CHAPTER 3
MANAGING PAIN IN PATIENTS WITH OPIOID USE DISORDER

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3.1 General Principles of Pain and OUD

Pain is a common condition in patients on medication-assisted therapy (MAT) for opioid use disorder (OUD). Reported rates of chronic pain hover between 50%-60% in patients receiving methadone or buprenorphine treatment [72, 73], and they are likely to suffer acute painful conditions (i.e., dental, infections, trauma), that may or may not be related to the general health consequences associated with addiction behaviors, which may require acute pain care. For those on full and partial opioid agonist therapy (OAT), patients present with opioid tolerance and hyperalgesia [74, 75], thus will require higher doses of opioids to manage acute pain and/or provide anesthesia than that required by the opioid-naïve patient. Because opioid withdrawal is likely to aggravate hyperalgesia, it is important that the maintenance OAT dose be continued during pain treatment.

Although both methadone and buprenorphine have intrinsic analgesic properties, the daily dosing regimen for OUD is intended to treat the symptoms of withdrawal and craving, and thus should not be considered to provide sufficient pain relief. For patients on naltrexone therapy, it can be expected that they will receive little to no opioid analgesia while opioid receptors are fully occupied; however, as the half-life approaches (4 hours for the oral formulation and 5-10 days for the injectable), pain relief can be appreciated, and patients may even be super-sensitive to opioid effects related to receptor resetting with antagonist treatment [76]. In all these cases, immediate-release (IR) opioids should be used in addition to MAT opioids, titrated to analgesic effect, while remaining vigilant for signs of toxicity and with naloxone readily available should these emerge. There is no evidence that opioids provided for pain exacerbate or worsen OUD outcomes, however there is concern that untreated pain may precipitate return to use.

Fortunately, for acute, chronic and surgical pain, treatment approaches are increasingly utilizing effective multimodal non-opioid or opioid-sparing regimens, which should be heavily relied upon to provide analgesia for those on MAT. In general, these include utilization of non-pharmacologic interventions including heat, cold, massage, bracing and stretching, and behavioral interventions such as distraction, graded exercise, and relaxation or mindful meditation. Non-opioid pharmacotherapies focus on around-the-clock use of acetaminophen or NSAIDS, with more specific medication adjuvants utilized for specific pain indications (see below). In some cases, regional procedures with lidocaine or steroid injections can be an important component of the pain management plan.

3.2. Manifestations of Pain and Opioid Treatment

3.2.1 Acute Pain

Acute pain exposure has been negatively correlated to OUD treatment retention related in part to insufficient pain relief, underscoring the need to aggressively manage acute pain in patients on MAT [77]. To avoid the risk of withdrawal and return to use, it is important to continue the maintenance MAT dose, which should be verified with the MAT provider. The state prescription drug monitoring program (PDMP) must also be consulted to determine if non-MAT opioids are being consumed according to the Controlled Substance Utilization Review and Evaluation System (CURES). This regulation specifically addresses non-MAT opioid use, and does not adequately address evaluation of patients receiving MAT in an OTP setting. Multimodal opioid-sparing techniques should be emphasized.

In addition to acetaminophen or NSAIDS, ketamine administered in a low dose as a continuous intravenous or subcutaneous infusion has been demonstrated to treat acute pain in the ambulatory setting, emergency room, or hospital for patients on MAT. Anesthesiologists typically recommend ketamine dosing regimens of a starting dose of 100–200 mg 24/hr, using a mixture of 200 mg ketamine and 5 mg midazolam made up to a total volume of 48 ml with normal saline and a rate of infusion of 1–2 ml/hr or 0.1mg/kg/hr [76, 78]. A regional anesthetic blockade may also be implemented where possible [79].

If opioids are required for patients on methadone, IR opioids can be utilized, ideally administered via PCA to enable self-titration and minimize perceived drug-seeking behaviors [80]. Although the same approach can be utilized for patients on buprenorphine therapy, some clinicians report that giving the total daily dose divided three or four times daily (i.e., 4–8 mg every 6-8 hours) can be useful in treating moderate pain; the ceiling effect of buprenorphine suggests that this strategy will be less effective in cases of severe acute pain [78]. Early recommendations that patients on buprenorphine be rotated to methadone or other full agonists (fentanyl or morphine) to enable more predictable IR opioid analgesic response appear unnecessary, and may expose the patient to greater risk of withdrawal or return to use than continuing the usual buprenorphine dose. Patients on nalthrexone therapy may require general anesthesia in cases of severe pain if IR opioid administration cannot override the receptor blockade.

3.2.2. Peri-operative Pain

Because opioids have been a peri-operative mainstay, utilized pre-operatively, intra-operatively and post-operatively, providing pain care for patients on MAT undergoing surgical procedures requires mention. Although no specific practice guidelines exist to address surgical pain-relief interventions in this population, the general principles outlined for acute pain can be implemented.

3.2.3. Pre-operative Management

Pre-operative opioid use assessment is critical to effective anesthesia and post-operative analgesia. In preparation, MAT dose and formulation should be verified with the provider and the PDMP consulted. It is also important to determine if the patient is regularly using benzodiazepines or alcohol to avoid these dangerous withdrawal syndromes [81]. The patient and family should be included in the management plan (admission to discharge), and liaisons with other healthcare professionals (i.e., pain medicine, psychiatry, nursing, social work) should be initiated.

If the patient will be NPO for greater than 24 hours post-surgery, plans to convert the patient from oral methadone or buprenorphine to IV equivalent should be instituted. Methadone can be administered parenterally; doses of half to two-thirds of the total daily oral dose can be given in three to four divided doses by intermittent intramuscular or subcutaneous injection or by continuous infusion [82, 83]. Some clinicians opt to convert to morphine or another full agonist first, and when performing an opioid rotation, it is recommended to reduce the calculated equianalgesic dose by 30–50% due to the possibility of incomplete cross-tolerance [84].

Although it has been suggested that patients on buprenorphine be rotated to methadone prior to surgery [85], there is no evidence that this improves pain management as opposed to continuing their usual OAT. Others recommend that patients on higher dose buprenorphine maintenance (i.e., 16 mg - 32 mg/day) be titrated down to 12 mg/day prior to surgery to minimize potential dose-dependent opioid antagonism effects. If possible, it is recommended that oral naltrexone be discontinued 72 hours prior to surgery so that opioids can be utilized if necessary [82], however this becomes impractical for patients on naltrexone XR or for unplanned procedures. In these cases, non-opioid approaches become essential.

3.2.4. Intra-operative Management

As noted, baseline opioid requirements should be met, and if possible, the usual prescribed OAT dose is taken on the day of surgery using a take-home dose provided by the MAT provider. Effective multi-modal opioid-sparing anesthetic techniques, which differ across surgical procedures [86], are highly recommended, and may include pre-emptive administration of acetaminophen, celecoxib or pregabalin; preloading the incision sites with local anesthetic before incision; and placement of an epidural catheter for intraoperative and postoperative use. Local and regional analgesia techniques are preferred when suitable. If opioids are used, higher opioid requirements can be anticipated; in spontaneously breathing patients, maintaining a respiratory rate of 12-14 can be used as a guide [81]. Instillation of long-acting lidocaine in the surgical wound prior to closure has been shown to significantly decrease pain and opioid requirement for several days following surgery. Local anesthetic techniques including wound infiltration, regional, or neuraxial block with spinal or epidural anesthesia. Local anesthetic catheters can prolong the benefits of regional anesthesia into the postoperative period [85].

3.2.5. Post-operative Management

Post-operative pain management should proceed as outlined for acute pain, with the goals of providing effective analgesia while maintaining opioid coverage for OUD treatment, and relying on multimodal, opioid-sparing approaches whenever possible. Non-opioid analgesics, including around-the-clock NSAIDS, acetaminophen, COX-2 inhibitors (coxibs), or ketorolac administration [79, 82], can be utilized; these are available in parenteral and other forms of administration, and associated with a reduction in postoperative opioid use and improved analgesia. Less well-tested agents include clonidine and dexmedetomidine, which elicit analgesia by agonism of the α-adrenergic receptor, and gabapentin and pregabalin, which inhibit pain transmission via blocking sodium-channels [87].

Regional blockade with local anesthetics can be useful in the early postoperative period as it theoretically removes the need for additional systemic analgesia. Although neuraxial opioids allow for lower doses of opioid exposure, these may not prevent opioid withdrawal and additional systemic opioids are often required [87]; further, it may be difficult to estimate an appropriate or safe dose.

When regional analgesia is not applicable and/or IR opioids are indicated, an intravenous PCA administration system is highly recommended, as it allows for individual dose titration and reduces workload for staff. Because patients on OAT

develop opioid tolerance, they often require higher doses than those usually prescribed opioids for the first time or in the short term (including higher PCA bolus doses). Similarly, it can be anticipated their pain severity scores will be higher and decrease more slowly, and that review and adjustment of dosing will be required more frequently.

Several studies indicate that after a variety of surgical procedures, first 24-hour PCA morphine requirements were, on average, three times greater in the opioid-tolerant versus opioid-naïve patients. Determining the appropriate setting of bolus size and lockout interval may be challenging. One recommended method is to begin with the patient's usual 24-hr opioid requirement, and base the size of the bolus dose at 50% of the hourly background infusion rate with a 5-minute lockout. Concerns that IR opioid provision may result in respiratory depression in OAT patients are not supported by clinical experience, likely related to the development of cross-tolerance; however, evidence of opioid toxicity should be carefully monitored for, and naloxone made readily available.

Patients on naltrexone therapy should be managed with multi-modal opioid sparing approaches to the degree possible. Competitive blockade of naltrexone can be overcome with opioid agonists, but the required doses are on the order of 10–20 times the usual doses by weight [78]. This becomes particularly hazardous as naltrexone dissociates from the opioid receptor and subsequent receptor super-sensitivity puts the patient at risk for opioid toxicity. Close monitoring and availability of naloxone become paramount when opioids are provided to those receiving naltrexone treatment for OUD.

As post-operative pain subsides, it is important to bring the patient on methadone or buprenorphine therapy back to the usual OAT dose as soon as possible. Ideally, naltrexone can be re-induced prior to hospital discharge.

3.2.6. Chronic Pain

As promulgated by the recent CDC Guidelines [88], it is increasingly appreciated that opioids should not play a primary role in the management of chronic pain, and that in some cases, functionality improves when opioids are tapered. Conceptualized as chronic illness for which complete remission is not expected, non-pharmacologic approaches become central, and include such evidence-based interventions as acupuncture, physical therapy, graded exercise, weight loss, cognitive behavioral/acceptance therapy, mindful mediation, and yoga. Non-opioid pharmacotherapies with demonstrated efficacy are the NSAIDS and acetaminophen; the anticonvulsants gabapentin and pregabalin; and the SNRIs duloxetine and venlafaxine. Certain tricyclic antidepressants have also been recommended, but are typically less useful due to associated adverse side effects. These same strategies are indicated for chronic pain patients on MAT. In fact, several of these (acupuncture, cognitive behavioral therapy, mindfulness meditation, antidepressants) are likely to provide benefit for the treatment of both pain and OUD [89-92].

However, there is a subpopulation of patients with chronic pain whose functionality and quality of life are maximized with ongoing opioid therapy, which may include patients on OAT and in stable recovery. Risk monitoring strategies utilized for all chronic pain patients on opioid therapy can include the use of treatment agreements, urine toxicology, and monitoring of PDMPs. Because patients with a history of a substance use disorder are at higher risk for return to use, opioid prescribing for chronic pain to patients on buprenorphine or methadone for the treatment of OUD requires expansion of the chronic pain treatment plan. The plan should include the integration of relapse prevention strategies, frequent assessment for evidence of aberrant drug use behaviors, and the expectation that they maintain good standing and engagement in addiction treatment [93]. Due to ongoing opioid blockade, opioid provision is not an option for patients on naltrexone MAT.

3.3. Managing Addiction in the Context of Pain

Critical to managing pain in patients on MAT is the understanding that the chronic disease of addiction requires continuous management; a single-minded focus on treating pain may allow the addiction to progress unchecked. The presence of pain, be it acute or chronic, is a stressor, and even if opioids are not prescribed for its management, the associated anxiety, functional losses, sleep disturbances, and general discomfort can set the patient up for a return to use of the drug which, in the past, had reliably provided psychic relief. Most important to ensuring that an exacerbation of substance use disorder does not occur is the establishment of a collaborative treatment relationship between the addiction treatment provider and the pain care provider, with regular communication about the patient's response to each. Obtaining the patient's permission to allow such communication should be part of the treatment plan.

There are specific strategies the addiction treatment provider can utilize to support recovery goals of in the context of pain treatment. Continued and active engagement in addiction treatment should be encouraged; even if the patient is hospitalized, virtual 12-step meetings, on-site mutual support group meetings, visits from sponsors or the MAT provider, or access to readings or web-based programming can be facilitated. It is necessary to continuously evaluate the presence and severity of stressors that might precipitate return to use (such as unrelieved pain, sleep issues, withdrawal symptoms, psychiatric symptoms, interpersonal conflicts, craving), as well as identify protective factors that promote recovery, and to support/strengthen these to the extent possible. If it becomes apparent that a return to use has occurred, it is critical that the MAT provider notify the pain treatment provider as soon as possible to reassess pain management strategies, minimize the extent of the exacerbation, and reinforce recovery efforts.

Summary guidelines for managing pain in patients on medication-assisted treatment:

- Continue usual MAT dose
- Utilize non-pharmacologic and non-opioid pain management strategies
- If necessary, use immediate release opioids, titrate to effect and monitor for toxicity
- Expect that larger doses of opioids will be required to manage pain
- Establish collaborative treatment relationship with MAT treatment provider