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Methadone and Buprenorphine in the Perioperative Setting: A Review of the Literature

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Abstract

Purpose of Review The purpose of this review is to highlight the most recent literature and guidelines regarding perioperative methadone and buprenorphine use.

Recent Findings Surgical patients taking methadone and buprenorphine are being encountered more frequently in the perioperative period, and providers are becoming more familiar with their pharmacologic properties, benefits as well as precautions. Recommendations pertaining to buprenorphine therapy in the perioperative settings have changed in recent years, owing to more clinical and basic science research. In addition to their use in chronic pain and opioid use disorders, they can also be initiated for acute postoperative pain indications, in select patients and situations.

Summary Methadone and buprenorphine are being more commonly prescribed for pain management and opioid use disorder, and their continuation during the perioperative period is generally recommended, to reduce the risk of opioid withdrawal, relapse, or inadequately controlled pain. Additionally, both may be initiated safely and effectively for acute pain management during and after the operating room period.

Keywords Methadone · Buprenorphine · Acute pain · Perioperative pain

Introduction

Acute pain, including postoperative pain, continues to be inadequately controlled in a vast number of patients, despite years of research and advances in pain management [1]. The resulting consequences include worse patient outcomes and satisfaction, prolonged recovery, increased cost of healthcare utilization, increased opioid use, and development of chronic pain. Effective and safe pain management requires a multifaceted approach, often involving a selection of pharmacologic agents alone or in combination. Opioid therapy continues to be the most frequently used and effective approach, despite many of its adverse effects and limitations. Methadone and buprenorphine, having unique pharmacologic properties and analgesic benefits, have been emerging as valuable choices in the perioperative setting, by selectively engaging conventional and non-conventional antinociceptive pathways while potentially reducing side effects associated with traditional opioids. Given their somewhat complex metabolism, dosing, concern for adverse effects and infrequent use, these agents are generally less readily administered in the acute pain setting by anesthesia and pain providers. The purpose of this review is to summarize the current literature on analgesic effectiveness, safety, and perioperative utilization of methadone and buprenorphine in pain management and provide recommendations regarding their utilization.

Pharmacology

Methadone is a highly potent μ-opioid receptor agonist, with a weaker affinity for κ and δ opioid receptors [2]. In addition, methadone demonstrates moderate N-methyl-D-aspartate antagonism [3], as well as inhibition of serotonin and norepinephrine reuptake [4]. Methadone undergoes a biphasic elimination process with the alpha phase lasting 8–12 h (as pertinent for analgesia purposes) and a beta phase lasting 30–60 h (pertinent for withdrawal prevention and usually sub-analgesic) [5]. Given the metabolism complexity, methadone is prescribed differently for maintenance (24 h) and

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analgesia (4–8 h). The prolonged half-life of methadone, in addition to its activity at multiple receptors important in pain pathways, plays a pivotal role in its use in both patients with chronic pain and opioid use disorder (OUD).

Buprenorphine is a partial μ-opioid receptor agonist with antagonism at the κ and δ receptors [6]. It has a very low oral bioavailability and is commonly administered via other routes [7]. It is approved in the transdermal and buccal form for chronic pain; for OUD, this is expanded to include sublingual, intramuscular, subcutaneous, and subdermal [8]. Buccal and sublingual formulations most commonly also contain naloxone, which is poorly absorbed through these routes of administration [8]. However, if injected, the naloxone's high availability blocks opioid receptor buprenorphine binding and triggers withdrawal, discouraging abuse. Buprenorphine's high affinity for the μ receptor and slow dissociation from the receptor can cause up to a 95% decrease in other opioid binding [6, 9]. Buprenorphine's "partial agonism" is believed to contribute to a safer side effect profile [10], including a "ceiling effect" for respiratory depression [11]. In Moss et al., fourteen healthy volunteers and eight opioid-tolerant patients were given either continuous buprenorphine infusions or a placebo. They were then given escalating doses of intravenous fentanyl and minute ventilation was monitored. Higher buprenorphine plasma concentrations were associated with smaller changes in minute ventilation, suggesting buprenorphine may protect against respiratory from strong μ-agonists [12]. The elimination half-life of buprenorphine is variable and depends on the route of administration, with studies providing ranges from 3 h to over 40 h [9, 13].

Clinical Applications - Opioid Use Disorder and Chronic Pain

Methadone has long been utilized in the treatment of OUD, with initial clinical applications starting in the 19650 s in response to the increasing opioid epidemic in New York City [14]. Numerous studies have demonstrated methadone maintenance therapy to be associated with benefits and a decrease in multiple morbidities, including a decrease in HIV/infective hepatitis rates, illicit substance use, and an increase in rates of retention in rehabilitation programs [15–18]. A large cohort study consisting of over 32,000 participants demonstrated that methadone for OUD had a statistically significant mortality benefit [19]. The World Health Organization added methadone to an "essential medication" list in 2005 [20] with the number of patients on methadone treatment continuing to increase [21].

While appealing due to its long half-life and anti-hyperalgesic effects, the data for methadone and chronic pain is less compelling than its use in OUD. A Cochrane review of the use of methadone in chronic neuropathic pain, looking into 3 studies and 105 participants, found "very low quality" evidence for methadone's efficacy and safety in chronic neuropathic pain without enough data for pooled analysis [18]. An older Cochrane review published in 2012 had a broader scope, looking at methadone's efficacy in patients with non-cancer pain [19]. Despite the theoretical increase in patient sampling, the authors also state that there was very limited evidence and that no conclusions could be made regarding the safety and efficacy of methadone vs placebo or other therapies. Methadone is more commonly used to treat cancer pain [20]. A Cochrane review published in 2017 demonstrated low-quality evidence that methadone had similar analgesic effects to other opioids, likely at a decreased cost [21].

Buprenorphine was first approved by the United State Food and Drug Administration in 2002 for the treatment of opioid dependence or opioid use disorder, and it has been increasingly studied and utilized [22]. A multicentered randomized control trial of 326 patients with OUD was terminated early after sublingual buprenorphine was shown to significantly decrease illicit opioid use and craving [23]. Like methadone, buprenorphine therapy in OUD has been shown to decrease illicit opioid use, reduce cases of HIV infection, and improve mortality [15, 17]. A 2016 randomized control trial of 177 participants demonstrated the efficacy of buprenorphine implants as being non-inferior to sublingual buprenorphine [24]. Long-acting subcutaneous buprenorphine implants have also been studied in the OUD population, with recent Phase III data demonstrating high levels of safety and efficacy [25].

Buprenorphine has been used in the chronic pain population [7]. A randomized control trial of 186 patients with painful diabetic neuropathy found that over 85% of patients in the treatment group experienced a more than 30% decrease in pain, a significant ($p < 0.001$) increase when compared to placebo [26]. However, the study was limited by a large number of participants withdrawing due to adverse events, mainly nausea and constipation, in both the treatment and control groups. The results published from two randomized control trials in patients with chronic low back pain showed significantly improved sleep scores relative to control [27]. While additional delivery mechanisms for buprenorphine now have a labeled use for moderate to severe chronic pain, buprenorphine is likely underdosed and underused in the chronic pain population [7].

Preoperative Concerns

Anesthesia practitioners not infrequently encounter patients on methadone and buprenorphine therapy presenting to the operating room for procedures. Important to

keep in mind, in the preoperative workup, is methadone's Qt prolongation, with increasing serum methadone concentration being correlated with increased prolongation [28]. While there are Clinical Practice Guidelines published in 2014 for outpatient QT monitoring for patients on methadone [29], to the author's knowledge there are no current guidelines for pre-operative EKG monitoring for patients on methadone. Suffice it to say that providers should have a recent EKG to establish a patient's current QT along with intra-op rhythm monitoring and guide additional management on a case-by-case basis. Additionally, methadone is metabolized via the CYP 450 system, with recent in vitro data suggesting that CYP 2B6 is the major (but certainly not only) CYP involved in the metabolism of methadone [30, 31]. This metabolism via the CYP system can lead to drug-drug interactions with other drugs metabolized via the CYP system, as well as contribute to the variability of response seen amongst patients receiving methadone. Providers should be aware of these interactions and always do a thorough screening for drug-drug interactions and seek help from their pharmacist if there are concerns.

Consideration and discussion pertaining to perioperative buprenorphine therapy revolve around its label as a "partial agonist" and its interaction with opioid receptors. Care should also be taken when initiating buprenorphine in the operative setting, especially with data from the OUD setting showing buprenorphine can increase overdose risk if the dose is raised too quickly [22]. Data from buprenorphine earlier testing showed that some full μ-agonists were unable to displace buprenorphine, further potentiated by its long half-life (24 h for sublingual, 48 for buccal, 26 for transdermal, and up to 60 days for some slow-release subcutaneous formulations) [32]. In that context, it was initially suggested that buprenorphine in the perioperative setting would bind too well to the opioid receptors and not be displaced by other PO or IV opioid medications given to control pain, causing difficulty controlling the patient's post-op pain or even worse, precipitating withdrawal. However, recent receptor data has shown that even when higher doses of buprenorphine are used, some opioid receptors remain available for binding [33, 34]. Thus despite buprenorphine's high affinity at the μ-receptor, there are still receptors unoccupied to bind full agonists required to treat acute pain [35]. Recent educational review and recommendations from a multi-society expert panel concluded that, to decrease risk of OUD recurrence, buprenorphine should not be routinely discontinued in the perioperative setting, and taper should be avoided. Furthermore, it can be initiated in untreated patients with OUD and acute pain to decrease the risk and death from overdose [36]. For additional pain control, they recommended multimodal analgesia and full μ agonists with high affinity for the μ receptor.

Acute Pain and Intraoperative Planning

Due to its longer half-life, μ-opioid receptor agonist effect, and several other pharmacokinetic and analgesic properties, methadone can be a valuable option in the perioperative setting, especially for procedures resulting in moderate to severe pain. It's utilization, however, remains limited, possibly due to concerns for delayed respiratory depression, unfamiliarity with dosing, attempts to decrease opioid utilization, and other reasons. [37]. However, there is a growing body of data demonstrating the beneficial effect of methadone in the perioperative period. A 2015 randomized control trial by Murphy et al. enrolled 156 adult cardiac surgery patients to receive either intraoperative methadone or fentanyl during their surgery. The methadone group showed a decreased morphine requirement in the first 24 h after surgery ($p < 0.001$), significantly decreased pain with coughing ($p < 0.001$), and increased patient satisfaction with pain control at 24 h ($p = 0.006$) [38]. A systematic review of cardiac surgery patients found four studies examining the effects of intraoperative methadone, finding an overall decrease in postoperative pain and opioid use [39]. Another randomized control trial published in 2017 involved 115 patients receiving posterior spinal fusion surgery and randomized them to either IV methadone at the start of surgery or IV hydromorphone at the time of closure. Similarly to the 2015 study, the patients in the methadone group used less hydromorphone for pain in the first 3 days post-op ($p < 0.001$), had better pain scores at rest and with movement ($p < 0.001$), and had higher overall satisfaction with their pain management ($p = 0.001$) [40]. A randomized control trial designed for "dose-finding" in the ambulatory surgery population found that intraoperative methadone 0.15 mg/kg was associated with improved pain control and similar side effects to traditional pain control (fentanyl, hydromorphone) [23]. Machado et al. enrolled 56 patients with morbid obesity (BMI > 35) and randomized them to intraoperative methadone or intraoperative fentanyl. The subset randomized to fentanyl had significantly higher postoperative morphine use and higher pain scores ($p = 0.01$ to $p < 0.001$), without significantly higher requirements for oxygen or decreased RASS scores [41]. A recent review paper examining intraoperative methadone in the pediatric population found decreased overall opioid use and lower pain scores when compared to shorter-acting opioids [42]. However, the authors noted that only a few interventional studies were available for review. A review paper on intraoperative methadone in the adult population found 13 studies that met the inclusion criteria [43]. The authors found that intraoperative methadone decreased pain scores through 48 h postoperatively compared to other opioids [43].

With respect to buprenorphine, there have been several recent studies demonstrating the effectiveness of treating

acute pain in the setting of maintaining buprenorphine dosing. In a sample of 29 patients admitted with cancer pain, Mercadante et al. demonstrated safe and effective breakthrough pain control with intravenous morphine while continuing the patient's transdermal dosing of buprenorphine [44]. This first showed the safety and feasibility of maintaining a patient's buprenorphine dose while treating acute pain exacerbations with IV μ-opioid agonists. A later case series demonstrated the effectiveness of full μ-opioid agonists in patients undergoing "major surgery" while maintaining their doses of sublingual buprenorphine [45]. A recent retrospective study looking at critically ill patients admitted to the ICU who were maintained on their buprenorphine dose for OUD led to lower cumulative opioid doses overall [46]. Discontinuation of buprenorphine in the peri-op period is further discouraged by the significantly higher rates of morbidity and mortality demonstrated in patients who discontinued buprenorphine maintenance treatment [47].

Postoperative Management

The initial approach to managing acute pain in patients receiving home opiates (e.g., methadone, buprenorphine) involves promptly continuing their regular opiate regimen, following verification with their outpatient prescriber [48]. The analgesic duration of methadone and buprenorphine is six to eight hours. Thus, once-daily dosing of home methadone and buprenorphine may be divided into doses given every eight hours if patients are anticipated to stay inpatient for more than a couple of days.

Considering opiate desensitization due to chronic exposure, the postoperative period warrants maximizing regional anesthesia, non-opiate medications, and complementary therapies [49, 50], particularly appropriate treatment of neuropathic pain with gabapentinoids and muscular pain and spasms with muscle relaxants (e.g., methocarbamol, tizanidine). Nonetheless, opiates remain the cornerstone for managing moderate to severe pain, especially in acute inpatient settings, aligning with the WHO Analgesic Ladder [51]. Notably, opiate-dependent patients, including those in treatment for opioid use disorder (OUD), may necessitate doses higher of opioid analgesics to effectively manage the noxious stimuli and inflammation commonly seen in postoperative pain [52].

For patients on home methadone/buprenorphine, postoperative pain can be addressed with supplementary pure mu-opioid receptor agonists (e.g., hydromorphone, oxycodone) and/or additional methadone/buprenorphine. Methadone may be gradually titrated up to account for postoperative pain as long as there is a plan to titrate back to home methadone dose before discharge or to a dose agreed upon with their outpatient prescriber. EKG should be checked to detect prolonged QTc with an increase of methadone. Shorter-acting mu-opioid receptor agonists can be dosed if the patient needs more immediate pain relief, taking into consideration that these patients may need higher doses of opiates. Greater preoperative doses of buprenorphine have been associated with greater postoperative opioid requirements [53].

For patients with untreated OUD or challenging pain control, initiating post-operative methadone and buprenorphine may confer benefits over typical short and long-acting pure mu-opioid receptor agonists due to methadone's moderate NMDA antagonism and inhibition of serotonin/norepinephrine reuptake [41]. Furthermore, methadone's long-acting agonism on mu-opioid receptors reduces craving and euphoria for opiates, which may mitigate the development or exacerbation of OUD. Multiple RCTs and meta-analyses have noted methadone's possible opiate-sparing effects, with continued analgesic effects up to three months after complex spine and cardiac procedures [54].

While there are numerous studies demonstrating the opiate-sparing effects of intraoperative methadone on postoperative pain and opiate usage, there is scarce data on the post-operative initiation of methadone and buprenorphine for patients not previously on these medications, preoperatively. For opiate-naive patients, the dosing of oral methadone ranges from 2.5 to 10 mg every eight hours. In a single-study, retrospective cohort study of adult patients, respiratory depression was more common among patients who were newly initiated on methadone post-operatively [55]. Given its multiple analgesic benefits and long duration of action, methadone could be initiated post-operatively in select patients and procedures with challenging postoperative pain management, complex pain states or opioid tolerant patients requiring escalating doses of traditional opioids. With regards to buprenorphine, the normal dose of sublingual buprenorphine for analgesia is 75 mcg every 12–24 h, which is lower than the normal starting dose of 2 to 4 mg when used for OUD. A meta-analysis comparing buprenorphine with morphine for acute pain management revealed no difference in pain, incidence of respiratory depression, or sedation, but revealed that buprenorphine use was associated with significantly less pruritus (OR = 0.31; 95% CI = 0.12–0.84; I2 = 6%; $P = 0.02$) [56]. Retrospective cohort study involving 146 patients who had undergone elective and emergency abdominal surgery and were transitioned postoperatively from intravenous opioids to oxycodone versus sublingual buprenorphine found significant reduction in opioid requirements and reduced pain score on movement [57]. In similar findings, patients receiving stem-cell transplant and experiencing severe mucositis pain were found to have reduced opioid requirements and pain upon initiation of buprenorphine-based pain protocol [58].

Conclusions

Methadone and Buprenorphine, long-acting opioids with unique pharmaco-kinetic profiles, targeting opioid and non-opioid analgesic pathways, shown to be effective in the treatment of OUD and chronic pain, have been emerging as valuable and effective agents in acute perioperative pain settings. Preoperative methadone and buprenorphine therapy is generally recommended to be continued in the perioperative therapy to avoid risks of withdrawal, relapse or poorly controlled pain. Intraoperative utilization of methadone has demonstrated reduced opioid consumption and pain scores and improved patient satisfaction. The duration of perioperative therapy, patient characteristics including multiorgan system function, and expected severity of pain should be carefully considered. This is especially important when initiating or adjusting the analgesic regimen. Larger scale better quality clinical trials are needed to further elucidate the efficacy and safety of these drugs in the perioperative setting and potentially allow for wider utilization of these two agents.

Author Contributions All three authors conducted research on the topic, wrote the main manuscript text and reviewed the manuscript.

Data Availability No datasets were generated or analysed during the current study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

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. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287–98. https://doi.org/10.2147/JPR.S144066.
2. Dinis-Oliveira RJ. Metabolomics of methadone: clinical and forensic toxicological implications and variability of dose response. Drug Metab Rev. 2016;48:568–76.
3. Sotgiu ML, Valente M, Storchi R, Caramenti G, Biella GE. 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(4):284–90.
4. Codd EE, Shank RP, Schupsky JJ, Raffa RB. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: structural determinants and role in antinociception. J Pharmacol Exp Ther. 1995;274(3):1263–70.
5. Fishman SM, Wilsey B, Mahajan G, Molina P. Methadone reincarnated: novel clinical applications with related concerns. Pain Med. 2002;3(4):339–48.
6. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine: the significance of receptor binding. Br J Anaesth. 1985;57(2):192–6.
7. Fishman MA, Kim PS. Buprenorphine for chronic pain: a systemic review. Curr Pain Headache Rep. 2018;22:1–7.
8. Warner NS, Warner MA, Cunningham JL, Gazelka HM, Hooten WM, Kolla BP, Warner DO. A practical approach for the management of the mixed opioid agonist-antagonist buprenorphine during acute pain and surgery. In: Mayo clinic proceedings, vol. 95. 6th ed. Elsevier; 2020. p. 1253–67.
9. Elkader A, Sproule B. Buprenorphine: clinical pharmacokinetics in the treatment of opioid dependence. Clin Pharmacokinet. 2005;44:661–80.
10. Cicero TJ, Surratt HL, Inciardi J. Use and misuse of buprenorphine in the management of opioid addiction. J Opioid Manag. 2007;3(6):302–8.
11. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994;55(5):569–80.
12. Moss LM, Algera MH, Dobbins R, Gray F, Strafford S, Heath A, van Velzen M, Heuberger JA, Niesters M, Olofsen E, Laffont CM. Effect of sustained high buprenorphine plasma concentrations on fentanyl-induced respiratory depression: a placebo-controlled crossover study in healthy volunteers and opioid-tolerant patients. PLoS ONE. 2022;17(1):e0256752.
13. Jonan AB, Kaye AD, Urman RD. Buprenorphine formulations: clinical best practice strategies recommendations for perioperative management of patients undergoing surgical or interventional pain procedures. Pain Physician. 2018;21(1):E1.
14. Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): a review of historical and clinical issues. Mt Sinai J Med (New York). 2000;67(5–6):347–64.
15. Degenhardt L, Larney S, Kimber J, Gisev N, Farrell M, Dobbins T, Weatherburn DJ, Gibson A, Mattick R, Butler T, Burns L. The impact of opioid substitution therapy on mortality post-release from prison: retrospective data linkage study. Addiction. 2014;109(8):1306–17.
16. D'Aunno T, Pollack HA, Frimpong JA, Wuchiett D. Evidence-based treatment for opioid disorders: a 23-year national study of methadone dose levels. J Subst Abuse Treat. 2014;47(4):245–50.
17. Gowing L, Farrell M, Bornemann R, Sullivan L, Ali R. Substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev. 2008;(2):CD004145. https://doi.org/10.1002/14651858.CD004145.pub3. Update in: Cochrane Database Syst Rev. 2011;(8):CD004145. https://doi.org/10.1002/14651858.CD004145.pub4. PMID: 18425898.
18. Pierce M, Bird SM, Hickman M, Marsden J, Dunn G, Jones A, Millar T. Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. Addiction. 2016;111(2):298–308.
19. Evans E, Li L, Min J, Huang D, Urada D, Liu L, Hser YI, Nosyk B. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006–10. Addiction. 2015;110(6):996–1005.
20. World Health Organization. WHO drug information. World Health Organization; 2022.
21. Abuse S. Mental health services administration. Trends in the use of methadone and buprenorphine at substance abuse treatment facilities: 2003 to 2011. NSSATS Rep; 2013. p. 1–5.
22. Shulman M, Wai JM, Nunes EV. Buprenorphine treatment for opioid use disorder: an overview. CNS Drugs. 2019;33(6):567–80.

23. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med. 2003;349(10):949–58.
24. Rosenthal RN, Lofwall MR, Kim S, Chen M, Beebe KL, Vocci FJ, PRO-814 Study Group. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial. Jama. 2016;316(3):282–90.
25. Andorn AC, Haight BR, Shinde S, Fudala PJ, Zhao Y, Heidbreder C, Learned SM, Fox NL, Nadipelli VR, Hassman D, Rutrick D. Treating opioid use disorder with a monthly subcutaneous buprenorphine depot injection: 12-month safety, tolerability, and efficacy analysis. J Clin Psychopharmacol. 2020;40(3):231–9.
26. Simpson RW, Wlodarczyk JH. Transdermal buprenorphine relieves neuropathic pain: a randomized, double-blind, parallel-group, placebo-controlled trial in diabetic peripheral neuropathic pain. Diabetes Care. 2016;39(9):1493–500.
27. Yarlas A, Miller K, Wen W, Lynch SY, Ripa SR, Pergolizzi JV, Raffa RB. Buprenorphine transdermal system improves sleep quality and reduces sleep disturbance in patients with moderate-to-severe chronic low back pain: results from two randomized controlled trials. Pain Pract. 2016;16(3):345–58.
28. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. 2005;95(7):915–8.
29. Chou R, Cruciani RA, Fiellin DA, Compton P, Farrar JT, Haigney MC, Inturrisi C, Knight JR, Otis-Green S, Marcus SM, Mehta D. 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(4):321–37.
30. Kharasch ED, Stubbert K. Role of cytochrome P4502B6 in methadone metabolism and clearance. J Clin Pharmacol. 2013;53(3):305–13.
31. Kharasch ED. Current concepts in methadone metabolism and transport. Clin Pharmacol Drug Dev. 2017;6(2):125–34.
32. AHFS® DI Essentials™. American Society of Health-System Pharmacists®, 4500 East-West highway, suite 900, Bethesda, MD 20814. 2004.
33. Quaye AN, Zhang Y. Perioperative management of buprenorphine: solving the conundrum. Pain Med. 2019;20(7):1395–408.
34. Comer SD, Walker EA, Collins ED. Buprenorphine/naloxone reduces the reinforcing and subjective effects of heroin in heroin-dependent volunteers. Psychopharmacology. 2005;181:664–75.
35. Silverman S. Opioid induced hyperalgesia: clinical implications for the pain practitioner. Pain Physician. 2009;12(3):679.
36. Kohan L, Potru S, Barreveld AM, Sprintz M, Lane O, Aryal A, Emerick T, Dopp A, Chhay S, Viscusi E. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med. 2021;46(10):840–59. **This articles provides information on buprenorphine pharmacology, the perioperative management of patients on buprenorphine for opioid use disorder, and the advantages of initiation of buprenorphine postoperatively. It provides recommendations pertaining to management of buprenorphine in the perioperative setting and initiation in the postoperative perioperative period in patients with suspected opioid use disorder**.
37. Murphy GS, Wu CL, Mascha EJ. Methadone: new indications for an old drug? Anesth Analg. 2019;129(6):1456–8.
38. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Marymont JH, Shear T, Parikh KN, Patel SS, Gupta DK. Intraoperative methadone for the prevention of postoperative pain: a randomized, double-blinded clinical trial in cardiac surgical patients. Anesthesiology. 2015;122(5):1112–22.
39. Lobova VA, Roll JM, Roll ML. Intraoperative methadone use in cardiac surgery: a systematic review. Pain Med. 2021;22(12):2827–34. **The article investigates the effects of intraoperative methadone, compared to fentanyl and morphine, on pain scores, opioid consumption, and adverse effects in adults undergoing cardiothoracic surgery. The systematic review provides summary of the pain levels, intravenous methadone utilization and perioperative opioid consumption as well as adverse effects in the immediate postoperative period**.
40. Murphy GS, Szokol JW, Avram MJ, Greenberg SB, Shear TD, Deshur MA, Vender JS, Benson J, Newmark RL. Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: a randomized, double-blinded, controlled trial. Anesthesiology. 2017;126(5):822–33. **This articles evaluates the postoperative analgesic requirements in patients undergoing posterior spinal fusion surgery and who received either intravenous methadone or hydromorphone during surgery. It assesses pain scores, opioid related side effects, hemodynamic variables and patients satisfaction with pain management. It also provides recommendations on how to further define the optimal dose of methadone in this patient population with severe postoperative pain**.
41. Machado FC, Palmeira CC, Torres JN, Vieira JE, Ashmawi HA. Intraoperative use of methadone improves control of postoperative pain in morbidly obese patients: a randomized controlled study. J Pain Res. 2018;2:2123–9. **The articles provides insights into not well studied intraoperative use of methadone, as compared to fentanyl, in obese patient population undergoing bariatric surgery. It evaluates pain scores and opioid utilization postoperatively, and 3 months after surgery**.
42. Azamfirei R, Procaccini D, Lobner K, Kudchadkar SR. The effects of intraoperative methadone on postoperative pain control in pediatric patients: a scoping review. Anesth Analg. 2023;7:10–213.
43. Machado FC, Vieira JE, de Orange FA, Ashmawi HA. Intraoperative methadone reduces pain and opioid consumption in acute postoperative pain: a systematic review and meta-analysis. Anesth Analg. 2019;129(6):1723–32.
44. Mercadante S, Villari P, Ferrera P, Porzio G, Aielli F, Verna L, Casuccio A. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. J Pain Symptom Manage. 2006;32(2):175–9.
45. Kornfeld H, Manfredi L. Effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery: a case series. Am J Ther. 2010;17(5):523–8.
46. Quaye A, Wampole C, Riker RR, Seder DB, Sauer WJ, Richard JM, Craig WY, Gagnon DJ. Buprenorphine continuation during critical illness associated with decreased inpatient opioid use in individuals maintained on buprenorphine for opioid use disorder in a retrospective study. J Clin Pharmacol. 2023;63(9):1067–73. **Article explores the incidence of buprenorphine continuation during critical illness among patients receiving buprenorphine for the treatment of opioid use disorder. It further studies relationship between non-buprenorphine opioid exposure and buprenorphine administration**.
47. Bentzley BS, Barth KS, Back SE, Book SW. Discontinuation of buprenorphine maintenance therapy: perspectives and outcomes. J Subst Abuse Treat. 2015;52:48–57.
48. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. 2006;144(2):127–34.
49. Kaye AD, Granier AL, Garcia AJ, Carlson SF, Fuller MC, Haroldson AR, et al. Non-opioid perioperative pain strategies for the clinician: a narrative review. Pain Ther. 2020;9(1):25–39.

50. Stromer W, Michaeli K, Sandner-Kiesling A. Perioperative pain therapy in opioid abuse. Eur J Anaesthesiol. 2013;30(2):55–64.
51. Anekar AA, Hendrix JM, Cascella M. Who analgesic ladder. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Apr 28]. Available from http://www.ncbi.nlm.nih.gov/books/NBK554435/.
52. Athanasos P, Smith CS, White JM, Somogyi AA, Bochner F, Ling W. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations. Pain. 2006;120(3):267–75.
53. Martin YN, Pearson ACS, Tranchida JR, Weingarten TN, Schulte PJ, Sprung J. Implications of uninterrupted preoperative transdermal buprenorphine use on postoperative pain management. Reg Anesth Pain Med. 2019;44(3):342–7.
54. Murphy GS, Avram MJ, Greenberg SB, Shear TD, Deshur MA, Dickerson D, et al. Postoperative pain and analgesic requirements in the first year after intraoperative methadone for complex spine and cardiac surgery. Anesthesiology. 2020;132(2):330–42.
55. Bova SE, Kruer RM, Nesbit SA, Grant MC, Jarrell AS. Perioperative methadone prescribing and association with respiratory depression. J Opioid Manag. 2020;16(6):443–9.
56. White LD, Hodge A, Vlok R, Hurtado G, Eastern K, Melhuish TM. Efficacy and adverse effects of buprenorphine in acute pain management: systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. 2018;120(4):668–78.
57. Heldreich C, Ganatra S, Lim Z, Meyer I, Hu R, Weinberg L, Tan CO. Complete opioid transition to sublingual Buprenorphine after abdominal surgery is associated with significant reductions in opioid requirements, but not reduction in hospital length of stay: a retrospective cohort study. BMC Anesthesiol. 2022;22(1):30.
58. Meyer I, Chan B, Cohen E, Dube E, Hu R, Yeomans M, Pontonio F, Heldreich C, O'Conghaile S, Holmes N, Maroon N, Weinberg L, Tan CO. Use of a buprenorphine-based pain management protocol is associated with reduced opioid requirements and pain on swallowing in oral mucositis: a retrospective cohort study. Support Care Cancer. 2022;30(7):6013–20.

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