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REVIEW

Multimodal Acute Pain Management in the Parturient with Opioid Use Disorder: A Review

Victor Koltenyuk[1], Ismat Mrad[2], Ian Choe[1], Mohamad Ibrahim Ayoub[3], Sangeeta Kumaraswami[4], Jeff L Xu[4]

[1]School of Medicine, New York Medical College, Valhalla, NY, USA; [2]Anesthesiology and Perioperative Medicine, University of Rochester, Rochester, NY, USA; [3]Department of Anesthesiology, New York University Grossman School of Medicine, New York, NY, USA; [4]Department of Anesthesiology, Westchester Medical Center/New York Medical College, Valhalla, NY, USA

Correspondence: Jeff L Xu, Department of Anesthesiology, Westchester Medical Center/New York Medical College, 100 Woods Road, Valhalla, NY, 10595, USA, Tel +1 914 493 7693, Fax +1 914 493 7927, Email jeff.xu@wmchealth.org

Abstract: The opioid epidemic in the United States has led to an increasing number of pregnant patients with opioid use disorder (OUD) presenting to obstetric units. Caring for this complex patient population requires an interdisciplinary approach involving obstetricians, anesthesiologists, addiction medicine physicians, psychiatrists, and social workers. The management of acute pain in the parturient with OUD can be challenging due to several factors, including respiratory depression, opioid tolerance, and opioid-induced hyperalgesia. Patients with a history of OUD can present in one of three categories: 1) those with untreated OUD; 2) those who are currently abstinent from opioids; 3) those being treated with medications to prevent withdrawal. A patient-centered, multimodal approach is essential for optimal peripartum pain relief and prevention of adverse maternal and neonatal outcomes. Medications for opioid use disorder (MOUD), previously referred to as medication-assisted therapy (MAT), include opioids like methadone, buprenorphine, and naltrexone. These are prescribed for pregnant patients with OUD, but appropriate dosing and administration of these medications are critical to avoid withdrawal in the mother. Non-opioid analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used in a stepwise approach, and regional techniques like neuraxial anesthesia and truncal blocks offer opioid-sparing options. Other medications like ketamine, clonidine, dexmedetomidine, nitrous oxide, and gabapentinoids show promise for pain management but require further research. Overall, a comprehensive pain management strategy is essential to ensure the well-being of both the mother and the fetus in pregnant patients with OUD.

Keywords: opioids, pregnancy, buprenorphine, methadone, naltrexone

Introduction

In 2021, the National Center for Health Statistics reported 71,238 deaths and 80,311 overdoses due to opioids in the United States.[1] With the progression of the opioid epidemic over the past decade, hospitals have seen an increase in the number of pregnant patients with opioid use disorder (OUD) who present to the labor and delivery unit.[2,3] These patients have high rates of comorbidities, including anxiety, HIV, depression, and hypertension.[4] It is also established that pregnant patients who use opioids have increased odds of major obstetrical morbidity and mortality, including prolonged hospital stay, preterm delivery, placental abruption, and in-hospital death.[5] Thus, caring for this vulnerable group of patients requires an interdisciplinary approach consisting of a team that includes obstetricians, anesthesiologists, addiction medicine specialists, psychiatrists, and social workers.[6–8]

OUD has been defined by the DSM-V (Diagnostic and Statistical Manual of Mental Disorders-V) as a "problematic pattern of opioid use leading to clinically significant impairment or distress".[9] Medical professionals can assess OUD in patients using the checklist in Table 1. Other related terms include nonmedical opioid use, which is the use of a prescription drug not in the way, amount, or time prescribed.[9] Drug misuse is another term, and it refers to the use of prescription drugs in a manner other than as directed and/or illegal drugs.

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Table 1 DSM-V Diagnostic Criteria for OUD; Two Out of the 11 Criteria are Needed for Diagnosis

Taking opioids in larger amounts or over a longer period of time than intended
Having a persistent desire or unsuccessful attempts to reduce or control opioid use
Spending excess time obtaining, using or recovering from opioids
Craving opioids
Continued opioid use causing inability to fulfill work, home, or school responsibilities
Continuing opioid use despite having persistent social or interpersonal problems or psychological problems
Lack of involvement in social, occupational, or recreational activities
Using opioids in physically hazardous situations
Continuing opioid use in spite of awareness of persistent physical or psychological problems
Exhibiting tolerance symptoms, as defined by either of the following:
A need for markedly increased amounts of opioids to achieve intoxication or desired effect, or
Markedly diminished effect with continued use of the same amount of an opioid.
Exhibiting withdrawal symptoms, as manifested by either of the following:
The characteristic opioid withdrawal syndrome, or
Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms

Note: Table content is data from the article of CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95.[9]

Conducting screening tests for OUD early during pregnancy can lead to detection of OUD and is associated with improved maternal and fetal outcomes.[10,11] Urine testing has been used to detect OUD, but this should only be done with full consent from the patient as well as in accordance with local laws.[12] A positive urine test is not diagnostic of OUD on its own. On the other hand, a negative urine test cannot be used to rule out OUD, as drug use may be sporadic. Finally, some synthetic opioids are not detected via urine tests. Verbal screening tools have been shown to be superior and include the National Institute on Drug Abuse (NIDA) quick screen for adolescents and young adults, and the "4Ps" (parents, partner, past, present) screening modality. However, these screening tests lack sufficiently high sensitivity and specificity.[13] Unfortunately, this patient population often seeks prenatal care late in their pregnancy course, and thus, routine preventative education might not occur. These patients account for a high proportion of unplanned pregnancies when compared to the general population.[14] Additionally, lifestyle factors associated with illicit drug use such as prostitution, theft, violence, and polysubstance abuse put them at risk for complications such as HIV and hepatitis infections. Recent efforts to develop more effective methods for screening in this population have included web-based modalities that involve text-message and phone-based screening, treatment, and referral for pregnant patients with OUD.[15] Untreated OUD in the parturient is shown to be responsible for increased preterm births, maternal eclampsia, placental abruption, and fetal intrauterine growth restriction.[10] It is well documented that patients with OUD have better outcomes when they have a more open relationship with their physician. Efforts to foster such trust are paramount for the pregnant patient with OUD.[16]

Given the potential for significant opioid tolerance in these patients, managing their acute pain is challenging. Moreover, these patients are likely anxious about their delivery, including being afraid of their peripartum pain being overlooked, and perhaps shame about being possibly judged by the medical professionals caring for them. Numerous studies have shown the negative effects of inadequate postpartum pain management in the parturient, including depression, delayed mother-infant bonding, and increased opioid use.[5–7] These patients face two major issues that stem from their prolonged opioid use: opioid tolerance and opioid-induced hyperalgesia. Neonatal abstinence syndrome

(NAS) may also be a consequence of OUD in a pregnant patient, and this should be considered when developing a pain management plan for the parturient. Thus, a stepwise, patient-centered, multimodal approach is critical for optimizing pain relief in the parturient with OUD.

Opioid Tolerance

Opioid tolerance is defined as a decrease in analgesic efficacy after continued opioid use.[17] This may develop in people who are using opioids for prolonged periods of time and may include patients being treated with opioids for chronic pain (for example, as part of treatment for cancer) or patients who use opioids recreationally.[18] One retrospective study showed that opioid-tolerant patients had longer hospital stays and increased risk of readmission.[19] The exact mechanism for opioid tolerance is unknown but likely results from desensitization and downregulation of opioid receptors following chronic exposure.[17] Specifically, some studies have suggested that modifications in the second messenger pathways and potential receptor trafficking are responsible for opioid tolerance.[18] The protein β-arrestin is thought to play an important role in opioid receptor endocytosis. One study showed that lack of β-arrestin in mice prevented the development of morphine tolerance and enhanced analgesic effects.[20] Another mechanism involves opioid-induced changes in inflammatory cytokine expression and increased glutamatergic signaling, leading to tolerance.[21]

Since these patients require a greater opioid dosing for the desired analgesic effect, they are at risk for opioid-related side effects, such as respiratory depression, constipation, and addiction.[22] The prevalence of OUD and opioid-related deaths in women has been increasing in the past decade.[23] In fact, the death rate of women from opioids has been rising since 2016.[24] It has also been shown that women are more likely to be prescribed opioids at higher doses and become dependent on them.[25,26] Women may also suffer more from chronic pain, for which opioids are becoming more common long-term treatments.[27] For these reasons, it is not surprising that the number of pregnant patients with opioid tolerance is growing.[28] It is critical for the pain management team to be aware of possible tolerance in pregnant patients with OUD to ensure their pain is being adequately addressed.

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) is characterized by sensitization of the nociceptive response following administration of opioids. It is typically preceded by opioid tolerance, and patients with OIH may become hypersensitive to both painful and simple stimuli such as cold and electrical stimuli.[29] The mechanisms underlying OIH have not been clearly defined. One postulated explanation is that reuptake of certain excitatory neurotransmitters such as glutamate are inhibited, allowing for continued activation of N-methyl-D-aspartate (NMDA) receptors. Another possible mechanism is increased availability of spinal dynorphin that leads to increases in excitatory neuropeptides such as calcitonin gene-related peptide (CGRP). There are also some genetic causes being investigated, one being a polymorphism in the catecholamine breakdown enzyme (COMT) that results in errors in dopamine and noradrenaline metabolism, causing altered levels in response to neurotransmitter activation.[30,31]

OIH poses a significant concern in people with previous opioid exposure. Several studies assessing pain sensitivity using cold pressor, electrical, and pressure pain modalities showed increased sensitivity to cold pressor pain in opioid-addicted patients using medications for OUD (MOUD) compared with controls.[32] A study assessing response to pain in 355 patients using opioid analgesics showed that opioid dose and duration of treatment was directly correlated with pain intensity and unpleasantness scores, with the effect being more profound in women.[33] This corroborates other studies that have shown increased baseline pain in patients following discontinuation of opioid receptor agonists. These findings are the basis of the widely accepted recommendation made by the American College of Obstetricians and Gynecologists (ACOG) to not employ supervised withdrawal in the analgesic plan for pregnant patients with OUD.[28,34] Given that these hyperalgesic states are more common in chronic opioid users, physicians should be vigilant for OIH while caring for patients with OUD.[35] Current guidelines recommend opioid cycling (switching between different opioid medications to maintain pain relief and limit side effects), physical therapy, and adjuvants for pain treatment.[36] Based on our understanding of the effects of increased pain on maternal bonding and fetal development, it is vital for the pain management team to be aware of these implications and have plans for treatment ready.[37]

Neonatal Abstinence Syndrome (NAS)

Prolonged opioid use in a pregnant patient is the primary cause for the development of NAS in neonates. Manifesting as acute withdrawal, NAS may result in dysregulation of the autonomic nervous system and cause issues with sensory processing, attention, and motor control.[38] These conditions may be further exacerbated by symptoms that the mother may be experiencing, including peripartum pain or withdrawal, all of which can contribute to impeded maternal-infant bonding.[15–17] Long-term neurodevelopment outcomes in the child have not been clearly outlined. However, one study showed that infants with NAS were more likely to be hospitalized for assaults and maltreatment during adulthood. It also found that NAS was an independent predictor of mental and behavioral disorders.[39] Other studies have shown that children who experienced NAS were more likely to have educational disabilities.[40] Treatment for NAS includes opioids such as morphine or methadone that are gradually reduced in a stepwise manner.[41–43] Effective prevention strategies for NAS are improved pre-conception healthcare and education of patients and providers about appropriate use of prescription opioids during pregnancy. Thus, it is critical for physicians to be aware of the consequences of prolonged fetal opioid exposure.

Antepartum Planning

Parturients with OUD can be differentiated into at least three subgroups: 1) Untreated OUD, in which patients are actively using opioids and have not initiated treatment with MOUD; 2) Currently abstinent from opioids with a history of OUD; 3) OUD that is actively being treated with MOUD. All patients should be evaluated by an anesthesiology team using a multidisciplinary approach. These patients may be concerned about not receiving adequate pain relief due to the stigma associated with their opioid use. They may also feel anxious about being judged by the medical staff and concerned about possible complications occurring during delivery or in the infant. These concerns must be addressed during antepartum planning to optimally build trust and rapport with the patient. Various available anesthetic options should be discussed. Examination of the airway is also important because of possible poor dentition or airway burns from previous drug use. Potential difficulties for intravenous access must be assessed in the setting of intravenous drug abuse. It has also been shown that opioid-dependent pregnant patients have higher rates of panic disorder and depression, so anesthesiologists should work in conjunction with the patient's psychiatrist when formulating their management plan.[44] It is imperative that trust between the patient and a multidisciplinary team is established well in advance and that the patient's expectations and wishes regarding pain management are fully respected.

Subgroups of OUD

Patients with Untreated OUD

Untreated OUD includes patients who actively use illegally obtained opioids, as well as those with chronic pain disorders who are on prescription opioids that are obtained either by prescription (for themselves or family), pill sharing with acquaintances, or through the black market. Nonprescription opioids are acquired exclusively via illegal drug markets.[45] Common opioids of misuse include semi-synthetic opioids like hydrocodone, oxycodone, and heroin, as well as synthetic opioids like fentanyl and furanyl fentanyl, a synthetic opioid sold illegally with a potency five times that of fentanyl.[46] When these patients present to the obstetric unit, they may be in acute distress due to overdose. Following hemodynamic and airway assessment and treatment, if necessary, the smallest effective dose of naloxone should be administered to avoid inducing acute withdrawal in the mother and fetus. Alternatively, they may be in opioid withdrawal, in which case oral buprenorphine should be administered. If they are in labor, epidural analgesia should be offered. Use of dilute local anesthetic solution with opioids is best practice for neuraxial labor analgesia. At our institution, Westchester Medical Center, we use 0.1% ropivacaine with 2 mcg/cc fentanyl. For complicated vaginal deliveries, for example those with third/fourth degree perineal lacerations, options include keeping the epidural in-situ and administering local anesthetic with or without narcotic infusions post-delivery.

In patients undergoing cesarean delivery, management options similar to vaginal delivery are recommended. Neuraxial anesthesia and analgesia with intrathecal morphine is recommended in the absence of any contraindication. Combined spinal-epidural anesthesia may be used for the cesarean delivery, with the epidural catheter being used postoperatively for pain relief. In both scenarios, opioids such as fentanyl and/or morphine may be used neuraxially, with higher doses of opioids or higher concentration of local anesthetic likely being required. Additionally, scheduled around-

The-clock acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) should also be administered in the absence of any contraindications.

Other non-opioid strategies that may be considered include neuraxial clonidine and regional techniques like truncal nerve blocks. Mixed agonists/antagonists such as butorphanol and nalbuphine (used for pruritus) are contraindicated, as these drugs can precipitate a withdrawal in the mother and fetus (Figure 1). Use of nitrous oxide may be considered, but in combination with opioids, there is a risk of respiratory depression, so the patient should be carefully monitored.[47–49]

Patients with History of OUD Who are Currently Abstinent from Opioids

This category includes patients with a history of OUD who have successfully achieved and maintained opioid abstinence or are currently receiving support through detoxification and counseling programs, such as 12-step recovery and Alcoholics Anonymous, or inpatient rehabilitation facilities.[50] While these patients do not experience acute withdrawal or have physical dependence on opioids, they remain at risk of relapse. For presumed vaginal deliveries, neuraxial labor analgesia is recommended for all patients in the absence of any contraindication. Patients with complicated vaginal deliveries, such as those with third/fourth degree perineal lacerations, may benefit from continued pain relief via the epidural catheter postdelivery using local anesthetic with or without opioids. Neuraxial opioids such as fentanyl and/or morphine may also be administered, although a subset of patients may prefer to avoid opioids.[51] Moreover, they may not be effective in abstinent patients managed on naltrexone. Scheduled around-The-clock acetaminophen and NSAIDs should be administered post-delivery in the absence of any contraindication. If additional pain relief is required, non-opioid medications such as neuraxial clonidine and truncal nerve blocks may be used. Local anesthetics alone or in combination with opioids may be administered as an infusion through the epidural catheter in the postdelivery period. If the patient requests a totally opioid-free approach, adding clonidine to the epidural infusion and increasing the concentration of local anesthetic solution for postoperative pain management should be considered (Figure 2).

In patients undergoing cesarean delivery, management options similar to vaginal delivery are recommended. Neuraxial anesthesia and analgesia with intrathecal morphine is recommended in the absence of any contraindication.

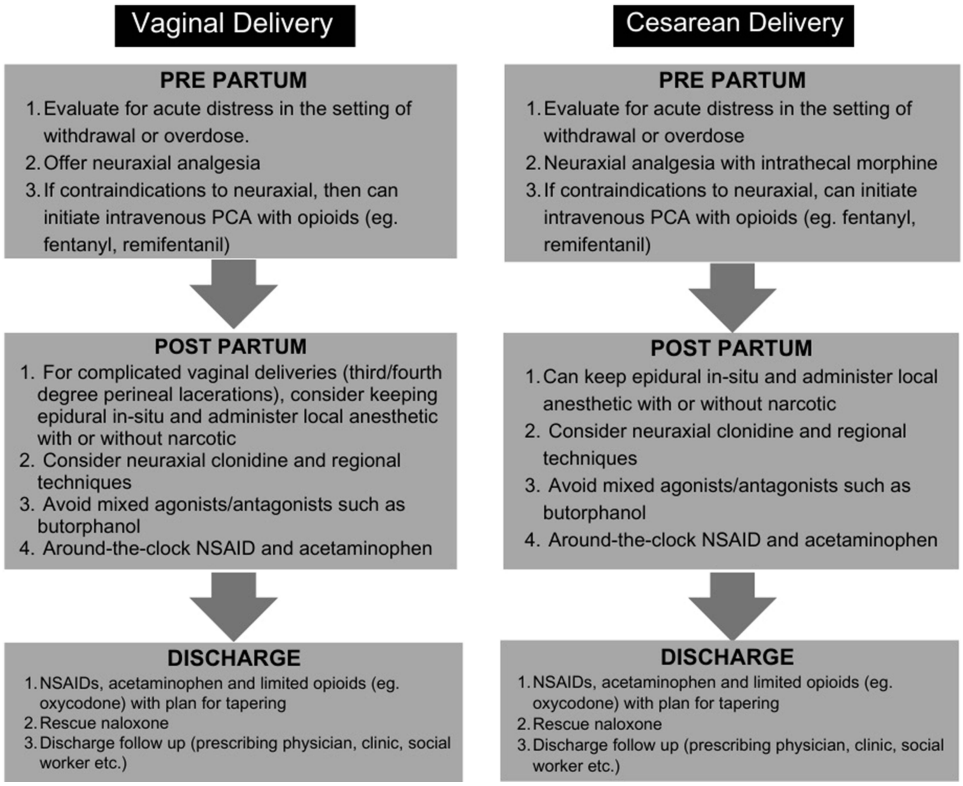

Figure 1 Practical approach for managing pain in the parturient with untreated OUD during vaginal delivery (left) and cesarean section (right).

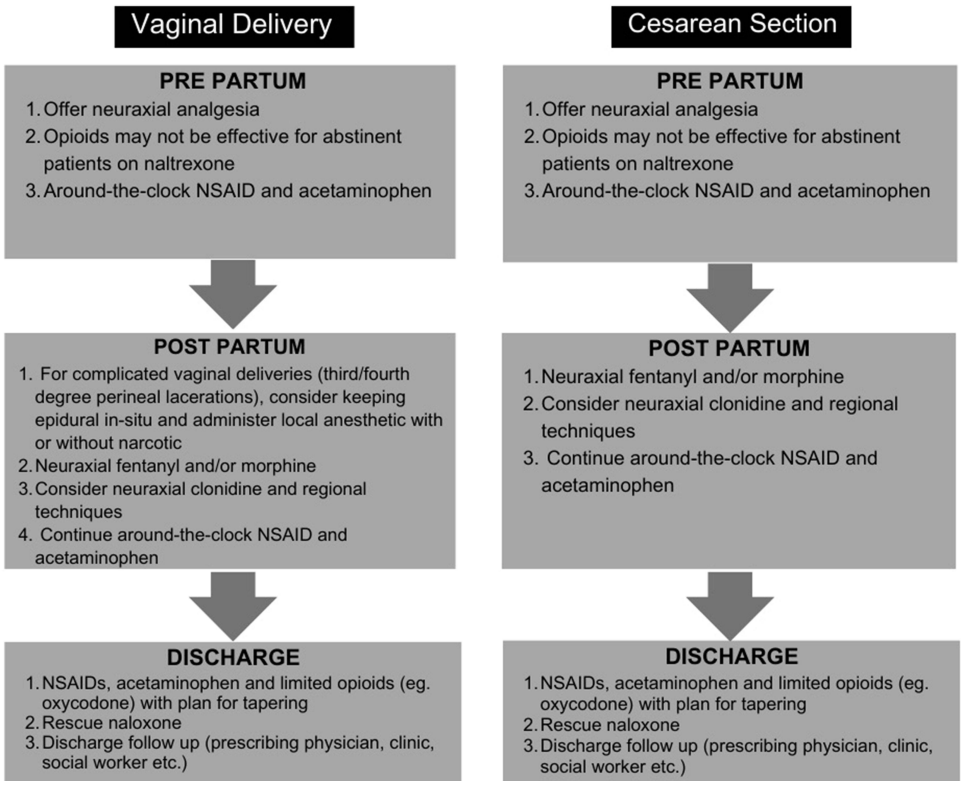

Figure 2 Practical approach for managing pain in the opioid abstinent parturient during vaginal delivery (left) and cesarean section (right).

Acetaminophen and NSAIDs can be administered preoperatively and postoperatively. In cases when postoperative opioid administration is necessary, abstinent patients should be educated on the risks of relapse and overdose due to their lack of opioid tolerance.[5] A multidisciplinary follow-up approach is necessary for these patients' continued care.[47,49]

Medication for Opioid Use Disorder (MOUD)

MOUD has been defined as the use of medications, in combination with counseling and other therapeutic techniques, to holistically treat patients with substance use disorders.[52] Opioid agonist/antagonist therapy is the mainstay of MOUD. These include three main medications: methadone, buprenorphine, and naltrexone. Patients presenting for delivery should be continued on their MOUD. Maintaining pregnant patients on MOUD rather than opting for supervised withdrawal is important for several reasons. Maternal opioid withdrawal poses substantial risks for both the mother and neonate. Fluctuating opioid levels may subject the fetus to repeated in-utero withdrawal episodes and can potentially cause motor hyperactivity and heightened oxygen consumption. This can lead to preterm labor, fetal hypoxia, or fetal demise. For these reasons, supervised withdrawal is not recommended, and pregnant patients should be continued on their MOUD.[53]

For all patients, the obstetric team should confirm the patient's dose of medication (methadone, buprenorphine, or naltrexone), the number of days remaining on the prescription, and the amount of drug the patient has left, either by verification using a prescription monitoring program registry or via communication with the patient's pharmacy, prescribing practitioner, or clinic. Patients with a plan for vaginal delivery should be offered neuraxial analgesia. Intravenous patient-controlled analgesia with potent opioids such as fentanyl can be used if there are contraindications to neuraxial anesthesia. Local anesthetic with or without opioids may be administered epidurally in the postdelivery period for pain management. Opioids such as fentanyl and/or morphine can be used neuraxially in the setting of complicated deliveries with perineal lacerations. Use of patient-controlled analgesia is additionally beneficial in these patients. Both acetaminophen and NSAIDs may be administered around-The-clock after delivery in the absence of any contraindication.[54,55] Truncal nerve blocks can be considered as an opioid sparing modality. Mixed agonists-antagonists such as nalbuphine for pruritus should be avoided, as they can precipitate withdrawal (Figure 3).

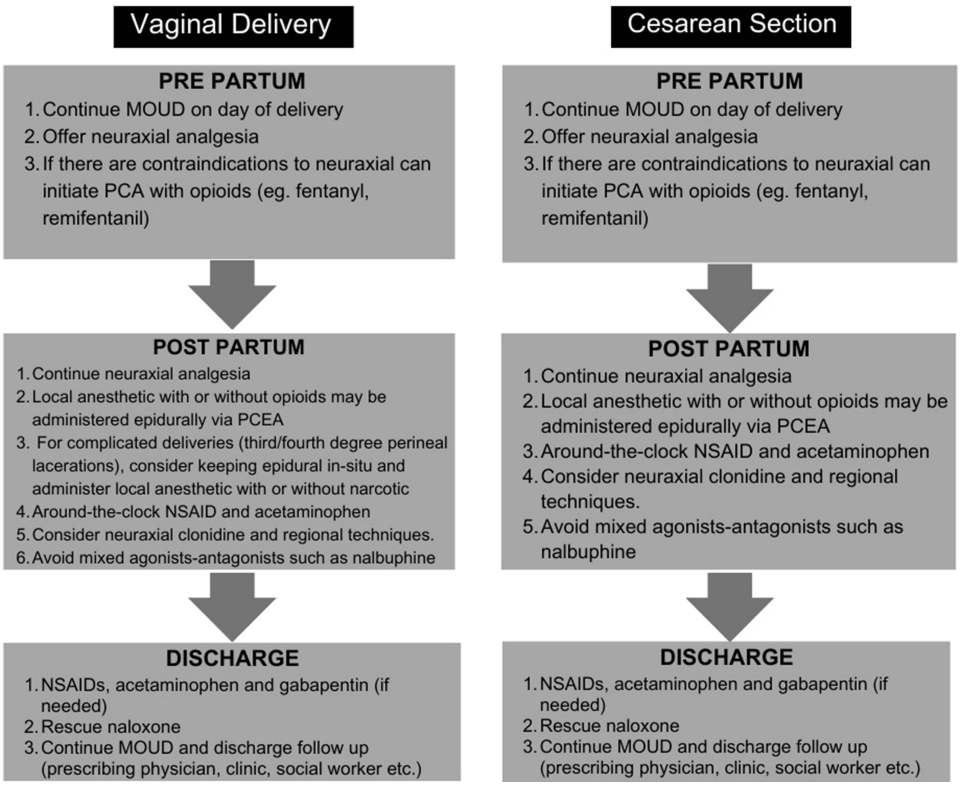

Figure 3 Practical approach for managing pain in the parturient with on MOUD during vaginal delivery (left) and cesarean section (right).

Methadone

Methadone is one of the main medications used to manage opioid withdrawal symptoms. It is a dual μ, κ, and σ opioid receptor agonist. It is formulated as a racemic mixture of R-methadone and S-methadone and is typically dosed once daily when treating OUD.[56] R-methadone is more potent and is responsible for most of the analgesic effects of the drug. However, S-methadone has a longer duration of action. Methadone causes analgesia, sedation, and euphoria, and it has a long half-life. This makes it beneficial in the treatment of opioid addiction because it prevents acute withdrawal symptoms while reducing the risk of relapse.[57] Methadone is metabolized in the liver and undergoes renal and fecal excretion with a half-life that ranges from 8 to 59 hours, depending on individual factors such as age, liver function, and other medications being taken such as cytochrome p450 inducers or inhibitors. Common cytochrome p450 inducers include rifampin, phenytoin, and carbamazepine. Inhibitors include azithromycin, ritonavir, and amiodarone.[58] It is safe in renal failure with no active byproducts.[56] Methadone can also be used in the management of chronic pain, but as a much lower dose given three times daily.[59] Given that it is a full μ agonist, it can be abused with no ceiling effect. A ceiling effect refers to a phenomenon in which use of a drug reaches a maximum effect, at which greater doses of the drug do not increase effectiveness.[60] Thus, its administration is restricted to supervised, government-approved locations known as methadone clinics. Unfortunately, this restriction becomes a barrier to access in rural areas or for patients with a lack of transportation to such facilities. According to the World Health Organization (WHO), 60 mg of methadone has been most effective at reducing the death rate related to opioid dependence.[61]

Occurrence of QT prolongation and the possibility of precipitating Torsades de Pointes is a well-known side effect of methadone; the higher the dose, the more likely the effect (>200 mg in healthy patients).[62] Methadone has had an Food and Drug Administration black box warning for this rare ventricular arrhythmia since 2006.[63] Thus, ECG monitoring is recommended with methadone dosages that exceed 150 mg/day and in patients with either risks for QT prolongation or symptoms that may attribute to arrythmias.[64] For the parturient taking methadone, it is recommended to continue using methadone in the peripartum period rather than discontinuing therapy, as this could lead to relapse and hyperalgesia.[57,65]

One retrospective study revealed that although women who were on methadone for OUD experienced similar pain compared to pregnant patients without OUD during cesarean delivery, they required 70% higher analgesic dosage.[57] This poses concerns for increased postpartum opioid use or even relapse. Due to changes to drug metabolism in the third trimester of pregnancy, splitting the once-daily dosing into a two- or three-times daily dosing may be more beneficial in treating OUD and the associated pain around birth. Increasing the dosage is not indicated, as it puts the mother at an increased risk of prolonged QT interval and subsequent arrhythmias.[47,49]

Buprenorphine

Buprenorphine is a partial μ receptor agonist and κ and δ opioid receptor antagonist. Buprenorphine is available in several formulations such as tablets, sublingual films, buccal films, transdermal films, extended-release injections, and implants. It is often administered as a sublingual tablet in combination with naloxone (suboxone) to avoid immediate opioid withdrawal. Buprenorphine is also more accessible than other MOUD like methadone, as it can be prescribed in the office setting. When adhered to, buprenorphine is effective at treating opioid dependence while attenuating the effects of other opioids. For the parturient, it should be continued at the same dose in the peripartum period.[54] Buprenorphine may also be the safer drug for mothers due to its lack of drug interactions. It is a partial agonist, meaning there is a decreased risk of respiratory depression at higher doses. Furthermore, it is metabolized primarily in the liver and excreted in the feces with a half-life of 25–70 hours, and it is safe in patients with renal failure. The effectiveness of buprenorphine relies on its adherence. Buprenorphine non-adherence is an ongoing issue and has been shown to be associated with illicit drug use.[66] One study found that patients using buprenorphine were adherent 71% of the time.[67] The reasons for buprenorphine nonadherence are multifactorial and range from wanting to use to using other illicit drugs or simply forgetting to take the medication. Recent efforts have included video-based tools to improve adherence.[68] Multiple studies have shown that buprenorphine use during pregnancy is associated with a lower risk of NAS.[43,69] One study found that the use of buprenorphine during pregnancy was associated with low birth rate and a lower risk of preterm birth compared to illicit opioid use. The study also found that there was no significant difference in the rates of stillbirth or neonatal death between women who used buprenorphine and those who used illicit opioids.[41,69,70] Buprenorphine is also more cost effective and accessible than methadone, as it can be prescribed in the office setting.

Studies have suggested that the use of buprenorphine in pregnant women with OUD is associated with improved neonatal outcomes.[69,70] The multi-center randomized double-blinded MOTHER (Maternal Opioid Treatment: Human Experimental Research) trial that evaluated neonatal outcomes in women using buprenorphine or methadone found that neonates born to mothers using buprenorphine required 89% less morphine for treatment of NAS, had 58% shorter period of treatment, and had 43% shorter hospital stay.[20] However, as it is an effective MOUD, high doses of opioids are required to displace buprenorphine from its receptor; thus, these patients require higher doses of opioids.[49] This poses a challenge to achieving pain control in a clinical setting. For the parturient on buprenorphine, it is recommended to administer the medication in a split-dose fashion 3–4 times per day.

Naltrexone

Another MOUD that can be effective is naltrexone, a non-selective opioid receptor antagonist against μ, κ, and δ receptors that is available in both short and long-acting forms. Naltrexone is metabolized by the liver and excreted by the kidney with a half-life of 4–10 hours and is safe in patients with renal failure.[71] Due to its mechanism of action, it causes withdrawal in first-time users and is mainly recommended for opioid-abstinent patients. A long-acting injectable formulation is available and is associated with better adherence as compared to the oral formulation, with effective opioid blockade for up to 6 weeks.[41] Maintaining women on naltrexone during pregnancy was associated with favorable outcomes.[72] For patients using the oral formulation of naltrexone, it is recommended to discontinue use at least 72 hours before the procedure. For the extended-release formulation, surgery should ideally be set for at least 4 weeks after the last injection.[49] Depending on the formulation used, this may be difficult and unrealistic.[73] When delivery is approaching, patients on naltrexone treatment should consider discontinuation of extended-release naltrexone and transition to the shorter-acting oral formulation to allow for less difficulty in delivery and postoperative pain management. The prescribing physician should be contacted to assess the safety of holding naltrexone. It is critical for patients to be observed under

close observation during their stay at the hospital to be cautious for any abnormalities that may arise. Reinitiating naltrexone early should be avoided due to possibly withdrawal symptoms that may occur. Therefore, it is recommended to restart naltrexone after 3–7 days of opioid abstinence. For vaginal deliveries, women may restart naltrexone at 48 hours postdelivery.[72] For cesarean deliveries, restarting of naltrexone may be delayed until postoperative pain is controlled on NSAIDs alone.[72] When naltrexone is started, it is a high-risk time for OUD relapse. Therefore, it is important to closely monitor the patient as the medication is restarted. If a patient undergoes surgery while receiving injectable naltrexone, standard doses of opioids may not be sufficient due to the opioid-blocking effect of intramuscular naltrexone. In contrast, after naltrexone is no longer occupying the receptors, opioid painkillers can result in an exaggerated response due to the upregulation of opioid receptors, leading to heightened sensitivity. Therefore, it is crucial to adjust the dosage of opioids accordingly and monitor the patient closely to avoid adverse reactions. Some studies have also found that long-term naltrexone use may result in hyperalgesia.[74]

There are also concerns about potential infant exposure, as animal data has suggested increased pain tolerance in offspring exposed to naltrexone in-utero.[75] One human study found that pregnant patients using naltrexone had more preterm births than the control group. Meanwhile, another study by the same authors found decreased incidence of NAS in neonates born to mothers using naltrexone compared to the buprenorphine treated group, but no other differences in outcomes.[65,76] Another large prospective study in 230 patients found that naltrexone was well-tolerated by both mother and fetus, making it a suitable alternative for certain patients.[77] Due to the lack of effectiveness of opioids in patients with OUD, effective peripartum pain management can be difficult. Therefore, alternatives such as regional and systemic non-opioid pain management techniques are recommended. Overall, naltrexone should be reserved for the opioid-abstinent patient, and potential risks for hyperalgesia and infant exposure should be carefully monitored.[41,78]

Regional Techniques

Neuraxial Anesthesia and Analgesia

Neuraxial modalities are the cornerstone of pain management in pregnant patients during the prepartum and peripartum periods.[79] Neuraxial techniques include spinal and epidural anesthesia, which involve administration of local anesthetics, opioids, or clonidine.[33,80] Neuraxial anesthesia is preferred to general anesthesia in the pregnant patient as it has been shown to result in both improved maternal and fetal outcomes.[81] Specifically, neuraxial morphine has repeatedly been identified to be an effective single dose analgesic. For the parturient with OUD undergoing vaginal delivery, neuraxial labor analgesia should be offered in the absence of any contraindication.[74] The epidural catheter may be kept in situ post-delivery if prolonged pain management needs are anticipated. For patients undergoing cesarean delivery, combined spinal-epidural anesthesia can be done with a plan to keep the epidural in situ postoperatively for at least 24–72 hours or as needed for pain control. Intrathecal narcotics should be administered, and consideration should be made for increasing the dose of preservative free morphine (150–300 mcg).[53,74] Additional neuraxial fentanyl added to the local anesthetic for spinal and epidural anesthesia for cesarean delivery reduces need for intraoperative analgesic supplementation with longer time to first postoperative analgesia request.[82] Epidural narcotics should be considered if intrathecal narcotics were not administered (for example, use of an indwelling epidural for an intrapartum cesarean delivery). Epidural narcotics may be readministered after 24 hours. All patients with OUD may receive intrathecal morphine regardless of treatment status. Due to the tolerance and hyperalgesia in these patients, they will often require a higher dose of intrathecal or epidural opioids.[53] Specifically, patients maintained on buprenorphine will need additional dosing due to opioid receptor antagonism. If needed, adjuvants such as neuraxial clonidine may also be indicated for patients with OUD.[53,74,83]

Truncal Blocks

In the realm of regional anesthesia, truncal blocks such as transversus abdominis plane (TAP) and quadratus lumborum (QL) blocks are options for cesarean delivery.[84] In the setting of complicated vaginal deliveries, a pudendal nerve block can be used as a powerful adjunct for analgesia.[85] Although shown to be less effective at relieving pain than intrathecal morphine, these are low-risk procedures that may be considered if patients refuse opioids or have a contraindication to neuraxial anesthesia.[86] One meta-analysis that examined use of TAP blocks for post-cesarean analgesia found that it

improved analgesia compared to patients who did not receive the block.[87] Use of liposomal bupivacaine in TAP blocks may be an effective approach for reducing opioid requirement and improving analgesia post-cesarean delivery.[86,88–90] Another meta-analysis showed that bilateral QL blocks reduced opioid consumption in women following cesarean delivery.[91] However, most studies comparing QL blocks with intrathecal morphine have failed to show the superiority of regional blocks.[91] Moreover, QL blocks have shown to confer greater opioid sparing and analgesic effects than TAP blocks.[92] These regional techniques, although opioid sparing, have not been studied in the parturient with OUD. They are also largely ineffective in dealing with visceral pain, as they mainly target somatic pain.[93]

Acetaminophen/NSAIDs

Achieving analgesia in the parturient with OUD requires a stepwise multimodal approach, as it does for the patient without opioid tolerance. One part of this approach should focus on non-opioid analgesics such as acetaminophen and NSAIDs. There are numerous studies that have demonstrated preoperative acetaminophen use to be effective in relieving pain for up to one day in the post-cesarean period.[47,94,95] However, a single dose of acetaminophen prior to cesarean delivery under spinal anesthesia in conjunction with morphine did not decrease the length of stay or use of opioid medications post-operatively.[96] An intravenous form of Acetaminophen is available as well. One study conducted retrospectively on patients who underwent cesarean delivery revealed that the utilization of intravenous Acetaminophen led to a reduction in the use of opioids and a shorter hospital stay as compared to the oral form.[97] However, the intravenous form is much more expensive, and oral acetaminophen is preferred due to its low cost and availability.

NSAIDs have shown similar opioid sparing results in opioid-naïve post-cesarean delivery patients. A combination of acetaminophen and NSAIDs has shown to be particularly effective compared to either alone.[98] According to a recent study, the potential hazards associated with the short-term utilization of NSAIDs might have been overstated. Specifically, the possibility of developing renal dysfunction, gastric complications, bleeding, and cardiac dysfunction does not seem to be significantly higher when NSAIDs are appropriately used after surgery, and it is unlikely that NSAIDs are responsible for bleeding complications.[99,100] In light of the opioid epidemic, it is crucial to be aware of alternative analgesic options that are safe for postoperative pain control. For patients undergoing vaginal delivery, much of the pain results from perineal lacerations and breast engorgement. For post-vaginal delivery patients, around-The-clock acetaminophen and NSAID administration has shown to be effective, and this approach should be used for the parturient with OUD without contraindications to either medication.[74] Moreover, this approach is recommended for patients on MOUDs, those abstinent from opioids, and those with untreated OUD.[101]

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) by the neuraxial or intravenous route is a viable mode of delivery and is an effective option for the parturient with OUD (as they can self-administer additional medication). Programmed intermittent epidural boluses are superior to continuous epidural infusions and, in combination with PCA, are useful for managing pain in the laboring patient.[53,102] Despite the opioid tolerance and hyperalgesia, opioids will still be effective, but higher doses are needed to achieve optimal pain relief. Giving such high doses requires titration to effect and rigorous monitoring, which can put the patient in significant distress until a proper balance of analgesia and safety is reached. Use of PCA should be an individualized decision that must be balanced against risks. Patient controlled epidural analgesia (PCEA) utilizing local anesthetics with or without opioids is also an option for patients who receive an epidural. This offers an opioid-sparing option, and higher concentration of local anesthetic can be used as needed. Unlike PCA, this involves the epidural remaining placed post-operatively, and the patient may need anticoagulation due to limited mobility and risk of deep venous thrombosis (DVT). Additionally, more frequent anesthesia follow-up and additional nursing responsibility are required. Coordinating care to achieve this can be complicated.[94]

Miscellaneous Adjuvants

Clonidine

Clonidine is an alpha-2-adrenergic agonist known for its sedative, antihypertensive, and vasodilatory effects. It is also used for symptomatic control of opioid withdrawal symptoms. Several studies have shown its efficacy as analgesic agents in these patients. In this patient population, use of neuraxial clonidine may be indicated.[74,83]

One meta-analysis showed that administration of clonidine and morphine intrathecally extended the time to first analgesia request and decreased postoperative opioid use.[103] Addition of clonidine to the neuraxial local anesthetic can increase analgesia. A dose of 0.5–1 mcg/kg (50–100 mcg) can be added to the local anesthetic solution to be injected spinally.[53] In the laboring patient, 2 mcg/cc clonidine can be added to the local anesthetic and opioid mixture administered epidurally.[53] In one study of seven women, post cesarean delivery analgesia with clonidine was effective aside from one instance of hypotension.[104] Moreover, this approach is especially useful for opioid-abstinent women. Another study found that patients receiving intrathecal bupivacaine with clonidine had a reduced area of incisional hyperalgesia 48 hours after cesarean delivery. However, there was no difference in other factors such as pain scores and postoperative morphine use.[105] Overall, studies regarding clonidine use have yielded mixed results, with many studies not showing differences in analgesia when administered with other analgesics such as ropivacaine.[106] More research should be done to explore clonidine's role in patients with OUD.

Nitrous Oxide

Nitrous oxide is an inhaled analgesic that has been used for pain relief during labor and delivery for many years. Its use is safe and well tolerated, with additional advantages being its low cost and high availability.[107] Nitrous oxide is metabolized by anaerobic bacteria in the gut and has a rapid half-life of five minutes.[108] It may be a suitable alternative for opioid abstinent patients; however, due to risks of respiratory depression with concomitant opioid use, it is not recommended for patients with untreated OUD.[109] One study found that pregnant patients using nitrous oxide did not prefer it to neuraxial analgesia.[48] While the use of nitrous oxide is generally safe for the newborn, a recent case control study found that nitrous oxide administration to the mother during birth was an independent predictor of neonatal vitamin B12 deficiency.[110,111] Nitrous oxide potentiates the effects of opioids; thus, there is an increased risk of respiratory depression when combined with other opioids. Physicians should exercise caution when administering nitrous oxide to the parturient with OUD, as these patients may require increased monitoring.

Ketamine

Ketamine is a dissociative anesthetic that has been used for pain relief during labor and delivery. It works by blocking N-methyl-D-aspartate (NMDA) receptors in the brain, which helps to reduce pain perception. It is metabolized in the liver and has a half-life of 45 minutes.[112] Ketamine has also been shown to have some potential benefits for the parturient with OUD, as it may reduce the need for opioids and help to manage opioid withdrawal symptoms. A retrospective study examined the use of ketamine for pain relief in women with OUD who were undergoing labor and found that ketamine was associated with a lower rate of postdelivery opioid use and a shorter hospital stay compared to other forms of analgesia.[94] Another randomized controlled study included 60 patients who underwent cesarean delivery and were given a single intravenous 30 mg bolus of ketamine. The results revealed decreased pain scores and opioid consumption in the first 24 hours post-operatively.[113] Several studies have showed that ketamine and its metabolites appear in low levels in breast milk.[114,115] Although these results suggest that risk to breastfed neonates is low, ketamine breast milk transmission and its use in pregnant patients with OUD has not been studied; thus, breastfed neonates of mothers who receive ketamine should still be carefully monitored.

Dexmedetomidine

Dexmedetomidine, an alpha-2 adrenergic receptor agonist, is now commonly used as an adjuvant for sedative, analgesic, and anti-sympathetic effects in general anesthesia, spinal anesthesia, nerve block anesthesia, topical anesthesia, and postoperative analgesia. There are potential side effects like hypotension and bradycardia, which must be taken into

consideration by clinicians.[116] A suggested dosing for post cesarean delivery analgesia is intravenous bolus 1 mcg/kg over 10–20 minutes, followed by an intravenous infusion of 0.4–1.2 mcg/kg/hour.[53]

Gabapentinoids

Gabapentinoids are anticonvulsant drugs that have been used for perioperative pain management.[117] The effectiveness of these drugs is less clear in pregnant patients. A retrospective 10-year study found that administration of gabapentin in the post cesarean delivery period did not decrease pain scores or opioid consumption in women using buprenorphine.[118] Another randomized, double-blind, placebo-controlled trial in non-pregnant surgical patients found that perioperative administration of gabapentin did not improve postoperative pain scores but did reduce the time to opioid cessation.[119] Gabapentin may also attenuate nausea and vomiting following spinal anesthesia.[120] Although gabapentin may moderately lower pain scores in opioid-naïve patients, their use is associated with drowsiness and increased risk of respiratory depression.[121] This risk has shown to be amplified when concomitantly administered with opioids.[117,122] For the pregnant patient, there is some concern of neonatal drug exposure both in utero and through breast milk absorption. Anticonvulsants have previously been associated with increased risks of developmental delays such as autism and ADHD when transmitted through breast milk.[123] Notably, a systematic review found that concentrations of gabapentinoids are detected in breastmilk and are associated with sedation and failure to thrive in infants.[124] Despite these concerns, higher quality studies are needed, and mothers using gabapentin should continue breastfeeding.[123] Considering the relative ineffectiveness in patients with OUD and the risk of infant exposure, gabapentin is not recommended for routine use and should be decided on a case-by-case basis.

Post-Delivery Planning

Patients with OUD may have higher pain and opioid requirements after delivery and may require oral opioids upon discharge. In this case, patients and their families should be adequately counseled regarding the risk of relapse and trained on the use of naloxone in case of an overdose. Encouragement should be given for breastfeeding in women who are using opioid agonists, not resorting to illicit drugs, and do not have any other contraindications, like HIV infection. It is important to counsel women on the need to discontinue breastfeeding if a relapse occurs. Those using MOUDs should be maintained on their current regimen. The discharge plan should ensure that the patient's acute pain is addressed after discharge, the patient is safe to be discharged with the minimum opioid prescription and a taper plan in place, and that care is resumed as part of MOUD management. Overdose prevention education and nasal naloxone is advised at time of discharge.[125] Patients should be informed that due to potential opioid tolerance, the required naloxone dose might be higher.[126]

It is important to note that a Plan of Safe Care (POSC) may be required for infants born to mothers with OUD. A POSC is a protocol developed for infants affected by substance abuse or in this case, experiencing NAS, to ensure their safety following discharge from the hospital. This plan might be arranged ahead of birth by the family or caregiver, or it can be developed after birth as part of a discharge process. Factors considered when assessing the newborn's safety are the mother's health and bonding with the child, mental health concerns or presence of domestic violence, and availability of a family support system. This protocol addresses the child's health by facilitating developmental screening, close medical follow-up for adverse outcomes following NAS, and other home visiting programs. The POSC should also address the health of the mother with OUD through instructions on special care for the infant, comprehensive social services, and childcare. Many states require healthcare providers to report incidences of neonatal exposure to substances to child protective services (CPS), although these reports do not qualify as child abuse unless there is evidence of abuse or neglect.[127]

These patients should be carefully monitored as the post-partum period carries an increased risk of discontinuation of MOUD.[128] Considering that the rate of opioid overdose is the highest 7–9 months post-partum, these patients should be followed up appropriately.[129] Patients should have an appointment with their psychiatrist, primary care provider, or a social worker, counselor, or nurse at the clinic within a week of discharge.[130] A multidisciplinary approach is critical when formulating a plan for discharge.

Conclusion

The opioid epidemic has led to an increased number of pregnant patients presenting with OUD, which necessitates an interdisciplinary approach to care. Patients with OUD experience profound societal stigma that can affect the physician–patient relationship, thus it is crucial to foster an open physician–patient relationship for achieving improved fetal and maternal outcomes. Acute pain management in the prepartum, peripartum, and postpartum periods can be challenging in patients with chronic opioid use due to opioid tolerance and opioid-induced hyperalgesia, but adequate pain relief must be provided to prevent negative psychological and neonatal outcomes. A stepwise, patient-centered, multimodal approach is necessary to optimize pain relief in the parturient with OUD. For the pregnant patient being treated for OUD with MOUD, it is recommended to continue MOUD administration throughout the hospital stay, with buprenorphine being the most cost-effective option. Non-opioid analgesics such as acetaminophen and NSAIDs can also be used to achieve pain relief, but a multimodal approach is necessary. Other options for pain management include neuraxial short acting opioids. In patients with untreated OUD, opioid-sparing modalities should be prioritized. For opioid abstinent patients, it is critical to be mindful of the potential for overdose if opioid use is required. In all cases, several other non-opioid medications such as ketamine, nitrous oxide, and gabapentinoids can be used for their analgesic and opioid-sparing effects. However, more research is needed to elucidate their role for pregnant patients with OUD.

Disclosure

The authors report no conflicts of interest in this work.

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