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Perioperative Management Considerations for Patients on Methadone and Buprenorphine

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Abstract

A 52-year-old female with a history of chronic pain and methadone therapy was scheduled for spinal cord stimulator removal. Patients with chronic pain or opioid use disorders (OUD) are often managed with prescriptions or medication-assisted treatments (MAT) involving methadone and buprenorphine. Existing case studies, expert opinions, and clinical practice advisories recommend continuation of methadone and buprenorphine perioperatively to avoid regimen disruptions and drug level fluctuations. Most recommendations are also in agreement for providers to implement multimodal analgesia and incorporate regional/neuraxial anesthesia when appropriate. Abrupt discontinuation of methadone can result in opioid withdrawal or place the patient at risk for relapse. Buprenorphine is a partial μOR agonist with high receptor binding affinity and slow dissociation properties. Perioperative buprenorphine management varies widely, but many guidelines and protocols recommend continuing buprenorphine preoperatively.

INTRODUCTION

One hundred million people in the United States live with chronic pain and around two million people suffer from substance abuse disorder related to opioids and heroin.[1-3] Deaths due to drug overdose have increased four-fold between 1999 and 2017.[4] Many patients undergoing surgery and anesthesia have chronic pain or OUD, requiring providers to understand and address the complexity of medications such as methadone and buprenorphine. Lack of awareness and ineffective pain management for these patients can result in higher opioid use from inadequate pain control, exacerbation of withdrawal or relapse, and increased risk of cardiac, respiratory, and neurological depression.[1-9]

CASE SUMMARY

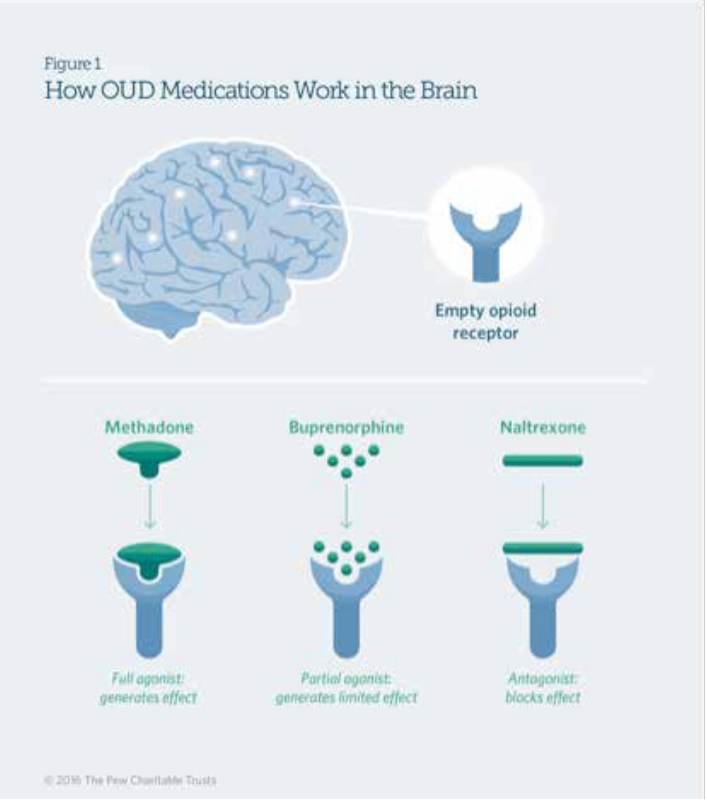
A 52-year-old, 146 kg, 167 cm, female presented for spinal cord stimulator removal. The patient's past medical history included asthma, mitral valve prolapse without any current issues or symptoms, arthritis, obesity with a body mass index (BMI) of 52, depression, anxiety, and chronic pain. The patient's past surgical history included stomach surgery, gallbladder surgery, abdominal hysterectomy, tubal ligation, right knee surgery, nerve anastomosis of left arm, and spinal cord stimulator placement. In 2010 the patient was shot multiple times in the left arm and right knee, which led to chronic pain and placement of spinal cord stimulator for pain management in 2014. The patient denied any previous complications with anesthesia. An anesthetic record from 2017 had noted the patient to be a difficult airway. Intubation was obtained after three attempts, with successful placement of endotracheal tube facilitated by utilization of Glidescope video laryngoscopy, cricoid pressure, and Eschmann tracheal tube introducer. Her outpatient medication list included albuterol, alprazolam, gabapentin, methadone, venlafaxine, cyclobenzaprine, and topiramate. Allergies to erythromycin and penicillin, which both cause respiratory distress for the patient, were reviewed and confirmed. Laboratory results from pre-surgery testing were unremarkable. Pre-anesthetic evaluation was performed, and the patient reported to have discontinued methadone intake about 6 months ago. The patient was classified as physical status III. Upon arrival to the operating room, the patient maintained supine position on stretcher. Physiologic monitors were applied, including pulse oximeter, noninvasive blood pressure (BP) cuff, electrocardiogram (ECG) monitoring, and capnography. Pre-induction vital signs were heart rate (HR) 76 beats per minute, BP 165/71 mm Hg, oxygen saturation (SpO_2)100%, respiratory rate of 13, and temperature of 36.2°C. The patient was preoxygenated via face mask with 100% FiO_2 at 15 L/min. Induction was initiated once patient's end-tidal oxygen concentration levels were above 85%. General anesthesia was induced intravenously with fentanyl 100 mcg, lidocaine 50 mg, propofol 200 mg, rocuronium 50 mg, and ketamine 30 mg. Due to a previous anesthesia record from 2017 indicating difficult airway, Glidescope video laryngoscopy was utilized, grade I view of vocal cords was obtained, and the airway was secured with a 7.0 mm endotracheal tube. Placement confirmation was verified through bilateral breath sounds, positive end tidal carbon dioxide capnography waveform, and symmetrical chest wall movement. Sevoflurane 0.6-2.1% was used as anesthetic maintenance agent with oxygen at 1 L/min and air at 1 L/min. Initial vital signs post-intubation was HR of 106 beats per min, BP of 162/134, SpO_2 of 100%. Patient was then placed in prone position on a Wilson frame for surgery.

Local anesthesia infiltration was performed by surgical team with wound closure. Patient was repositioned to supine position on the stretcher. Intravenous medications including ketamine 20 mg, ondansetron 4 mg, methocarbamol 1 g, neostigmine 3 mg, and glycopyrrolate 0.4 mg were administered during emergence of anesthesia. Train-of-four monitor revealed 4/4 twitches with sustained tetany for 5 seconds. Spontaneous respirations and adequate tidal volumes were maintained. After oropharyngeal suctioning and extubation criteria were met, the endotracheal tube was removed. Oxygen at 4 L/min via facemask was applied as patient was transported to post-anesthesia care unit (PACU). Post-procedure vital signs were HR 75 beats per minute, BP 140/70 mm Hg, SpO_2 100%, respiratory rate of 16, and temperature of 36.1°C. No anesthesia or surgical complications were noted. Patient was discharged from PACU within the same day.

DISCUSSION

The opioid abuse pandemic and increasing numbers of patients with chronic pain presents a multitude of challenges perioperatively and little has been studied to provide high quality evidence as guidance to optimal pain management.[1-6] Patients with chronic pain or OUD are vulnerable and at risk for ineffective pain management, marginalization, opioid withdrawal, and relapse. Existing MAT for chronic pain or OUD involves opioid agonists such as methadone, partial agonists such as buprenorphine, or antagonists such as naloxone. Methadone, buprenorphine, and naloxone will complicate the patient's care perioperatively, due to their pharmacological profile and interpatient variabilities.[1-10]

Figure 1. Effect of OUD medications on opioid receptors[15]



Pharmacology of Methadone

Methadone, a synthetic opioid, is a racemic mixture of the R-methadone and S-methadone enantiomer. R-methadone enantiomer is a full μOR agonist, while the S-methadone enantiomer is an N-methyl-D-aspartate (NMDA) antagonist and prevents serotonin and norepinephrine reuptake.[1,2,4-7] Recent studies suggest that methadone has a higher potency than previously reported, with a median conversion ratio of methadone to morphine of about 7.75 to 1.[7] Administration of methadone orally reaches peak plasma drug concentration between two to three hours, with an average half-life of 23 hours.[6] The biphasic pattern of elimination observed in methadone is the reason for its effectiveness

in MAT for chronic pain or OUD. The alpha-elimination phase of methadone correlates with its duration of analgesia, which is between 6 to 12 hours. The beta-elimination phase lasts between 30 to 60 hours with sub-analgesic effects, which is sufficient in preventing withdrawal symptoms.[7] Pain management providers often prescribe methadone to be taken three to four times daily in correspondence to its analgesic and elimination properties.[4-8] Methadone is commonly prescribed for patients that abuse heroin due to its μOR affinity and prolonged half-life. Therefore, chronic methadone can attenuate the euphoric effects from heroin to decrease dependence and abuse. Methadone has also been utilized in acute pain management in anticipation of significant postoperative pain.[4,6]

Perioperative Management of Patients on Methadone

The pharmacological profile of methadone including its potent analgesic effects and extensive half-life are important factors to consider perioperatively.[1,2,4-7] Life threatening complications such as accumulated toxicity, opioid withdrawal, and overdose can occur in terms of methadone abuse or inadequate management.[7] Current literature reports a single 40 mg dose of oral methadone could result in death, especially in opioid naïve patients. Therefore, providers will also need to be aware of an increased risk of cardiac, respiratory, and neurological depression in patients that are receiving opioids.[1] It is imperative to perform a thorough preoperative assessment to gather information on the patient's history of methadone therapy. Details of methadone dosing, level of compliance, and patient's previous experiences with anesthesia are all necessary information to form an anesthetic plan.[1,2,4-7] Patients that are diverting their methadone or ingesting other illicit drugs may require further testing such as urine drug screen, electrocardiogram, and liver and renal function tests.[5,7]

Current recommendations advise patients on methadone to adhere to their regimen and continue their normal dose on the day of their surgical procedure.[1,2,4-7] Patient compliance prevents drug level fluctuations and possible withdrawals.[5,7] Prescribed daily dose of methadone is inadequate in managing acute pain, therefore providers should consider multimodal pain management strategies.[1,2,4-7] Opioid-free anesthesia is preferred especially in patients with a history of opioid addiction.[1] Consider incorporating agents such as volatile anesthetics, ketamine, benzodiazepines, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, alpha-2 adrenergic receptor agonists, local anesthetics, and regional/neuraxial anesthesia.[1,2,6,7] There is a lack of research and data on the preferred opioid of choice in treating patients with chronic pain or OUD. The goals of administering subanesthetic doses of ketamine, wound infiltration with local anesthesia, and other nonopioid interventions are to decrease opioid requirements while improving pain scores.[11]

Postoperatively, patient's maintenance methadone dose should be continued as soon as possible.[1,2,4-7] If opioids are required for breakthrough pain, some articles recommend short-acting opioids.[1,2] Studies have reported opioid-dependent patients require four times more narcotics than opioid naïve patients.[11] In anticipation of moderate to severe pain postoperatively, patient controlled analgesia (PCA) may be appropriate.[1,6] Lastly, it is important to note that partial opioid agonists such as buprenorphine and butorphanol will precipitate withdrawal symptoms and should be avoided.[2]

The patient presented in the case study had a history of methadone consumption due to chronic pain that resulted from gunshot inflicted tissue and nerve damage on her left arm. Although the patient reported discontinuing methadone therapy, multimodal analgesia and administration of short-acting opioids were still implemented. Local anesthesia was also applied by the surgical team intraoperatively. The patient had minimal to no pain in PACU and was discharged within the same day.

Pharmacology of Buprenorphine

Buprenorphine is another common medication approved by the U.S. Food and Drug Administration (FDA) for chronic pain or OUD. Buprenorphine has unique pharmacological features as a partial agonist at the μOR and an antagonist of the kappa opioid receptors.[3-6] As a partial agonist, buprenorphine has a ceiling effect that minimizes additional opioid effects despite repeated or increased dosing.[2-4,8-10] Due to the ceiling effect, buprenorphine causes less respiratory depression and has a lower abuse potential compared to methadone.[2-4,6-9] Despite being a partial agonist, buprenorphine has a high affinity for the μOR, therefore it will compete with and displace other full opioid agonists.[2,3,8-10] Buprenorphine is an effective treatment for OUD as it relieves withdrawal symptoms through its partial opioid agonist effects if the μOR were not occupied. If buprenorphine is administered or ingested during an euphoric state under the influence of full agonists such as heroin or other opioids, buprenorphine will displace the full agonist and trigger precipitated withdrawal due to a decrease in agonist effect.[2,8,9]

Buprenorphine is available through various routes including sublingual, buccal, transdermal, and injectable formulations.[2,4,9] Buprenorphine can be administered alone or in combination with an opioid antagonist such as naloxone. The combination of buprenorphine and naloxone decreases the abuse potential due to their bioavailability when administered sublingually compared to parentally. Sublingually, buprenorphine has a high bioavailability as it avoids first pass metabolism while naloxone is poorly absorbed. If the combination of the two drugs are injected parenterally, both agents are highly bioavailable which allows naloxone to become active and counteract the euphoric effects.[2-4,6,8,9]

Buprenorphine and Mu Opioid Receptor Affinities

Buprenorphine has features such as high μOR affinity, slow dissociation from the receptor, and prolonged duration with a half-life of 25-60 hours.[2,4,10] The majority of opioid analgesic and anesthetic agents bind to the μOR, which causes supraspinal analgesia. Additionally, μOR agonists are responsible for euphoric effects, sedation, respiratory depression, decreased intestinal motility, and physical dependence.[12] Receptor binding affinity is measured by the equilibrium dissociation constant (Ki).[10,12,13] Opioids with low Ki values have stronger binding affinity at the μOR. The Ki value of buprenorphine is 0.216 nM, exceeded only by sufentanil with a Ki value of 0.138 nM (Table).[10,12,13] A case series recommended utilization of opioids such as hydromorphone or sufentanil with Ki values closer to buprenorphine to achieve better analgesia.[10]

Figure 2. Summary of opioid receptor signaling[14]

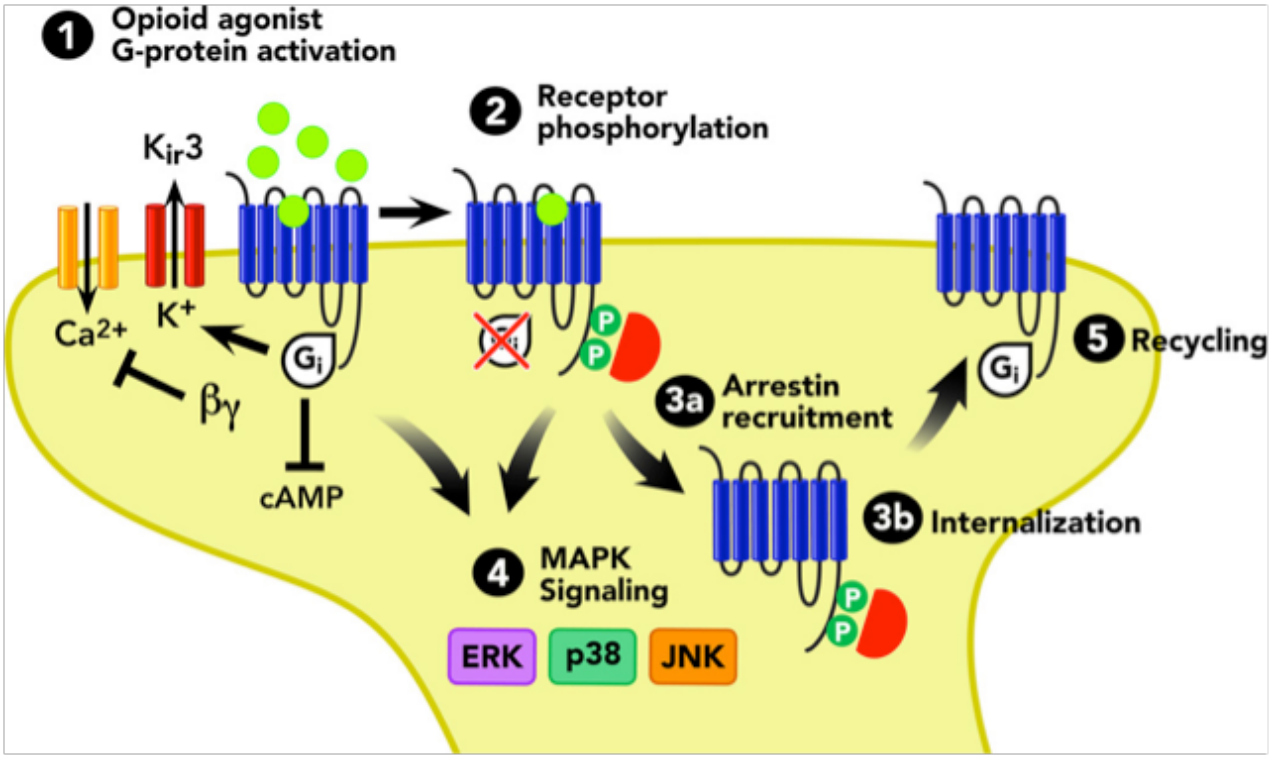


Table. Mu Opioid Receptor Affinity Measured by the Equilibrium Dissociation Constant (Ki)[12-13]

Drug	Ki (nM)
Hydrocodone	41.58
Oxycodone	25.87
Alfentanil	7.391
Methadone	3.378
Nalbuphine	2.118
Morphine	1.168
Fentanyl	1.346
Butorphanol	0.7622
Oxymorphone	0.4055
Hydromorphone	0.3654
Buprenorphine	0.2157
Sufentanil	0.1380

Perioperative Management of Patients on Buprenorphine

As a partial agonist with strong μOR affinity, buprenorphine attenuates the effect of other μOR agonists. The ceiling effect of buprenorphine decreases risks of respiratory depression and overdose but presents a challenge in surgical analgesia.[9] Therefore, patients taking buprenorphine are at high risk for ineffective pain management leading to severe postoperative pain.[2,9] Inadequate pain relief may cause longer postoperative recovery times, increased anxiety levels, and provoke drug-seeking behaviors.[9]

There is a lack of high-quality research and evidence regarding perioperative management of patients on buprenorphine. Most guidelines and protocols are derived from expert opinion, case studies, and clinical practice advisories.[3,4,11] Preoperatively, current literature suggest anesthesia providers to perform comprehensive assessments to obtain patients' history of buprenorphine therapy and other pertinent information. It is important to review patient's compliance level with prescriptions, pain management history, and previous experiences with anesthesia.[2,5,11] Diagnostic testing and toxicology screening should also be considered for objective information.[2,3,10] There are conflicting views and concepts regarding preoperative continuation of buprenorphine.[2-4,11] Some reports recommend discontinuing buprenorphine two to five days prior to surgery to ensure μOR availability.[2] Other sources noted there is a lack of evidence that discontinuing buprenorphine would prevent relapse episodes.[3] Furthermore, patients that discontinued buprenorphine were found to have a significant increase in opioid requirements postoperatively.[4]
Continuing buprenorphine preoperatively is advocated in some literature to maintain stable serum drug levels and to avoid exacerbations of withdrawal or relapse.[2-4,11] Optimal perioperative pain management should incorporate non-opioid analgesia as a priority.[2-4,9,11] Providers could include ketamine, acetaminophen, NSAIDs, gabapentinoids, and alpha-2 adrenergic receptor agonists.[3] Local anesthesia infiltration and regional/neuraxial anesthesia should be utilized where possible.[2-4,9-11] Initiating full μOR agonists may be appropriate when inadequate analgesia persists with multimodal management.[2-4,11] Clinicians need to be aware that successful pain management with patients on buprenorphine often requires increased doses of opioids.[2-4,9-11] Due to the high μOR receptor binding affinity of buprenorphine, other potent full agonists with high Ki values may be required to overcome the

receptor.[10] Hydromorphone and sufentanil are examples of μOR agonists with Ki values similar to buprenorphine.[3,10,11]

SUMMARY

While methadone and buprenorphine are the leading medications for treating chronic pain and OUD, optimal perioperative management of these medications have not been well established. Due to the unique pharmacological profiles of methadone and buprenorphine, it is imperative to perform thorough preoperative evaluations to assess for patient compliance to their prescribed medications, and to discuss concerns of diversion, or possible withdrawal and relapses perioperatively. Current guidelines and protocols recommend patients to continue their medication regimen unless instructed differently by their prescribing provider.[1-11] Optimal perioperative management of patients on methadone may include short-acting opioid agonists, multimodal analgesia, regional/neuraxial anesthesia, and other non-opioid interventions.[1,2,4-7] Optimal perioperative management of patients on buprenorphine may include multimodal analgesia, regional/neuraxial anesthesia, and opioid agonists with similar μOR binding affinity to buprenorphine.[2-4,9-11]

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Emily Coleman is completing the final year of obtaining a Doctor of Nursing Practice at Texas Christian University. Coleman graduated from The University of Texas at Austin with a Bachelor of Science in Nursing. Coleman was one of twelve accepted into the undergraduate Nursing Honors Program and completed a secondary analysis as her honor's thesis. Before beginning her doctoral education, Coleman was a medical intensive care nurse at UT Southwestern. Her background in pulmonary and critical care medicine involved caring for patients with pulmonary hypertension, sepsis, renal failure, respiratory failure, and more. Her current professional interests include pharmacology, regional anesthesia, obstetric anesthesia, and pain management.