesia). If opioid withdrawal persists, subsequent daily methadone doses can be increased in 5- to 10-mg increments (103). This method allows titration of the opioid analgesic for pain control in the absence of opioid withdrawal. When the acute pain resolves, discontinue the therapy with the full opioid agonist analgesic and methadone and resume maintenance therapy with buprenorphine, using an induction protocol (98,102). If the patient is discharged while full opioid agonist analgesics are still required, then discontinue methadone therapy and treat the patient as stated in the third buprenorphine approach.

If buprenorphine therapy needs to be restarted (buprenorphine induction) after acute pain management (that is, the third and fourth approaches), it is important to keep in mind that buprenorphine can precipitate opioid withdrawal. Thus, a patient receiving a full opioid agonist regularly should be in mild opioid withdrawal before restarting buprenorphine therapy (98, 102).

## Conclusion

Addiction elicits neurophysiologic, behavioral, and social responses that worsen the pain experience and complicate provision of adequate analgesia. These complexities are heightened for patients with opioid dependency who are receiving OAT, for whom the neural responses of tolerance or hyperalgesia may alter the pain experience. As a consequence, opioid analgesics are less effective; higher doses administered at shortened intervals are required. Opioid agonist therapy provides little, if any, analgesia for acute pain. Fears that opioid analgesia will cause addiction relapse or respiratory and CNS depression are unfounded. Furthermore, clinicians should not allow concerns about being manipulated to cloud good clinical assessment or judgment about the patient's need for pain medications. Reassurance regarding uninterrupted OAT and aggressive pain management will mitigate anxiety and facilitate successful treatment of pain in patients receiving OAT.

## Acknowledgements

The authors thank Jessica Richardson for editorial assistance.

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**Table 1****Pain and Addiction Terminology\***

<b>Term</b>	<b>Definition</b>
Physical dependence	Normal physiologic adaptation defined as the development of withdrawal or abstinence syndrome with abrupt dose reduction or administration of an antagonist
Tolerance	Normal neurobiological event characterized by the need to increase the dose over time to obtain the original effect
Cross-tolerance	Normal neurobiological event of tolerance to effects of medication within the same class
Substance (opioid) dependence (addiction)	Chronic neurobiological disorder defined as a pattern of maladaptive behaviors, including loss of control over use, craving and preoccupation with nontherapeutic use, and continued use despite harm resulting from use with or without physical dependence or tolerance
Pseudoaddiction	Behavioral changes in patients that seem similar to those in patients with opioid dependence or addiction but are secondary to inadequate pain control
Drug-seeking behaviors	Directed or concerted efforts on the part of the patient to obtain opioid medication or to ensure an adequate medication supply; may be an appropriate response to inadequately treated pain
Therapeutic dependence	Patients with adequate pain relief may demonstrate drug-seeking behaviors because they fear not only the reemergence of pain but perhaps also the emergence of withdrawal symptoms
Pseudo-opioid resistance	Adequate pain relief continue to report persistent severe pain to prevent reduction in current opioid analgesic dose
Opioid-induced hyperalgesia	A neuroplastic change in pain perception resulting in an increase in pain sensitivity to painful stimuli, thereby decreasing the analgesic effects of opioids

\* Adapted from references 40–44.

**Table 2**  
**Recommendations for Treating Acute Pain in Patients Receiving Opioid Agonist Therapy\***

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**Addiction treatment issues**

Reassure patient that addiction history will not prevent adequate pain management.

Continue the usual dose (or equivalent) of OAT.

Methadone or buprenorphine maintenance doses should be verified by the patient's methadone maintenance clinic or prescribing physician.

Notify the addiction treatment program or prescribing physician regarding the patient's admission and discharge from the hospital and confirm the time and amount of last maintenance opioid dose.

Inform the addiction treatment maintenance program or prescribing physician of any medications, such as opioids and benzodiazepines, given to the patient during hospitalization because they may show up on routine urine drug screening.

**Pain management issues**

Relieve patient anxiety by discussing the plan for pain management in a nonjudgmental manner.

Use conventional analgesics, including opioids, to aggressively treat the painful condition.

Opioid cross-tolerance and patient's increased pain sensitivity will often necessitate higher opioid analgesic doses administered at shorter intervals.

Write continuous scheduled dosing orders rather than as-needed orders.

Avoid using mixed agonist and antagonist opioids because they may precipitate an acute withdrawal syndrome.

**If the patient is receiving methadone maintenance therapy and requires opioid analgesics**

Continue methadone maintenance dose.

Use short-acting opioid analgesics.

**If the patient is receiving buprenorphine maintenance therapy and requires opioid analgesics, 4 options are available and should be chosen on the basis of the anticipated duration of pain, treatment setting, and response to the chosen option**

Continue buprenorphine maintenance therapy and titrate short-acting opioid analgesics (for pain of short duration only).

Divide buprenorphine dose to every 6–8 hours.

Discontinue buprenorphine maintenance therapy and use opioid analgesics. Convert back to buprenorphine therapy when acute pain no longer requires opioid analgesics.

If the patient is hospitalized, discontinue buprenorphine therapy, treat opioid dependence with methadone at 20–40 mg, and use short-acting opioid analgesics to treat pain. Have naloxone available at the bedside. Discontinue methadone therapy and convert back to buprenorphine therapy before hospital discharge (for inpatients only).

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\* These recommendations are applicable only for patients receiving OAT who require opioid analgesics. OAT = opioid agonist therapy.