Current Pain and Headache Reports (2019) 23: 49
https://doi.org/10.1007/s11916-019-0783-z

OTHER PAIN (A KAYE AND N VADIVELU, SECTION EDITORS)

Comprehensive Perioperative Management Considerations in Patients Taking Methadone

Elyse M. Cornett[1] · Ryan J. Kline[2] · Spencer L. Robichaux[3] · Jeremy B. Green[3] · Boris C. Anyama[4] · Sonja A. Gennuso[1] · Eva C. Okereke[1] · Alan D. Kaye[3]

Published online: 17 June 2019

Abstract

Purpose of Review Well-informed staff can help decrease risks and common misconceptions regarding opioid-tolerant patients, especially those taking methadone.

Recent Findings In 2015, opioid pain relievers were the second most used drug at 3.8 million. Overdose death was three times greater in 2015 than in 2000. Medication-assisted treatment was sought by more than 2 million individuals with substance use disorder, one of which is methadone.

Summary Chronic pain affects millions of adults in the USA. Opioid therapy is widely used among these adults. Related to the risk of abuse and dependence, guidelines suggest that opioid therapy may not be considered first-line treatment. A multidisciplinary approach, including thorough preoperative evaluation, the utilization of multimodal pain management strategies, and opioid-sparing techniques in both the intraoperative and postoperative periods will allow for the best possible outcome.

Keywords Methadone · Opioids · Pain · Pain management · Perioperative · Multimodal analgesia

Introduction

One hundred million adults in the USA live with chronic pain and more than 2 million individuals seek treatment for substance abuse, including opioid abuse [1]. Within this population, there are a large number of opioid-tolerant individuals (e.g., those taking methadone, buprenorphine, and naltrexone for opioid agonist therapy (OAT) methadone-maintained treatment (MMT) and treating perioperative pain in this population can be challenging from the patients' point of view and the health care providers' point of view. For example, hospital staff may misinterpret a request for pain medication as drug-seeking behavior and thus discontinue maintenance opioids during the perioperative period unnecessarily. On the other

This article is part of the Topical Collection on *Other Pain*

✉ Elyse M. Cornett
ecorne@lsuhsc.edu

Ryan J. Kline
rkline@lsuhsc.edu

Spencer L. Robichaux
srobi9@lsuhsc.edu

Jeremy B. Green
jgre21@lsuhsc.edu

Boris C. Anyama
banyama@sgu.edu

Sonja A. Gennuso
sgennu@lsuhsc.edu

Eva C. Okereke
eokere@lsuhsc.edu

Alan D. Kaye
akaye@lsuhsc.edu

[1] Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, Shreveport, LA 71103, USA

[2] Department of Anesthesiology, LSU Health Sciences Center New Orleans, Room 659, 1542 Tulane Ave, New Orleans, LA 70112, USA

[3] Department of Anesthesiology, LSU Health Sciences Center, Room 656, 1542 Tulane Ave, New Orleans, LA 70112, USA

[4] Saint George's University School of Medicine, University Centre Grenada, West Indies, Grenada

hand, health care providers who are unaware of the risks associated with opioid-tolerant patients may mistakenly give high doses of opioids without regard for cardiac, respiratory, and neurological depression, potentially causing life-threatening side effects in these patients [2–4]. Therefore, communication between all patient care staff is of the utmost importance, including incorporation of multimodal pain management strategies. These strategies include the use of non-opioid medications (NSAIDs, gabapentinoids), neuraxial or regional anesthesia, and psychological treatment, all in an effort to reduce perioperative pain and pain perception [1–4, 9].

Dependence, addiction, and abuse may be identified at any time during the perioperative period. Opioid tolerance, withdrawal, and opioid-induced hyperalgesia may occur and are complex neurobiological/physiological phenomena involving multiple cell signaling pathways. Quick recognition and appropriate treatment are especially crucial for those on long-term opioid therapy such as methadone [4, 7, 8, 10].

Cardiac, respiratory, and neurological depression associated with morphine must be closely monitored. Patients taking > 100 mg of oral morphine equivalent/day have a nine-fold increase in the risk of inadvertent overdose or adverse events compared to those patients who take < 20 mg/day. It should also be noted a single 40 mg dose of oral methadone in an opioid-naïve individual is large enough to result in death. Methadone's long plasma half-life may be the cause of these events [4, 11–14]. However, it is important to remember that all opioids are capable of causing these same adverse events, and a proper perioperative plan can decrease risk as well as decrease the patient's pain [15].

Finally, while patients treated with methadone usually need escalating doses of opioids in the perioperative period, patients treated with naltrexone (a μ-receptor antagonist) for a substance abuse disorder may have an increased sensitivity to opioid receptor agonists after discontinuing the drug, secondarily due to an upregulation of receptors in the central nervous system. However, they may have an increased requirement for opioids (e.g., on monthly intramuscular depot injections, or unable to stop for the appropriate preoperative time period related to emergency surgery) and should be carefully monitored during treatment with opioids [1, 4, 6, 7]. The focus of this chapter will be on both acute and chronic pain, methadone, and management during the perioperative period.

Pain and Addiction

Pathophysiology

The pathophysiology of addiction is complex. Current research suggests addiction results from adaptations to normal neuronal pathways that evolved to promote self-preservation through positive reinforcement of beneficial stimuli, termed reward, and negative reinforcement of detrimental stimuli termed aversion [16]. Regulation of reward and aversion is principally mediated by the opioid system in which three distinct opioid receptors (mu, kappa, and delta) act centrally to regulate hedonic tone, mood, learning, and memory. Individual endogenous opioids serve as natural ligands to specific opioid receptors; the agonism of these opioid receptors in response to a stimulus determines how that stimulus is perceived and how it is reinforced. Specifically, agonism of kappa opioid receptors (KORs) expressed in the nucleus accumbens (NAc) inhibits dopamine release to result in a dysphoric mood, and thereby negatively reinforces detrimental stimuli [17, 18]. In contrast, stimulation of mu opioid receptors (MORs) expressed on GABAergic interneurons in the ventral tegmental area (VTA), NAc, and the thalamus promotes the release of dopamine and results in euphoria, thus reinforcing beneficial stimuli [19, 20]. Although the role of delta opioid receptors (DORs) in addiction is less understood, active research into these receptors is underway. DORs are expressed throughout the addiction circuitry, and agonism of these receptors mitigates anxiety and depression; additionally, DORs also regulate learning and memory [21, 22].

Opioid receptors are also expressed outside of the addiction circuitry, while KOR and DOR receptors are expressed in various tissues and have been demonstrated to have specific analgesic properties in vivo, currently their clinical role remains unclear [23]. In contrast, MORs are expressed in peripheral tissues, spinal cord, and the brain stem. The MORs act to modulate the perception of pain and agonism of these receptors inhibits the release of substance P peripherally and inhibits both ascending and descending pain pathways of the central nervous system [24].

Substance Abuse

Substance abuse is a serious global health issue and a major health concern in the USA. The number of opioid-related deaths has almost tripled in the USA since 2005 [25–27]. Most abused opioid medications function as pure MOR agonists to mitigate the perception of pain. However, these medications also act centrally on MORs in the VTA, NAc, and thalamus stimulating the reward pathway producing euphoria, and ultimately promoting addiction and further substance abuse in certain patients [16, 28, 29]. Addiction is not an acute process, but rather develops in susceptible individuals after chronic use of opioid agonists. Chronic stimulation of MORs via exogenous opioids alters the balance of MOR, KOR, and DOR signaling through dopamine D2 receptor expression [16, 30]. Ultimately, chronic usage of opioids enhances KOR and mitigates MOR signaling leading to what has been described as a "low-reward high-aversion" state.

Opioid-Induced Hyperanalgesia

In addition to changes in the reward pathway, chronic use of exogenous opioids alters the homeostasis of nociceptive neuronal pathways leading to a phenomenon termed opioid-induced hyperanalgesia [31]. Interestingly, as seen with addiction, opioid-induced hyperanalgesia does not occur in all patients chronically treated with opioid agonists, but rather manifests only in a subset of patients implying that there is a genetic or acquired susceptibility [32, 33]. As the name implies, chronic use of opioid agonists can paradoxically lead to increased sensitivity to pain; however, the presentation of opioid-induced hyperanalgesia can vary markedly. In the mildest form, opioid-induced hyperanalgesia can present as a loss of the opioid analgesic effect due to central sensitization or the development of tolerance to a specific dosage of opioid agonist. More severe cases may present with worsening pain, which spreads diffusely to include previously unaffected areas. In extreme cases, patients can develop pain to new sources or even innocuous stimuli; however, such cases and presentation are relatively rare. The prevalence and clinical significance of opioid-induced hyperanalgesia are likely underappreciated as the presentation is difficult to distinguish from that of inadequate pain control, which could be treated by increasing the opioid dosage. While the opioid crisis has increased clinical awareness, recognition, and research efforts of opioid-induced hyperanalgesia, evidence-based treatment guidelines are still lacking [34]. Current non-evidence-based treatment strategies include switching affected patients to non-opioid pain medications, such as NSAIDS, steroids, gabapentinoids, anticonvulsants, and low-dose ketamine with clonidine [35]. Additionally, related to incomplete cross-tolerance between different opioid agonists, it is also recommended to consider an opioid rotation regimen [36, 37]. The clinical significance of opioid-induced hyperanalgesia extends beyond chronic, everyday pain and must also be considered in all aspects of the perioperative setting, as discussed in more detail below.

Acute Pain vs. Chronic Pain Treatment in the Patient Experiencing Addiction

Treatment of pain in addicted patients is often difficult and driven by individual changes in normal neuronal circuitry due to chronic usage of opioid agonists, therefore necessitating personalized treatment strategies tailored to the patient's condition. The choice of treatment strategy depends on several factors including, but not limited to, the duration, nature, and severity of the pain, as well as patient-specific comorbid disease.

Chronic pain and opioid withdrawal have been effectively treated with methadone, a long-acting MOR agonist and NMDA antagonist [38], or a newer available agent, buprenorphine, a partial MOR agonist and KOR antagonist [39]. Over the past decade, the number of people receiving methadone and buprenorphine in opioid treatment facilities has been steadily increasing, with more than 1.1 million people receiving treatment in 2016. While both methadone and buprenorphine are both potent analgesics, their duration of action in producing effective analgesia is shorter than their effective duration for preventing opioid withdrawal [40, 41]. For this reason, adjunct analgesic therapy is often needed. Another indication for adjunct analgesic therapy is the acquisition of acute pain such as in the postoperative setting. Managing acute pain in addicted patients or those receiving long-term methadone therapy is difficult as these patients exhibit varying degrees of opioid tolerance and will likely require a greater than normal dose of a short-acting opioid to relieve their pain. Additionally, NSAID or acetaminophen-opioid combination medications should be utilized, if permissible. The effective analgesic dosage will vary between patients thus necessitating careful titration under close observation to mitigate the risk of CNS or respiratory depression. Aside from the medical complications, an additional concern in treating acute pain in addicted patients with opioid agonists is the propensity to cause relapse. Interestingly, recent studies have shown that in the presence of acute pain, the euphoric effect of opioid agonists is diminished and the heightened stress state accompanying undertreated pain may actually pose a greater relapse risk in addicted patients [42]. Further clinical research is warranted to identify effective analgesic treatment strategies in addicted patients that minimize medical complications and the associated risk of relapse.

Methadone

Methadone is a unique opioid that exerts its effects across multiple receptor subtypes, making it a well-validated drug for peri- and postoperative pain control following spine [43] and cardiac surgery [44]. In addition to acute and chronic pain control, methadone is arguably most known for its use in the treatment of opioid dependence and withdrawal secondary to its long elimination half-life [45]. As the number of long-term opioid users continues to grow, physicians are presented with the difficult task of adequately, yet safely, managing the balance of acute and chronic pain control.

Methadone is a synthetic mu-opioid agonist of the diphenylpropylamine class and is structurally unrelated to morphine. Clinically, methadone is used as a racemic mixture of the R- and S- enantiomers, levomethadone and dextromethadone, respectively [45, 46]. While levomethadone is almost entirely responsible for the opioid effects, dextromethadone acts as an antagonist at NMDA receptors with little to no effect on opioid receptors. There is evidence that dextromethadone antagonism of the NMDA receptor prevents the development of opioid-related hyperalgesia that is triggered by the presence of the

levomethadone racemate [47]. Furthermore, dextromethadone also prevents the reuptake of serotonin and norepinephrine [45]. Rat models have demonstrated methadone's ability to reduce neuropathic pain secondary to NMDA antagonism [48], while others have theorized that this activity is potentially responsible for decreased opioid cravings [49, 50].

Pharmacokinetics and Pharmacodynamics

Methadone is a lipophilic drug that is most commonly administered by mouth, although parenteral forms are frequently used in the perioperative period for pain control. Methadone is well absorbed following via PO administration, with a bioavailability ranging from 36 to 100%. Onset of action is seen in as little as 30 min via the oral route, with peak plasma concentrations having a variable time course of 1 to 7.5 h. Duration of analgesia ranges from 4 to 8 h following a single dose but increases to a range of 22 to 48 h with repeated doses. Methadone has a typical half-life elimination of 8 to 59 h, although genetic variability of the CYP3A4, CYP2B6, and CYP2D6 enzymes has yielded metabolism rates ranging from 4 to 190 h [45, 46, 51].

Methadone demonstrates avid plasma protein binding (85–90%), primarily to alpha-1 acid glycoprotein. It is metabolized in the liver via N-demethylation, most notably via CYP3A4, CYP2B6, and CYP2C19, with contributions for CYP2C9 and CYP2D6, from methadone to 2-ethyl-1.5-dimethyl-3,3-diphenylpyrrolinium (EDPP) and other inactive metabolites. Because of this hepatic metabolization, there is a risk of drug accumulation in patients with hepatic impairment after multiple doses. Following hepatic biotransformation, unmetabolized methadone and its metabolites are primarily eliminated via the renal system with some contribution from fecal excretion. Because of its basic nature, the excretion of methadone is increased when urine pH is < 6 [45, 46, 51].

Adverse Drug Effects and Interactions of Methadone

Methadone's action at the opioid receptors can manifest in traditional opioid-related side effects, including respiratory depression, sedation, miosis, and constipation. Unlike more rapid onset opioids, methadone's characteristic respiratory depression does not peak until after its peak analgesic effects have passed. Similarly, its respiratory depression is additive with other substances, such as alcohol, benzodiazepines, and barbiturates, while conditions such as sleep apnea, CNS disturbances, and severe lung disease should prompt practitioners to initiate treatment in a conservative fashion [52–54].

As mentioned earlier, Methadone blocks the reuptake of serotonin and norepinephrine, and therefore can lead to serotonin syndrome if given with other serotonergic drugs such as serotonin and norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRIs), select tricyclic antidepressants (TCAs), as well as monoamine oxidase inhibitors (MAOIs) [55]. Patients taking the above medications should be monitored for signs and symptoms of serotonin syndrome including mental status changes, autonomic instability, hyperreflexia, and/or gastrointestinal symptoms.

Dextromethadone's activity at the human ether-a-go-go (hERG) receptor has been associated with the development of QT prolongation, Torsades de Point (TdP), and sudden cardiac death. A majority of cases occur in patients receiving chronic treatment with large doses, although cases have been associated with normal maintenance doses. Risk factors for the development of QT prolongation include cardiac hypertrophy, diuretic use, hypokalemia, and hypomagnesemia. Caution should be used in patients with the above risk factors or in those with a history of cardiac conduction abnormalities [55]. The American Pain Society and Heart Rhythm Society recommend baseline EKGs in patients with the following risk factors: age > 68, female gender, history of liver disease, history of electrolyte abnormalities, structural heart disease, genetic predisposition, concomitant use of QT-prolonging drugs, or previous history of syncope. Intermittent EKGs should be monitored with continued use, as well as with increasing doses [50, 54].

While single perioperative doses of methadone are a long-validated treatment for postoperative analgesia with a relatively safe side effect profile, it is important to consider consulting with a pharmacist or physician experienced in the management of methadone if dealing with a patient on chronic methadone for maintenance. As previously discussed, methadone is subject to numerous drug interactions, particularly other drugs associated with QT prolongation, as well as drugs that can potentially affect the metabolism of methadone [4, 46, 55]. Table 1 lists medications that increase the risk of QT prolongation and TdP with methadone. Table 2 lists select drugs that may increase methadone levels (adapted from [45, 55]).

Methadone and the Perioperative Setting

Preoperative

Methadone is advised to be continued on the day of surgery as well as post-op, with exceptions based upon surgical indication. For example, if NPO status is indicated, alternative analgesic therapies should be considered (e.g., PCA) with normal methadone dose being resumed PO as soon as possible thereafter [11]. During preoperative evaluation and planning of anesthesia in a patient undergoing methadone therapy, it is recommended to develop a clear line of communication with the patient to facilitate the treatment process. Provider reviewing of old patient records for previous surgeries and information about particular analgesia and dosage is warranted, as well as a urine drug screen, complete blood count, ECG,

Table 1 Medications that increase the risk of QT prolongation and TdP with methadone

Substantial risk	Reported risk
Amiodarone	Atazanavir
Azithromycin	Doxepin
Ciprofloxacin	Cotrimoxazole
Clarithromycin	Itraconazole
Erythromycin	Voriconazole
Fluconazole	Ritonavir
Levofloxacin	Quetiapine
Chlorpromazine	Furosemide
Citalopram	Protamine
Cocaine	
Droperidol	
Haloperidol	
Escitalopram	
Fluoxetine	
Sertraline	
Ondansetron	

LFTs, and renal function tests may also be indicated based upon provider assessed concern of polydrug abuse. Continuation of methadone maintenance dose is advised both before and on the day of surgery to prevent unnecessary serum drug level fluctuations. Additionally, a detailed history of methadone dose, frequency of dosage, and time since most recent dose should be gathered in attempts to assess the level of opioid tolerance. In those patients receiving IV administration of methadone, PO doses exceeding 200 mg per day, and concurrent medications that may lead to QT prolongation, the anesthetist should be aware of the possibility of further QT prolongation and development of Torsades de pointes. Such concurrent medications that may further prolong the QT interval include chlorpromazine, clarithromycin, disopyramide, erythromycin, haloperidol, and amiodarone. In such specific patient subsets, a preoperative ECG is indicated [11].

Table 2 Select drugs that may increase methadone levels

Amiodarone	Cimetidine	Ritonavir
Diltiazem	Esomeprazole	Efavirenz
Verapamil	Omeprazole	Modafinil
Nifedipine	Pantoprazole	Nelfinavir
Clopidogrel	Ciprofloxacin	Nevirapine
Ticlopidine	Clarithromycin	Rifampin
Amitriptyline	Erythromycin	Rifabutin
Citalopram	Fluconazole	Phenytoin
Escitalopram	Itraconazole	Carbamazepine
Fluoxetine	Ketoconazole	Phenobarbital
Sertraline	Isoniazid	St. John's wort
Paroxetine	Alprazolam	Estradiol
Bupropion	Diazepam	
Duloxetine	Midazolam	
Diazepam	Doxorubicin	
Haloperidol	Imatinib	
Celecoxib	Diphenhydramine	
Cannabinoids		

Intraoperative

Achieving effective analgesia while also preventing intoxication and withdrawal is extremely important. Anesthetic agents must be titrated accordingly depending upon specific patient needs, with the majority of patients on concurrent methadone therapy requiring greater than normal doses for successful induction and maintenance [56]. Nutritional deficiencies may be especially present in this patient population which may subsequently result in hypoproteinemia, indirectly increasing the free-fraction of protein bound drugs. In those patients with a history of opioid addiction on methadone therapy, non-opioid-based anesthesia is preferred, with treatment regimens consisting of ketamine, volatile anesthetics, paracetamol, NSAIDs, COX-2 inhibitors, and benzodiazepines with particular caution as discussed above. If it is decided that an opioid-based regimen is needed, particular opioid dose requirements may need to be increased, ranging from 50 to 100% based upon the patient. It must be noted that in patients having undergone successful opioid withdrawal and abstinence, the use of opioid therapy in the anesthesia regimen may result in delayed emergence and prolonged respiratory depression while conversely, inadequate analgesia in the same patient could result in reactivation of addiction in those previously abstinent. A remifentanil infusion has been noted to be beneficial if opioid therapy is used based upon its short duration and favorable safety profile. Avoidance of mixed opioid agonist–antagonists is preferable when patients are on a concurrent opioid withdrawal therapy [56].

Postoperative

During the post-op period, the maintenance methadone dose should be continued. As such, alternative opioids are used for acute pain control as deemed necessary and continuously tapered thereafter. Using regional anesthesia when possible offers an ideal route for pain control in patients that are concurrently on methadone therapy, but patients may also continue to have high pain scores despite alternative analgesia modalities. Within this patient population, immediate-release short-acting opioids should be used sparingly, with extended-release formulations preferred in those who are considered opioid-tolerant or opioid "adjusted." Once discharged from the hospital, these patients will require close follow-up, especially so if requiring high doses of long-acting opioids for analgesia. It should be noted that preadmission and preoperative

maintenance doses of methadone provide no analgesia for relief in an acute pain setting and may also lead to a decrease in pain threshold. Healthcare providers should keep this in mind when managing opioid-responsive pain as indicated by the extent of the surgical procedure for each respective patient as clinically necessary [11]. In patients with preexisting opioid tolerance, the addition of a background infusion is typically necessary. This brings up the issue of "opioid debt" when considering the addition of an infusion to management postoperative and acute pain. In those patients who routinely use opioids, a tolerance is typically developed, and such patients are deemed to be "opioid-tolerant." The concept of "opioid debt" refers to the dosage of opioid per day being inadequate to achieve normalized, prehospitalization serum drug level that the patient is adjusted to. This concept becomes crucial when serum opioid levels become low enough such that early and subsequent late withdrawal occurs, and in opioid-tolerant patients on a high dosage therapy plan, the addition of a background infusion should be considered. Such addition of PCA in such patients maintains an adequate level of analgesia but should not be used to establish initial intended analgesia [57]. In the opioid-tolerant patient, it has been proposed that opioid loading while in the operating room during emergence is beneficial, using agents such as morphine up to 20 mg IV. Those patients who are undergoing major surgical procedures are routinely administered ketamine, shown to be beneficial both in the reduction of opioid tolerance levels and improved postoperative pain control. IV methadone for continued analgesia should be avoided due to concerns of QT interval prolongation as previously mentioned as well as serum drug accumulation with repeated doses [58].

Acute Management Plan

In those patients with continued opioid tolerance and among those on concurrent methadone therapy, multimodal forms of analgesia for acute postoperative pain is strongly supported, in part based upon the theory that use of combinations of analgesic agents are acting at different target sites in various pathways, subsequently reducing total opioid requirements. Specific concerns when treating patients for acute pain who are undergoing methadone therapy include prolonged QT interval, as mentioned above, increased somnolence, fever, shock, or overlying medical conditions that may affect hemodynamic stability, and thus, methadone dosage should be decreased or held accordingly. The anesthetist should be knowledgeable that among those receiving methadone therapy, the need for additional opioids at higher dosages and at a greater frequency than those not receiving methadone is often present [14].

Opioid-Sparing Techniques

Recent recommendations promote the use of paracetamol, NSAIDs, or COX-2 inhibitors unless specifically clinically contraindicated. Additionally, ketamine is gaining popularity in acute pain management of opioid-tolerant patients and those undergoing methadone therapy. Specifically, administering the drug in a low dose as a continuous IV infusion or subcutaneous infusion for 1–3 days can be quite useful as a drug adjunct. The use of gabapentinoids has become more prevalent as well, specifically during surgery recovery periods. Lastly, the use of local anesthetic interventions including wound infiltration or regional or neuroaxial blocking should be used when possible to enhance analgesia vs. adding additional opioid therapies [4] [59]. As more and more patients are placed on methadone therapy, it becomes crucial for the anesthesiologist to be knowledgeable about pre and postoperative treatment algorithms as well as distinct drug interactions in attempts to optimize patient care and enhance their recovery.

Multimodal Analgesia

Multimodal analgesia refers to the combination of different pharmacologic drugs and interventions, which can provide additive or synergistic effects that can be used to treat pain in the perioperative period. This combination of different pharmacological drugs can be a mainstay for any patient undergoing surgery, especially patients with opioid tolerance and dependence or patients that are currently on methadone therapy. Multimodal analgesia aims to target various pain receptors throughout the body to help combat the perception of pain. Multimodal analgesia also reduces postoperative opioid analgesic requirements, which ultimately reduces associated side effects of opioid cnsumption. The decreased use of opioids can help to combat the emerging opioid crisis that we are currently facing. Additionally, multimodal analgesia for patients on current methadone therapy can help reduce the risk of opioid overdose or opioid withdrawal. Opioids in general, including methadone, have various adverse events that are associated with their administration such as opioid induced ventilatory impairment [60]. By targeting various non-opioid pain receptors, these adverse events can be decreased or even eliminated.

Useful Agents in Multimodal Analgesia

There are a variety of pharmacologic agents, including opioids, that can be used to target various pain receptors when practicing multimodal analgesia. Acetaminophen is thought to work by targeting prostaglandin concentrations in the brain, although its exact mechanism of action is unknown. Prostaglandins are known for causing inflammation and

swelling. Therefore, by decreasing prostaglandin concentrations, the pain threshold is relatively increased. NSAIDS also have an effect on prostaglandin synthesis as well. NSAIDS exert their effects by decreasing peripheral prostaglandin synthesis and inhibiting cyclo-oxygenase enzymes, which lead to decreased cell inflammation and ultimately translate to less pain. NMDA receptor antagonists can also be used for the treatment of pain. Ketamine is an NMDA receptor antagonist. NMDA receptors are located in both the peripheral and central nervous systems and are thought to play a role in the development of the "wind up" phenomenon. An NMDA receptor antagonist such as ketamine acts to block this central sensitization that can occur and thus preventing the central sensitization that can lead to hyperalgesia and allodynia [61]. Patients that are on chronic opioids including methadone therapy can have neuronal changes in the nervous system that is similar to this phenomenon, and NMDA receptors antagonists can be very helpful for this reason.

Gabapentinoids act on the presynaptic calcium channels that inhibit calcium channel influx resulting in a decreased release of excitatory neurotransmitters. They are also useful in decreasing and even preventing the central sensitization that can occur resulting in further hyperalgesia and allodynia. Patients that receive gabapentinoids tend to have better postoperative pain management in general. A single preoperative dose of gabapentinoids has been shown to decrease perioperative opioid consumption by up to 30 mg of morphine equivalents in the first 24 h of surgery [62]. This could potentially result in less opioid-induced complications.

Local anesthetics are another group of drugs that can be useful in multimodal analgesia. Typically, local anesthetics can be used in infiltration for central neuraxial and peripheral nerve blocks. The use of central and peripheral nerve blocks either by a single shot or continuous technique should be considered if it is a possibility and the patient has no contraindications to procedure [63]. Intravenous lidocaine, however, has been shown to have some anti-inflammatory, antihyperalgesia, and analgesic properties when given by this route. This is thought to occur by inhibition of sodium channels, NMDA receptors, and G protein-coupled receptors [61]. Infusions are useful in abdominal procedures because they decrease the duration of postoperative bowel dysfunction.

Alpha-2 adrenergic receptor agonists are useful for the control of pain because activation of these receptors presynaptically can inhibit the release of norepinephrine and activation postsynpatically inhibits sympathetic activity. These drugs exert their action on supraspinal, spinal, and peripheral receptors resulting in a decrease of pain intensity and opioid medication administration. Clonidine and dexmedetomidine are that two commonly used drugs in this class. The administration of non-opioid adjuncts and regional anesthesia to patients on methadone therapy could help to reduce postoperative opioid consumption and opioid related side effects [61].

Prevention of Withdrawal and Conversion from IV to Oral Opioid

Opioid withdrawal is typically manifested as an intense desire and craving for opioids followed by physical symptoms. Although these physical symptoms are nonlife-threatening, they can be rather unpleasant. Symptoms of opioid withdrawal include, but are not limited to irritability, abdominal discomfort, nausea, vomiting, diarrhea, sweating, fever, and insomnia. Prevention of withdrawal is an important practice for patients on chronic opioid or methadone therapy. Methadone has a long half-life (ranging from 8 to 60 h), but the analgesic effect of methadone only last for about 6–8 h [11]. Because of methadone's long half-life, patients who do not receive their medication for a few days are unlikely to experience withdrawal. Rather, they will need to receive some sort of alternate analgesia. It is recommended that patients continue their methadone therapy during the postoperative period as soon as they are able to tolerate oral intake. If patients are going to have nothing in their mouth for 48 h, some sort of alternative intravenous opioid may be needed. As the patient's situation improves, and they later become able to tolerate oral opioids, conversion to oral opioids should be undertaken as oral can be continued in the outpatient postoperative period if needed. When converting from intravenous opioids to oral opioids, a rule of thumb is 60 mg of IV morphine equivalents given over 24 h is equal to approximately 150 mg equivalents of oral morphine equivalent. Additionally, some physicians suggest 50% of this calculated dose as a sustained release oral medication (morphine sulfate) twice a day and then one sixth of the total calculated dose as an immediate release formulation every 4 h as needed [4].

Opioid Rotation

When a patient develops intolerable side effects due to a certain opioid medication, an opioid rotation can be utilized. Opioid rotation refers to switching from one opioid to another, and this method is useful if a patient is no longer responding to a particular opioid's analgesic effects or if the patient is having some side effect from a particular opioid that is no longer tolerable, such as nausea or puritis. Sometimes a patient can develop tolerance to the analgesic part of the opioid, but not to the side effects, even with increasing doses. If this happens, opioid rotation can be used to reduce the side effects and improve analgesia since some patients respond differently to different opioids due to incomplete cross-tolerance [4, 64].

Conclusion

Opioid-tolerant patients present a challenge in the perioperative period for pain control, and those taking methadone have

their own set of challenges that must be met. Patients taking methadone, as well as buprenorphine and naltrexone, may have a history of chronic pain and addiction, and may further have complex neurobiological alterations including opioid tolerance, opioid-induced hyperalgesia, substance abuse, and withdrawal. A multidisciplinary approach, including thorough preoperative evaluation, the utilization of multimodal pain management strategies, and opioid-sparing techniques in both the intraoperative and postoperative periods, will allow for the best possible outcome. Those providing pain management to patients taking methadone must be aware of its complex pharmacodynamics and pharmacokinetics, of its interaction with other drugs, and its well-documented cardiorespiratory risks, taking those factors into account when providing care in the perioperative period. Again, providing care in the perioperative period to patients taking methadone can be complex, but a well-informed anesthesia provider can allow for the best possible outcome.

Compliance with Ethical Standards

Conflict of Interest Elyse M. Cornett, Ryan J. Kline, Spencer L. Robichaux, Jeremy B. Green, Boris C. Anyama, Sonja A. Gennuso, and Eva C. Okereke declare no conflict of interest. Alan D. Kaye serves on the Speakers Bureau of Depomed and Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Cooney MF, Fnp-Bc K, Broglio A-B. Acute pain management in opioid-tolerant individuals. TJNP J Nurse Pract. 2017;13:394–9.
2. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. United States: NIH public Access. 2006;144:127–34.
3. Hines S, Theodorou S, Williamson A, Fong D, Curry K. Management of acute pain in methadone maintenance therapy inpatients. Drug Alcohol Rev Wiley/Blackwell (10.1111). 2008;27:519–23.
4. Simpson G, Jackson M. Perioperative management of opioid-tolerant patients. BJA Educ Oxford University Press. 2017;17:124–8.
5. Harrison TK, Kornfeld H, Aggarwal AK, Lembke A. Perioperative considerations for the patient with opioid use disorder on buprenorphine, methadone, or naltrexone maintenance therapy. Anesthesiol Clin Elsevier. 2018;36:345–59.
6. Boer ME. Perioperative pain management in patients on opioid replacement therapy: an integrative review. 2017.
7. Coluzzi F, Bifulco F, Cuomo A, Dauri M, Leonardi C, Melotti RM, et al. The challenge of perioperative pain management in opioid-tolerant patients. Ther Clin Risk Manag Dove Press. 2017;13:1163–73.
8. Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE. Acute pain management in opioid-tolerant patients: a growing challenge. Anaesth Intensive Care. 2011;39:804–23.
9. Kumar K, Kirksey MA, Duong S, Wu CL. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. Anesth Analg United States. 2017;125:1749–60.
10. American Society of Anesthesiologists, Sinatra RS, Mitra S, Raymond S. Perioperative management of acute pain in the opioid-dependent patient. Anesthesiology [American Society of Anesthesiologists, etc]. 2004;101:212–27.
11. Peng PWH, Tumber PS, Gourlay D. Review article: Perioperative pain management of patients on methadone therapy. Can J Anesth. 2005;52:513–23.
12. Faul M, Bohm M, Alexander C. Methadone prescribing and overdose and the association with Medicaid preferred drug list policies — United States, 2007–2014. MMWR Morb Mortal Wkly Rep. 2017;66:320–3.
13. Brown R, Kraus C, Fleming M. Methadone: applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med J. 2004;80:654–9.
14. Bryson EO. The perioperative management of patients maintained on medications used to manage opioid addiction. Curr Opin Anaesthesiol. 2014;27:359–64.
15. Krebs EE, Becker WC, Zerzan J, Bair MJ, McCoy K, Hui S. Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain. 2011;152:1789–95.
16. Koob GF, Buck CL, Cohen A, Edwards S, Park PE, Schlosburg JE, et al. Addiction as a stress surfeit disorder. Neuropharmacology. 2014;76:370–82.
17. Ranganathan M, Schnakenberg A, Skosnik PD, Cohen BM, Pittman B, Sewell RA, et al. Dose-related behavioral, subjective, endocrine, and psychophysiological effects of the κ opioid agonist salvinorin a in humans. Biol Psychiatry. 2012;72:871–9.
18. Bruchas MR, Land BB, Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res. 2010;1314:44–55.
19. Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J Neurosci. 1992;12:483–8.
20. Fields HL, Margolis EB. Understanding opioid reward. Trends Neurosci. 2015;38:217–25.
21. Chu Sin Chung P, Kieffer BL. Delta opioid receptors in brain function and diseases. Pharmacol Ther. 2013;140:112–20.
22. Pellissier LP, Pujol CN, Becker JAJ, Le Merrer J. Delta Opioid Receptors: learning and motivation. Handb Exp Pharmacol 2016.
23. Iwaszkiewicz KS, Schneider JJ, Hua S. Targeting peripheral opioid receptors to promote analgesic and anti-inflammatory actions. Front Pharmacol. 2013;4:132.
24. Kanjhan R. Opioids and pain. Clin Exp Pharmacol Physiol. 1995;22:397–403.
25. Vadivelu N, Kai AM, Kodumudi V, Sramcik J, Kaye AD. The opioid crisis: a comprehensive overview. Curr Pain Headache Rep. 2018;22:16.
26. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A brief history of the opioid epidemic and strategies for pain medicine. Pain Ther. 2018;7:13–21.
27. Theisen K, Jacobs B, Macleod L, Davies B. The United States opioid epidemic: a review of the surgeon's contribution to it and health policy initiatives. BJU Int. 2018;122:754–9.
28. Manhapra A, Becker WC. Pain and addiction. Med Clin North Am. 2018;102:745–63.
29. Kaye AD, Jones MR, Kaye AM, Ripoll JG, Galan V, Beakley BD, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. Pain Physician [Internet]. 2017 [cited 2018 Mar 14];20:S93–109. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28226333
30. Williams JT, Ingram SL, Henderson G, Chavkin C, von Zastrow M, Schulz S, et al. Regulation of -opioid receptors: desensitization,

phosphorylation, internalization, and tolerance. Pharmacol Rev. 2013;65:223–54.
31. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 14:145–61.
32. CHU L, CLARK D, ANGST M. Opioid tolerance and hyperalgesia in chronic pain patients after one month of Oral morphine therapy: a preliminary prospective study. J Pain. 2006;7:43–8.
33. Rosenblum A, Joseph H, Fong C, Kipnis S, Cleland C, Portenoy RK. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. JAMA. 2003;289:2370–8.
34. Arout CA, Edens E, Petrakis IL, Sofuoglu M. Targeting opioid-induced hyperalgesia in clinical treatment: neurobiological considerations. CNS Drugs. 2015;29:465–86.
35. Kaye AD, Cornett EM, Hart B, Patil S, Pham A, Spalitta M, et al. Novel pharmacological nonopioid therapies in chronic pain. Curr Pain Headache Rep. 2018;22:31.
36. Induru RR, Davis MP. Buprenorphine for neuropathic pain—targeting hyperalgesia. Am J Hosp Palliat Med. 2009;26:470–3.
37. Mercadante S, Portenoy RK. Opioid poorly-responsive cancer pain. Part 2: basic mechanisms that could shift dose response for analgesia. J Pain Symptom Manag. 2001;21:255–64.
38. Anderson IB, Kearney TE. Use of methadone. West J Med. 2000;172:43–6.
39. Welsh C, Valadez-Meltzer A. Buprenorphine: a (relatively) new treatment for opioid dependence. Psychiatry (Edgmont). 2005;2:29–39.
40. Fishman SM, Wilsey B, Mahajan G, Molina P. Methadone reincarnated: novel clinical applications with related concerns. Pain Med. 2002;3:339–48.
41. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. J Pain Symptom Manag. 2005;29:297–326.
42. Karasz A, Zallman L, Berg K, Gourevitch M, Selwyn P, Arnstein J, et al. The experience of chronic severe pain in patients undergoing methadone maintenance treatment. J Pain Symptom Manag. 2004;28:517–25.
43. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Deshur MA, et al. Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery. Anesthesiology. 2017;126:822–33.
44. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Shear T, et al. Intraoperative methadone for the prevention of postoperative pain. Anesthesiology. 2015;122:1112–22.
45. Sunilkumar M, Lockman K. Practical pharmacology of methadone: a long-acting opioid. Indian J Palliat Care. 2018;24:10.
46. Eap CB, Buclin T, Baumann P. Interindividual variability of the clinical pharmacokinetics of methadone. Clin Pharmacokinet. 2002;41:1153–93.
47. Salpeter SR, Buckley JS, Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. J Palliat Med. 2013;16:616–22.
48. Sotgiu ML, Valente M, Storchi R, Caramenti G, Biella GEM. Cooperative N-methyl-d-aspartate (NMDA) receptor antagonism and μ-opioid receptor agonism mediate the methadone inhibition of the spinal neuron pain-related hyperactivity in a rat model of neuropathic pain. Pharmacol Res. 2009;60:284–90.
49. Vetulani J. Drug addiction. Part III. Pharmacotherapy of addiction. Pol J Pharmacol. 53:415–34.
50. Wiles JR, Isemann B, Mizuno T, Tabangin ME, Ward LP, Akinbi H, et al. Pharmacokinetics of oral methadone in the treatment of neonatal abstinence syndrome: a pilot study. J Pediatr. 2015;167:1214–1220.e3.
51. Davis MP, Walsh D. Methadone for relief of cancer pain: a review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. Support Care Cancer. 2001;9:73–83.
52. Kampman K, Jarvis M. American Society of Addiction Medicine (ASAM) National Practice Guideline for the use of medications in the treatment of addiction involving opioid use. J Addict Med. 2015;9:358–67.
53. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain — United States, 2016. MMWR Recomm Reports. 2016;65:1–49.
54. Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, et al. Methadone safety: a clinical practice guideline from the American pain society and college on problems of drug dependence, in collaboration with the Heart Rhythm Society. J Pain. 2014;15:321–37.
55. Volpe DA, Xu Y, Sahajwalla CG, Younis IR, Patel V. Methadone metabolism and drug-drug interactions: in vitro and in vivo literature Review. J Pharm Sci. 2018;107:2983–91.
56. Review M, Garg R, Hariharan UR. Concerns of addiction to anaesthesiologists in the perioperative period. 2015;2:9–11.
57. Macintyre PE. Safety and efficacy of patient-controlled analgesia. 2001;87.
58. Weinbroum AA. A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg. 2003;96:789–95.
59. Macintyre P, Scott D, Schug S. Acute pain management: scientific evidence. 2010.
60. Greenberg S. Opioid-induced ventilatory impairment: an ongoing APSF initiative - Anesthesia Patient Safety Foundation. Anesth Patient Saf Found Newsl.
61. Ramaswamy S, Wilson JA, Colvin L. Non-opioid-based adjuvant analgesia in perioperative care. Contin Educ Anaesth Crit Care Pain Oxford University Press. 2013;13:152–7.
62. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg. 2007;104:1545–56.
63. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain. 2016;17:131–57.
64. de Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation for toxicity reduction in terminal cancer patients. J Pain Symptom Manage Elsevier. 1995;10:378–84.