Perioperative pain management in opioid tolerant and opioid use disorder patients: Considerations for the foot and ankle surgeon

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Perioperative management of patients with long term use of opioids has become an increasing challenge. Complicating the care of these patients are the misconceptions regarding opioid prescribing in the opioid-tolerant community and those on maintenance therapy. Healthcare providers receive limited education on pain management including multimodal pain control. Perioperative considerations should be examined. Prescribers are encouraged to consider utilizing a multi-modal regimen in this population. A comprehensive literature review was performed, focusing on perioperative pain management in opioid tolerant patients. Expert opinions and material in this review is provided by a board-certified Addiction Medicine Specialist and board-certified Foot and Ankle Surgeon at a level one trauma center. Pain control in the opioid-tolerant patient population can be challenging for the Foot and Ankle surgeon. Pre-operatively, patients' risk factors for chronic opioid use should be assessed through screening tools. Intra-operatively, sound dialogue between the surgeon and anesthesiologist is imperative with new and emerging techniques. Postoperatively opioid-tolerant patients should resume preoperative dosing of opioids at a minimum. A multimodal pain regimen is associated with superior pain relief and decreased opioid consumption. Patients on maintenance therapy including Methadone, and Buprenorphine should continue these medications during the perioperative period. These patients may benefit from an addiction medicine consultation for more comprehensive care.

Keywords: foot and ankle, opioid-tolerant, pain management, perioperative management, surgery

Caring for patients who have long-term use of opioids and Opioid Use Disorder (OUD) is of increasing concern. Over the last two decades, we have seen an increase in both the use and misuse of opioids. The media is full of tragic stories of overdose deaths. In the most recently documented reporting year the number of opioid overdose related mortality has now topped 100,000 in the United States. Furthermore, these numbers have worsened during the COVID-19 pandemic [1].

Additionally complicating the care of our patients, healthcare providers receive limited education on pain management and addiction medicine. Given the limited, and sometimes inaccurate knowledge, many providers are very anxious about prescribing opioid therapy to treat patients' pain including during the perioperative period. In this article, we will discuss the challenges of caring for patients who are opioid-tolerant. This tolerance can be the result of several subsets of patients including:

1. Malignant and non-malignant chronic pain patients on large doses of opioids.
2. Opioid addiction-patients actively using opioids illicitly or in non-prescribed manners.
3. Patients with a history of addiction, now on medication for opioid use disorder (methadone, buprenorphine, naltrexone).

Expert opinions and material provided in this review are provided by a board-certified Addiction Medicine Specialist and board-certified Foot and Ankle Surgeon at a level one trauma center and supported by current academic literature.
### Table 1 DSM-5 Criteria for Opioid Use Disorder

#### Criteria and Language

Identifying patients with addiction is vital as we work to treat patients’ pain. This is complicated by the fact that upwards of 32% of our patients being treated for chronic pain, may also have co-occurring addiction [2]. It is important for us to clarify the diagnostic criteria which is used to identify who may have an addiction or co-occurring addiction and pain. Additionally, we will discuss the best language to use when discussing these patients.

<table>
<thead>
<tr>
<th>Opioid Use Disorder Criteria</th>
<th>Summarized Diagnostic and Statistic Manual 5th edition (DSM-5) Diagnostic Categories and Criteria For Opioid Use Disorder</th>
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<tbody>
<tr>
<td>1.</td>
<td>Opioids are often taken in larger amounts or over a longer period than was intended.</td>
</tr>
<tr>
<td>2.</td>
<td>There is a persistent desire or unsuccessful efforts to cut down or control opioid use.</td>
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<td>3.</td>
<td>A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects</td>
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<td>4.</td>
<td>Craving, or a strong desire or urge to use opioids.</td>
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<td>5.</td>
<td>Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.</td>
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<td>6.</td>
<td>Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.</td>
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<td>7.</td>
<td>Important social, occupational, or recreational activities are given up or reduced because of opioid use.</td>
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<tr>
<td>8.</td>
<td>Recurrent opioid use in situations in which it is physically hazardous.</td>
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<tr>
<td>9.</td>
<td>Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.</td>
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<tr>
<td>10.</td>
<td>Tolerance, as defined by either of the following:</td>
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<tr>
<td></td>
<td>a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect.</td>
</tr>
<tr>
<td></td>
<td>b. A markedly diminished effect with continued use of the same amount of an opioid.</td>
</tr>
<tr>
<td>Note:</td>
<td>This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.</td>
</tr>
<tr>
<td>11.</td>
<td>Withdrawal, as manifested by either of the following:</td>
</tr>
<tr>
<td></td>
<td>a. The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal).</td>
</tr>
<tr>
<td></td>
<td>b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.</td>
</tr>
<tr>
<td>Note:</td>
<td>This criterion is not considered to be met for those individuals taking opioids solely under appropriate medical supervision.</td>
</tr>
</tbody>
</table>

The most updated criteria for substance use disorder come from the Diagnostic and Statistic Manual 5th edition (DSM5). The most recent definition contains eleven diagnostic criteria (Table 1) for OUD. The number of criteria an individual meets defines the severity of the disorder (mild 2-3, moderate 4-5, severe 6 or more). An important note when caring for patients prescribed opioid therapy for pain is that the criteria related to tolerance and withdrawal (criterion
10 and 11) can occur as a normal physiologic response to opioid therapy. When diagnosing co-occurring OUD in these patients, we would need to use the other nine criteria.

Language

The language healthcare providers use to describe our patients can significantly impact the quality of care provided. Stigma against people with substance use disorders is particularly impactful, as many providers may be averse to treating patients with addiction. Addiction is a chronic, treatable brain disease that should be viewed like other chronic medical conditions healthcare providers manage [3].

Given the known negative impact of stigma and bias on this patient population, it is important that we use appropriate, patient-centered language when discussing patients and their care. Rather than using the terms “addict,” “alcoholic,” or “abuser,” patient-centered language would address “a person with a substance use disorder” or “a person with an addiction.” Additional care should be taken to avoid the word “abuse.” This term was removed as a diagnostic term from the DSM5 and is a step toward conceptualizing addiction as a treatable disease [3].

Common Misconceptions Caring for Opioid Tolerant Patients

There are a multitude of misconceptions physicians and healthcare providers can have when caring for our patients who are opioid-tolerant. These misconceptions are often more pronounced in our patients who are using or in recovery from OUD but can be seen when caring for any patient that requires additional opioids for perioperative pain management.

Misconception #1: Baseline opioid therapy (for pain or addiction treatment) will treat acute postoperative pain [4,5]

When patients require opioid therapy daily (for pain or treatment of OUD), this dose is treating the underlying chronic condition. When an individual has an acute pain event, such as surgery, this dose will not provide adequate pain relief because there is now an increase in painful stimuli within the patient’s body compared to their baseline. Additionally, methadone or buprenorphine for the treatment of opioid use disorder is not dosed in a manner that would utilize the medications’ analgesic properties. There are multiple ways, to be discussed in this article, to manage pain in these patient populations. Often this includes focusing on multimodal therapy and prescribing additional opioid pain medication at opioid-tolerant dosing.

Misconception #2: Use of opioid therapy will cause addiction or relapse

A common concern, especially in patients in treatment for addiction, is that prescribing opioids will cause a relapse to active drug use. Multiple studies have not shown an increase in the risk of relapse in the setting of acute pain [4]. Most likely, the opposite may be true; patients with the additional stress of unrelieved pain may be more at risk of relapse.

Misconception #3: Additional opioids for analgesia will cause respiratory and Central Nervous System (CNS) depression

While safety when prescribing opioids is a rational concern, additional opioids in the opioid-tolerant patient population are unlikely to lead to a significant risk of respiratory or CNS depression. Multiple studies, discussed by Alford, et al., suggest that tolerance to these side effects develops reliably and rapidly [4]. Additionally, the acute pain itself may serve to mitigate the risk of respiratory and CNS depression when given additional opioids [4].

Misconception #4: Reporting pain may be a manipulation to get more opioids related to opioid addiction [4]

Patients with OUD and opioid tolerance are often anxiety-laden regarding pain control in the hospital setting. This anxiety may be based on previous experiences of stigma or discrimination within the healthcare system. Physicians and other health care providers are also reluctant to give medications to patients currently on high doses of opioids or on medications for opioid use disorders. In these situations, it may be true that if patients do not ask for medication for pain, they may not receive it.

As physicians and providers, it is important to evaluate the patient clinically when pain is a concern. Assessing pain is subjective and challenging. Approaching patients with a thorough clinical assessment and understanding of underlying pathology or surgical intervention can help the healthcare team be more objective in their decisions to prescribe appropriate pain medications.
Preoperative Management

Part of the preoperative evaluation should include the identification of opioid tolerant patients and establishing a treatment protocol before taking the patient to the operating room. Although there has been increased awareness of opioid use and misuse within the medical community, there remains a paucity of literature on the preoperative steps to manage these patients. This section will discuss appropriate screening methods and tools, opioid use databases and urine drug screens, preoperative dosing, the role of proper education, incorporation of opioid treatment agreements, and when to engage in a multidisciplinary treatment approach.

Screening Methods and Tools

Screening patients for risk factors of complicated pain control or chronic opioid use should be included in the preoperative evaluation. The incidence of chronic opioid use varies based on both patient characteristics, as well as surgical intervention performed [6]. Significant risk factors for chronic opioid use in opioid-naive patients who are undergoing surgical intervention include male sex, >50 years old, preoperative benzodiazepine or antidepressant use, history of depression, and history of alcohol or drug abuse [7]. Identifying medications that if discontinued would lead to withdrawal is an important step in the preoperative evaluation. Furthermore, providers should evaluate each patient for psychiatric disorders as well as substance use disorder comorbidities [8]. Patients should be screened for generalized anxiety disorder, depression, illicit substance use, and alcohol consumption. Anxiety has been associated with a higher risk of opioid misuse in chronic pain patients [8].

Screening tools, such as the Pain Catastrophizing Scale and Opioid Risk Tool (ORT), have been developed for evaluating patients at higher risk for opioid misuse. The Pain Catastrophizing Scale is utilized to assist in identifying patients who are at risk of experiencing helplessness, anxiety, and catastrophic thinking associated with their pain [9]. The ORT helps identify behaviors of individuals that are at higher risk of opioid use disorder if prescribed opiates for chronic pain [9]. This tool was developed to assist physicians in identifying patients that may be at higher risk of developing aberrant behaviors when prescribed opioids for chronic pain [10]. ORT looks at various categories, including family and personal history of substance abuse, age, preadolescent sexual abuse, and psychological disease. In their original study, Webster found that 94.4% of patients categorized as “low risk” did not show any aberrant behavior, while 90.9% of “high risk” patients were found to display aberrant behavior [10]. Screening tools can provide subjective information for the foot and ankle surgeon in identifying patients at higher risk of OUD before taking patients to the operating room.

Databases and Drug Screens

In addition to utilization of the ORT, physicians should consider reviewing objective information including prescription drug monitoring programs (PDMP) and obtaining a urine drug screen prior to prescribing opioids. PDMPs are databases that provide physicians with information on the filling of controlled substances [11]. Examining the PDMP before prescribing allows physicians to review the patients controlled substance prescription history. PDMPs are valuable in identifying patients that are at higher risk of misuse of or dependence on opioids [12]. They allow physicians to identify patients who receive controlled substances from multiple providers or are prescribed multiple medications that increase the risks associated with opioids [11].

Another tool that physicians can utilize is urine drug screens (UDS). Katz and Fanciullo reported that subjective information cannot always be relied upon, making the information provided by the UDS invaluable for monitoring opioid use [13]. The urine toxicology screen should be ordered to specifically look at methadone, buprenorphine, fentanyl, and other opioids. The UDS can help identify patients with a higher risk for drug addiction or diversion. Patients with abnormal test results, including negative results of prescribed medications or positive results of drugs of misuse that are not prescribed, warrant further investigation. Foot and ankle surgeons should consider implementing the ORT to identify individuals with chronic pain who are at higher risk for developing aberrant behaviors, while supplementing this evaluation with review of the PDMP prior to opioid prescription and obtaining a UDS to monitor patients on chronic opioid therapy.
Preoperative Opioid Dosing

Prior studies in the orthopedic literature have shown that patients with a history of chronic opioid use are more likely to face increased acute pain and slower pain resolution following surgical intervention despite appropriate adjustments in opioid administration [14]. Menendez found that patients with opioid dependence undergoing elective orthopedic procedures are significantly more likely to have prolonged hospital length of stay, increased postoperative complications, and higher mortality [15].

Diagnosing patients with opioid tolerance early in the preoperative period allows for an opportunity to minimize the risk of acute withdrawal, optimize preoperative status, and develop a postoperative analgesic plan [16].

There is currently no validated system to categorize and treat these patients [17]. There is also no consensus on whether opioids should be continued at regular doses or reduced prior to surgery. However, recent reports in the orthopedic literature have shown that preoperative reduction in opioids in opioid-tolerant patients can have an improvement in clinical outcomes [18] and reduce the incidence of opioid-induced hyperalgesia (OIH) [19].

Literature is lacking on protocols for weaning prior to surgery and no agreed-upon optimal tapering regimen has been established. Some studies have recommended that weaning to 50% of baseline has improved outcomes [18]. It is known that any opioid taper should be performed gradually over an extended period of time. However, no recommendations for this timeframe within the preoperative period have been established in the literature. Clearly more research is needed on this topic within the orthopedic community to establish appropriate tapering strategies. This highlights the importance of identifying patients with opioid use, as these patients will require special attention in the preoperative and postoperative periods.

Proper Opioid Education

Patient education on the risks of chronic opioid use and postoperative pain management should be discussed during preoperative visits, including patient goals and expectations. The Centers for Disease Control and Prevention has emphasized the importance of educating patients on the risks of opioid use prior to initiation of therapy [22]. Patients should be educated on the appropriate use of opioids, including the risks of long-term usage, strategies for the safe storage and disposal of opioids, and the importance of avoiding sharing medications with others [12].

Having a basic understanding of the theories behind developing chronic pain can be beneficial to supplement these conversations. One such theory, the fear-avoidance model, proposes that there are 2 responses to pain: adaptive (i.e., confrontation) and nonadaptive (i.e., avoidance). The nonadaptive response can lead to fear of movement and physical disuse in the postoperative period [20]. Pain catastrophizing (i.e., an exaggerated negative response to the anticipation of pain) can lead to an abnormally increased response to pain postoperatively [21].

Holman, et al., found in their study of an orthopedic trauma cohort that patients who were counseled preoperatively on opioid use duration were significantly more likely to adhere to those timelines of cessation compared to those who were not counseled [23]. It should also be mentioned that they found that these results may not affect long-term use after the postoperative period [23]. Education and development of treatment plans play an important role in opioid prescribing, but there needs to be more research on this topic in developing guidelines and strategies that physicians can implement into their own practice.

Opioid Treatment Agreements

Another area to explore in the preoperative period is whether patients can commit to a reduction in opioid dose. It may not be realistic to achieve a complete cessation of opioids before surgical intervention. However, gauging commitment to cessation in the preoperative period may be beneficial to establishing a framework for discontinuing opioids postoperatively [17]. A tool that clinicians can utilize in these circumstances is an opioid treatment agreement. Treatment agreements can help set up clear expectations for the patient regarding their responsibilities and the expectations they can have of the care team. Although they are implemented frequently, the efficacy of opioid treatment agreements remains equivocal [12].
**Multidisciplinary Approach**

As patients with chronic opioid use require special attention, referral to an addiction medicine specialist and/or pain management specialist should be considered. These specialists can consider the risks and benefits of multimodal approaches and consideration for cognitive behavioral therapy. A multidisciplinary approach to these patients should be considered.

**Intraoperative Management**

Intraoperative management of a patient with OUD or an opioid tolerant patient involves the surgeon, anesthesiologist, and other operative personnel. Appropriate planning and consideration prior to the day of surgery will mitigate inappropriate care for this patient group. This section will address intraoperative opioid dosing, utilization of regional and local anesthetic, and adjunctive intraoperative medications to decrease opioid requirement.

**Intraoperative Opioid Dosing**

On the day of surgery, surgeons should further educate patients on how to prevent opioid withdrawal. Clinicians should gather a history of the last opioid dose taken, including the date and time of administration. Oftentimes, patients will omit their daily opioid dose secondary to confusion with preoperative fasting [25]. It is recommended that patients take at least 50% of their baseline dose to prevent withdrawal [25]. At the authors institution patients are instructed to continue taking analgesic medication at their baseline dose of opioids throughout the entire perioperative period. If patients miss their opioid dose, it should be provided before surgical intervention. Intraoperative management requires a sound dialogue between the surgeon and anesthesiologist. The choice of intraoperative pain management is at the discretion of the anesthesiologist. Regarding the opioid-tolerant patient, current literature does not suggest a preference for one opioid for pain management over another including fentanyl, remifentanil, sufentanil, or alfentanil [5,26]. Opioid-induced hyperalgesia has been reported with all forms of intraoperative pain management [26]. Intraoperative opioid requirements necessary to provide sufficient analgesia in the opioid-tolerant population can reach 50 to 300 percent of that required for the opioid-naïve patient [27].

**Regional and Local Anesthetic**

The use of pre-operative regional and local anesthesia has been shown to help limit intraoperative and postoperative opioid requirements. In a review by Kumar et. al, the use of peripheral nerve blockade (PNB) in the lower extremity reduced intraoperative and post-operative consumption of opioids [28]. Additionally, they found a higher patient satisfaction rate with pre-operative implementation of local or regional anesthesia [28]. These findings were echoed in a recent systematic review [29]. Utilization of PNB combined with general or spinal anesthesia reduced postoperative opioid consumption in 86% of investigated studies and postoperative pain levels were improved in 75% of investigated studies. Combined delivery of any combination of femoral and sciatic blocks, popliteal and saphenous blocks, or popliteal and ankle blocks was found to be an effective method of improving postoperative opioid consumption, pain scores, and patient satisfaction scores [29].

**Adjunctive Intraoperative Medications**

The use of single-dose Intravenous (IV) Dexamethasone has been explored in perioperative pain management. Waldron et. al performed a meta-analysis investigating the preoperative administration of 1.25-20 mg of dexamethasone and its analgesic effects [30]. They found that patients receiving dexamethasone had statistically significant lower pain scores and required fewer opioids at 2 and 24 hours post-op. Additionally, they found shorter patient stays in the post-anesthesia care unit. Though blood glucose levels were found to be higher at 24 hours, there was no significant increase in infection or delayed wound healing with a single use of dexamethasone [30]. Ketamine, an NMDA receptor antagonist, has recently been shown to be an effective adjunct in intra-operative and post-operative pain management. A study by Joly, et al., found small doses of intraoperative ketamine were able to reduce hyperalgesia [31]. Plasma concentrations of 250 ng/ml intraoperatively and 100 ng/ml postoperatively have been described as the desired target range. These ketamine concentrations are in the range known to counteract hyperalgesia [31]. In a systematic review performed by Bell et. al, intraoperative ketamine was found to be successful in reducing postoperative morphine requirements in the first 24 hours following surgery and significantly reduces postoperative nausea and vomiting [32].

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Post-operative management

Studies have shown that less than 50 percent of patients undergoing surgical procedures report adequate pain relief in the postoperative period [33]. Postoperative pain control can be especially challenging in the opioid-tolerant population. Opioid requirements for opioid-tolerant patients reach four times the requirements needed for opioid-naive patients. Postoperative opioid pain regimen has been found to continue three times longer in an opioid-tolerant cohort than an opioid-naive cohort [34]. The American Pain Society (APS) has published a clinical practice guideline with recommendations on effective treatment strategies to manage postoperative pain. According to this guideline, they suggest that clinicians utilize multi-modal analgesia with the combined use of opioids, non-opioid analgesic medications, and non-pharmacological interventions. This was classified as a strong recommendation with high-quality evidence [35].

A multimodal analgesia regimen is defined as the use of various analgesic medications and techniques that target assorted mechanisms of action in the central and or peripheral nervous system. These medications have a synergistic effect. Specifically, APS recommendations for multimodal analgesia for orthopedic procedures include the use of systemic pharmacologic therapy, local, intra-articular, or topical techniques, regional anesthetic techniques, neuraxial anesthesia techniques, and nonpharmacological therapy. Systemic pharmacological agents include the use of opioids, scheduled nonsteroidal anti-inflammatory drugs (NSAIDs) with acetaminophen, gabapentin and pregabalin, and IV ketamine. These can be used in conjunction with topical or local anesthesia administered preoperatively or postoperatively. Non-pharmacological therapy includes the use of cryotherapy, compression, and Transcutaneous electrical nerve stimulation (TENS) units [35]. Randomized control trials have demonstrated that a multimodal regimen including simultaneous use of combinations of several medications acting at various receptors is associated with superior pain relief and decreased opioid consumption compared with the use of a single medication administered through a single technique [36,37].

Opioid Management

A critical aspect of the preoperative work-up of opioid-tolerant patients includes establishing baseline dosages of analgesic medications. These patients should receive their baseline opioid dosing at minimum following surgery. They often require higher than baseline dosing following orthopedic surgery due to the acute noxious stimulus. For reference, Gupta, et al., found that, following elective foot and ankle surgery, opioid-naive patients consumed a mean of 22.5 opioid pills for adequate pain relief [38]. In the opioid-tolerant patient, the foot and ankle surgeon should consider a 25-100% increase from baseline dosage in the first 24-48 hours. Opioid pain management should not be withheld post-operatively in the opioid-tolerant population with fears of adding to or initiating latent addiction. Insufficient pain control has been shown to lead to increased cravings and relapse [39].

Oral administration of opioids is the preferred route of administration versus the IV route in those patients that can tolerate oral intake following surgery. It has been found that pain scores are equivalent between each route with the oral administration group having lowered amounts of morphine equivalents ingested [40]. Considerations should be made to monitor opioid-induced respiratory depression in the postoperative period.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are most effective in the treatment of inflammatory pain. Two classes of NSAIDs exist. Non-selective NSAIDs are inhibitory to both the COX-1 and COX-2 enzymes which produce substrates responsible for blood clotting and inflammation. This includes common over-the-counter products such as Ibuprofen, Aspirin, and Naproxen. Selective NSAIDs inhibit the COX-2 enzyme alone, such as Celecoxib. The use of NSAIDs, as part of the multimodal regimen, has been shown to effectively reduce postoperative pain as well as opioid consumption [41,42].

NSAID use in orthopedic surgery has historically been avoided, secondary to fears of adverse effects on bone healing. These fears have been substantiated in recent control trials, however, negative effects on bone healing may be dose or time-dependent as low-dose and short-duration exposure did not affect union rates [43,44]. Additional findings on bone
healing showed those taking NSAIDs for a short duration of less than two weeks did not show any significant risk of nonunion compared to those who received NSAIDs for a longer duration of over four weeks [44].

Other considerations include risk profiles of NSAID use. All NSAIDs are associated with decreased kidney function and an increase in significant cardiac events. Non-selective NSAIDs increase patients’ risks for gastrointestinal ulcers or bleeds. With these adverse effects in mind, care should be taken to avoid NSAID use in patients with cardiac, renal, or gastrointestinal diseases.

Acetaminophen

Acetaminophen is a readily available adjunct, utilized for mild to moderate pain control. NSAIDs and acetaminophen differ in mechanism of action and the combined use of both in the postoperative period has shown to be more effective than the use of one alone [45]. In a double blinded randomized control trial preemptive and preventative dosing of IV acetaminophen was shown to decrease opioid demand and prolonged need for opioids following orthopedic lower extremity surgery [46]. Alternatively, oral dosing of acetaminophen has been effective in treating post-operative pain. Toms, et al., found a single dose of acetaminophen reduced moderate to severe postoperative pain by up to 50% in over half of their patient cohort [47]. Optimal dosing and route of administration remain largely undetermined at this time [48]. Adverse effects of acetaminophen use include hepatic toxicity. Prescribing surgeons should avoid excessive use of this medication in those suffering from acute or chronic liver disease or chronic alcohol use. Recent reports suggest the maximum daily dose of acetaminophen should be 3g to avoid such complications [49].

Gabapentinoids - Gabapentin and Pregabalin

Gabapentinoids are second-generation anticonvulsants most often used in the treatment of chronic neuropathic pain. The mechanism of action includes blocking voltage-dependent calcium channels leading to decreased neuronal firing. The use of these medications as part of the multi-modal regimen following surgical procedures has demonstrated mixed results. Buvanendran, et al., found that perioperative use of pregabalin reduced chronic neuropathic pain following total knee arthroplasty with reduced opioid consumption and improved range of motion in the first 30 days of rehabilitation [50]. A randomized control trial by Hah et. al. found no significant effect on postoperative pain resolution but did find a significant increase in opioid cessation with the use of gabapentin [51]. Optimal dosing for adequate pain relief remains unclear, however, it is recommended these medications be dosed 2-3 times a day to maintain therapeutic levels [49]. The APS recommends perioperative use of gabapentin or pregabalin in patients undergoing major surgery or opioid-tolerant patients as a strong recommendation with moderate-quality evidence [35]. Adverse effects of gabapentinoids include mild to moderate sedation, especially in the elderly population. Care should be taken in those with acute or chronic renal disease as these medications are renally excreted.

Musculoskeletal Agents

Common musculoskeletal agents used in the post-operative multimodal regimen include ibuprofen, methocarbamol, tizanidine, and cyclobenzaprine. These agents are utilized and effective in the treatment of painful muscle spasms as they have a depressive CNS effect leading to muscle relaxation. The data on the use of muscle relaxants in the postoperative setting is sparse. Favorably, the use of muscle relaxants as a post-operative multi-modal adjunct has shown to provide symptomatic pain relief and significantly reduce opioid consumption in orthopedic spine procedures [52,53] In a survey of 64 Foot and Ankle surgeons, 13% reported using muscle relaxants in the postoperative period as a part of their post-operative multi-modal approach [54]. These medications should be prescribed with caution to those who use alcohol, benzodiazepines, and other CNS depressants as there can be a synergistic effect.

Ketamine

Ketamine is antagonistic to N-methyl-D-aspartate receptors leading to analgesia and reducing opioid tolerance. There is extensive literature that evaluates the use of ketamine as a part of the opioid-sparing multimodal regimen for those undergoing major surgery. With emerging research, some institutions have implemented ketamine as the standard of care for managing post-operative pain in opioid-tolerant patients [48,55]. Jouguet-Lacoste, et al., reported a mean reduction of opioid consumption of 40% when using low-dose IV infusion of ketamine (infusion rate less than 1.2 mg/kg/h) perioperatively [55].
Figure 1 Summary of appropriate management practices for MOUD patients.

They also found a reduction in pain scores. No major complications were reported with low dose IV infusion of ketamine up to 48 hours following surgery. Bell, et al., reviewed 18 randomized control trials to evaluate the effectiveness of perioperative ketamine use for acute postoperative pain [32]. They found subanesthetic doses of ketamine in the perioperative period reduced morphine requirements in the first 24 hours postoperatively, and reduced nausea and vomiting with little to no adverse effect [32]. In orthopedic literature, ketamine is effectively being incorporated into the multi-modal approach in joint replacement surgeries. Significantly lower pain scores and reduced cumulative morphine consumption has been reported [56,57]. The APS recommends consideration of perioperative use of IV ketamine in opioid-tolerant patients with moderate quality of evidence. Adverse effects of ketamine may include increased hallucinations and nightmares.

Patient-Controlled Analgesia (PCA) Pump

A relatively newer post-operative pain modality includes patient-controlled analgesia (PCA) pumps. This includes morphine, fentanyl, remifentanil, and other analgesics administered through IV, extradural, or transdermal routes. A study investigating the use of remifentanil in chronic pain patients following surgery showed a decreased time to achieve clinically sufficient pain relief [58]. Titration of the selected opioid includes self-administration of small bolus doses to reach a minimum-effective analgesic concentration. There is a maximum concentration of the administered opioid of around six minutes followed by a lockout period. A lock-out period does not allow the patient to administer a new dose, allowing a peak analgesic effect and lowering overdose risks [58]. Richebé, et al., describe the advantages of PCA in the opioid-tolerant population as easy and immediate use, providing stable plasma levels, pain relief with a lower total opioid consumption, and fewer confrontations between patients and the healthcare team which negates anxiety and acute withdrawal episodes [26]. Disadvantages include potential abuse, respiratory depression, and challenges regarding appropriate bolus size and lockout interval. The APS recommends consideration of PCA with basal infusion of opioids in the opioid-tolerant population with appropriate monitoring. However, high-level evidence is lacking.

Transcutaneous electrical nerve stimulation (TENS) Unit

TENS is a physical modality utilized for multi-modal pain control. These are small portable devices that deliver low-voltage electrical currents. The proposed mechanism is that the current will activate inhibitory pain pathways, reducing central excitability and ultimately reducing pain. Bordal, et al., found, through a systematic review of randomized control trials, that TENS units use significantly reduced postoperative analgesic requirements by about 25% [59]. The APS recommends consideration of the TENS unit as an adjunct to treat post-operative pain with moderate quality of evidence, however, there is insufficient evidence to suggest optimal settings and frequency [35].

Recommendations for patients on medications for opioid use disorder (MOUD)

Part of the challenge for surgeons managing postoperative pain in the opioid-tolerant population is proper management of those patients on MOUD including methadone, suboxone, or naltrexone.

Methadone

Methadone is a synthetic long-acting opioid agonist used to treat opioid dependence and chronic pain. The mechanism of action includes binding to mu-opioid receptors and decreasing opioid cravings,
pain, and withdrawal symptoms. Daily methadone dosing should be verified with the patient, and or the patient's methadone clinic. Methadone is to be continued in the perioperative period at the patient's standard daily dosing [8,49]. Common dosing is 60-120mg daily. Surgeons are encouraged to communicate with the patient's methadone clinic provider before the start of postoperative management. It has been established that the use of methadone when used as MOUD is insufficient in providing pain relief in the acute post-surgical setting, with additional strategies required [4,60]. In a large part this is because the duration of action of Methadone for preventing withdrawal symptoms is estimated at 24-48 hours, however, the analgesic effect is only 4 to 8 hours [49]. In addition to the continuation of methadone in the postoperative setting, clinicians are highly encouraged to utilize multi-modal methods, including opioid tolerant dosing of short acting opioids, for proper pain control as described above [8]. A verification letter should be written by the surgeon to establish the last dosing of methadone while inpatient to provide to the patient’s methadone clinic.

**Buprenorphine**

Buprenorphine acts as a partial mu-receptor agonist with high affinity and slow dissociation properties. Buprenorphine is often administered as a sublingual film (Suboxone) at 12mg. Suboxone is a combination of 2 opioids: buprenorphine and naloxone. Indication for suboxone use is the reduction of withdrawal symptoms, detoxification, and maintenance therapy for opioid-tolerant individuals. Buprenorphine should not be discontinued in the post-operative period. If stopped an “opioid debt” may occur which must be overcome with an additional opioid, increasing the risk of over-dosing or under-dosing [61]. Like methadone, buprenorphine alone is not sufficient to provide adequate analgesia and multi-modal pain regimens are encouraged [8,49,61]. The University of Kentucky Healthcare System has developed guidelines with an emphasis on continuing the home dose of buprenorphine and encouraging close follow-up with OUD providers [62].

**Naltrexone**

Naltrexone is a long-acting opioid antagonist with a high affinity for mu-receptors. Effects of naltrexone include inhibiting sedation, euphoria, and analgesia of opioids. If naltrexone use continues pre-operatively, this will likely lead to increased opioid requirements postoperatively. Oral naltrexone should be discontinued 2 to 3 days before surgery to optimize the effectiveness of postoperative opioid analgesia. Injectable naltrexone should be ceased a minimum of 4 weeks before surgical intervention [8,49]. Considerations should be made to coordinate closely with the patient's OUD provider or hospital system pain management team for post-operative management of patients with naltrexone use.

**Conclusion**

Opioid tolerance is an increasingly relevant issue facing healthcare teams today. Pain control in the opioid-tolerant patient population can often be a daunting issue for the Foot and Ankle surgeon. As such, the purpose of this article has been to present a comprehensive review of current literature regarding perioperative opioid management in this population with expert opinion from specialists at a high-volume level 1 trauma center.

Preoperative, Intraoperative, and postoperative considerations should be made with the most up-to-date evidence-based data available. Pre-operatively, physicians should be aware of the patient's risk factors for chronic opioid use. Physicians should take time to review patients' PDMP and UDS as needed. Providers should discuss goals and expectations for pain control with patients, including possible opportunity to reduce opioid use preoperatively and establishing tentative plans for postoperative analgesia. Intra-operatively, sound dialogue between the surgeon and anesthesiologist regarding opioid dosing is imperative, local and regional anesthetic blocks should be performed, and adjunctive analgesic medication should be considered. Post-operatively opioid-tolerant patients should resume preoperative dosing of opioids at a minimum, often requiring a 25-100% increase in dosing in the first 24-48 hours.

Those patients on MOUD including methadone and buprenorphine should continue these medications during the perioperative period with close coordination with other members of the patient's care team. These medications alone are not sufficient to provide adequate postoperative analgesia in opioid-tolerant patients. The addition of short acting opioids at opioid-tolerant dosing is needed to provide analgesia for acute postoperative pain. Naltrexone should be discontinued prior to surgery. A

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multimodal pain regimen in the opioid-tolerant cohort is associated with superior pain relief and decreased opioid consumption. If not previously established, these patients may benefit from pain management or addiction medicine consultation post-operatively for more comprehensive care.

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<th>Preoperatively</th>
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<tbody>
<tr>
<td>- Assess PDMP and patient’s actual usage</td>
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<td>- Urine toxicology screen can be considered for compliance with medications</td>
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<tr>
<td>- Obtain opioid exposure history and assess risk factors for opioid withdrawal</td>
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<tr>
<td>- Reduction of opioid dose as able, obtain opioid contract</td>
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<tr>
<td>- Set patient expectations for who will prescribe pain medications</td>
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<tr>
<td>- Educate patients on risks of opioid use, consider Addiction Medicine referral</td>
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<th>Day of Surgery &amp; Intraoperatively</th>
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<tr>
<td>- Provide at least 50% of baseline dose prior to OR to prevent acute withdrawal</td>
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<td>- Choice of pain management intraoperatively is at discretion of anesthesiologist</td>
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<tr>
<td>- Use of local and regional anesthesia techniques</td>
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<tr>
<td>- Consider use of single dose IV Dexamethasone</td>
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<td>- Consider use of Ketamine</td>
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<th>Postoperatively</th>
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<tr>
<td>- Should receive baseline dose opioids at minimum, consider a 25-100% increase in dosage from baseline for first 24-48 hours</td>
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<tr>
<td>- Multimodal analgesic regimen with scheduled opioid medications</td>
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<tr>
<td>• Scheduled Acetaminophen every 4 to 6 hours</td>
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<tr>
<td>• Scheduled NSAID every 4 to 6 hours</td>
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<tr>
<td>• Other considerations – Gabapentinoids, Musculoskeletal agents, Ketamine, PCA Pump, TENS unit</td>
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<tr>
<td>• Consider dosing strategy for primary, PRN, and BTP</td>
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<tr>
<td>- Continue maintenance therapy - Methadone, Buprenorphine</td>
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<tr>
<td>- Consider Pain Management/Addiction Medicine consultation</td>
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</table>

Table 2 Summary of recommendations for perioperative opioid management in the opioid tolerant patient.
References


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