



REVIEW ARTICLE

Review of Literature: Efficacy of Intraoperative Intravenous Methadone in Reducing Postoperative Opioid Consumption

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Abstract

Research Topic

Review of Literature: Efficacy of Intraoperative Intravenous Methadone in Reducing Postoperative Opioid Consumption in Various Surgical Populations.

Background: This article will review the current literature on the efficacy of intraoperative intravenous methadone in reducing postoperative opioid consumption in bariatric, ambulatory, complex spine, and cardiac surgeries.

Project Aim: The purpose of this article is to educate anesthesia providers on the latest data regarding the utilization of intravenous (IV) methadone as an effective strategy in reducing postoperative pain and opioid requirements, chronic post-surgical pain, opioid-related adverse events, and improved patient satisfaction in various surgical populations. There is hesitancy in the anesthesia field with administering long-acting narcotics due to fear of respiratory depression, prolonged drowsiness/sedation, and postoperative nausea and vomiting. At the conclusion of this article, the reader will be able to identify the benefits of intraoperative IV methadone while maintaining a better safety profile over other narcotic modalities in reducing postoperative pain in specific surgical populations.

Keywords

Methadone, Intraoperative methadone, Methadone postoperative pain

46,000. In 2017, HHS declared the opioid crisis a public health emergency and published a report titled a 5-Point Strategy to Combat the Opioid Crisis: better prevention, treatment, and recovery services; better data; better pain management; better availability of overdose-reversing drugs; better research. There has not been a reduction in opioid-related deaths in the last decade despite public awareness.

Novel opioid-sparing modalities must be explored in perioperative pain management to combat the opioid crisis. Greater than 40% of surgical patients experience inadequate postoperative pain management [2]. This has been correlated with increased morbidity, decreased physical function, diminished quality of life, impaired sleep, and prolonged opioid use during and after hospitalization [2]. Growing research of intravenous methadone use intraoperatively has shown promise in reducing postoperative opioid consumption by up to 50%, lowering the risk of chronic postsurgical pain, and improving patient satisfaction while maintaining the safety profile compared to other narcotic-based intraoperative pain regimens [3].

Review of Literature

Pharmacology

Methadone is available clinically in the United States as a racemic mixture of the *R* and *S* enantiomers [4]. Enantiomers are one of two types of stereoisomers that are non-superimposable, mirror images of one another with identical chemical and physical properties but possess different chemical reactions with other enantiomer molecules. Many biological molecules are

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According to the United States Department of Health and Human Services (HHS), [1] between 2017 and 2020, annual deaths due to overdose of synthetic opioids other than methadone were greater than



Citation: Karunanidhi P (2022) Review of Literature: Efficacy of Intraoperative Intravenous Methadone in Reducing Postoperative Opioid Consumption. Int J Anesthetic Anesthesiol 9:142. doi.org/10.23937/2377-4630/1410142

Accepted: July 06, 2022; **Published:** July 08, 2022

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enantiomers and a drug's enantiomers can have distinct physiological effects, which is true of methadone [5]. Methadone is both a μ -opioid receptor agonist and a potent N-methyl-D-aspartate (NMDA) receptor antagonist as a racemic mixture [4]. Levomethadone (*R* enantiomer) is a μ -opioid receptor agonist with high affinity for the μ receptors, but low affinity for δ -opioid, κ -opioid, and NMDA receptors. Dextromethadone (*S* enantiomer) possesses a high affinity for NMDA receptors as a glutamate antagonist with no clinically significant affinity for opioid receptors [6]. Methadone also inhibits the presynaptic reuptake of serotonin and norepinephrine, which can play a role in antinociception and mood enhancement [4].

Methadone is equipotent to morphine with an onset time of 8 minutes, but with a significantly longer duration of action. The plasma half-life is highly variable (13-100 hours), but patients require redosing every 4-8 hours to maintain analgesia [7]. Methadone is as a short-acting opioid with 3 to 4 hours of analgesia with lower intravenous dosages of 5 to 10mg due to rapid redistribution, but with larger intravenous dosages of 20mg or more, the duration of analgesia is determined by elimination leading to a clinical analgesic effect of approximately 35 hours resembling the elimination half-life [8]. Methadone blood concentrations versus time simulations indicate the minimum effective analgesic blood concentrations of methadone is approximately 30 ng/mL based upon its pharmacokinetic properties. The threshold for significant respiratory depression (5-6 breaths/minute) is approximately 100ng/mL. The intraoperative goal for methadone dosing is to achieve blood concentration levels below the respiratory depression threshold to maximize the analgesic duration of methadone [9].

Oral methadone metabolism varies significantly between individuals, leading to difficulty with initial dosing. This effect is less pronounced when administered intravenously. Methadone is metabolized via the cytochrome P450 (CYP450) system, which include CYP3A4, CYP2B6, and CYP2D6 enzymes. The interindividual metabolism variability is attributed to genetic variability in metabolism. Medications that either induce or inhibit these enzymes can affect the rate of metabolism [8].

Postsurgical acute pain is a significant risk factor for chronic pain, seen in 10 to 50% of patients [8]. According to Werner and Kongsgaard, [10] chronic postsurgical pain is defined as pain persisting at least 3 months after surgery, that was not present before surgery, or that had different characteristics or increased intensity from preoperative pain, localized to the surgical site or referred area, and other possible causes of the pain were excluded.

Surgical pain activates NMDA receptors, which are implicated in the development of hyperalgesia, allodynia,

opioid tolerance, and chronic pain. Methadone is postulated to reduce postoperative opioid consumption and decrease the risk of chronic pain development in various surgical populations due to its action as a long-acting μ -opioid receptor agonist and NMDA antagonist. Methadone may be prescribed for the prevention of opioid withdrawal symptoms and in the treatment of chronic pain [8].

Cardiac Surgery

A high percentage of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) experience acute postsurgical pain, especially during the initial 48 hours postoperatively. Postoperative adverse events related to inadequate pain management in this surgical population include pulmonary dysfunction, myocardial ischemia, and arrhythmias secondary to pain activation of the sympathetic nervous system. It is imperative to implement appropriate pain management strategies to attenuate adverse events [11].

The largest intraoperative clinical trial evaluating the opioid-sparing effects of methadone was conducted on patients undergoing cardiac surgery with CPB at NorthShore University Health System [11]. One hundred fifty-six patients were randomized to be given either 0.3mg/kg of methadone intravenously (maximum dose of 30 mg) or 12 μ g/kg of fentanyl intravenously (maximum dose of 1200 μ g) before cardiopulmonary bypass. One-half of either methadone or fentanyl at induction was administered via an infusion pump over 5 minutes. The remainder of the drug was infused over the following two hours. Anesthesia maintenance consisted of sevoflurane with no additional opioids administered. Pain, sedation, nausea, vomiting, itching, ventilatory, hemodynamic, and satisfaction assessments were conducted at 2, 4, 8, 12, 24, 48, and 72 hours post-extubation after admission to the ICU. There were no significant differences in patient demographics between the methadone and fentanyl groups [11].

Total doses of intravenous morphine and oral 10-mg hydrocodone/325-mg acetaminophen tablets administered were compiled and compared between the methadone and fentanyl groups in this study. The methadone group had decreased morphine requirements in the first 24 hours after cardiac surgery and improved pain scores at 12 hours postoperatively compared with the fentanyl group. Five patients in the methadone group required no morphine in the initial 24 hours, and four out of those five required no morphine during the entire hospitalization. Overall intravenous morphine requirements were reduced by 43% in the methadone group versus the fentanyl group during the first three postoperative days. There were no differences between the two groups in oral narcotic consumption. Overall patient satisfaction with pain management measured on a 100-mm verbal analog scale was higher in the methadone group (median 90 to

100) versus the fentanyl group (median 70 to 90). There were no differences in adverse events between the two opioid groups [11].

The researchers performed follow-up pain questionnaires after discharge to assess the patients' frequency and intensity of pain at 1, 3, 6, and 12 months after surgery. Of the 156 patients in the initial study, 104 (67%), 100 (64%), 83 (53%), and 65 (42%) patients at 1, 3, 6, and 12 months, respectively, responded to the survey. Postsurgical pain frequency at one month was significantly lower in the methadone group (median less than once a week) compared to the fentanyl group (median twice a week), but no differences were found at 3, 6, and 12 months. Both groups had low median pain scores beyond one month; therefore, no significant differences were found between the two groups beyond one month [12].

Two Brazilian studies assessing the opioid-sparing effects of methadone in cardiac surgical patients observed similar results in patients randomized to receive either intraoperative methadone or morphine. A study by Udelsmann, et al. [13] enrolled 55 patients who received intravenously either 20mg of methadone, 20mg of morphine, or saline (control) during anesthetic induction. The methadone group required significantly less postoperative analgesics (45% needed none), and the incidence of nausea and vomiting was lower in the first 24 postoperative hours. A study by Carvalho, et al. [14] randomized 100 patients to receive either 0.1 mg/kg of methadone or morphine intravenously at the end of coronary artery bypass grafting. Significantly fewer patients in the methadone group required postoperative opioids than in the morphine group (29% vs. 43%), and pain scores on a 0 to 10 scale were lower in the methadone group at 24 postoperative hours. Few studies exist on the effects of methadone in cardiac surgical patients, but these three studies identified beneficial results in the methadone group versus other opioid groups with regards to overall postoperative opioid requirements, pain levels, and incidence of adverse events.

Spine Surgery

Gourlay, et al. [15] conducted the first perioperative study investigating the prolonged analgesic effects of methadone. The researchers administered 20mg of methadone intravenously at anesthetic induction to 23 patients undergoing orthopedic or general surgeries (11 spinal fusion and 12 general surgical patients). Nine patients (39%) required no postoperative pain medication during the 72 hour observation period, six patients (26%) requested non-narcotic analgesics (first dose at 27 hours), and eight patients required narcotic medication (first dose at 18 hours). The median duration of analgesia for the 23 patients from the 20 mg of methadone administered during anesthetic induction was 27 hours.

Two studies have evaluated the effects of methadone in adults undergoing complex spine surgery since 1982. Gottschalk, et al. [3] randomized 29 patients undergoing multilevel thoracolumbar spine surgery with instrumentation and fusion to receive intravenously either methadone (0.2mg/kg) at induction or a continuous sufentanil infusion (0.25mcg/kg/h after a loading dose of 0.75mcg/kg). Postoperative analgesia was managed with a fentanyl, morphine, or hydromorphone patient-controlled analgesia (PCA) at the discretion of the attending neurosurgeon. No significant differences were noted in demographic data between the two groups. Opioid requirements and pain scores were approximately 50% lower in the methadone group at the 48-hour benchmark, with opioid reduction extending up to 72 hours. The incidence of adverse events and side effects were comparable in both groups.

Murphy, et al. [16] enrolled 115 patients undergoing posterior spinal fusion surgery. The patients were randomized to receive intravenously either methadone 0.2mg/kg at start of surgery or hydromorphone 2mg at surgical closure. Hydromorphone consumption, pain scores, and patient satisfaction with pain management were measured on the first three postoperative days. Median hydromorphone requirements were lower in the methadone group on postoperative days 1, 2, and 3. Overall opioid requirements were reduced by more than 50% in the methadone group. Pain scores at rest and with activity were lower in the methadone group. The methadone group displayed higher overall patient satisfaction throughout the 72 postoperative hours, and the incidence of opioid-related adverse events did not differ between the two groups.

The researchers in the previous study performed follow-up pain questionnaires at 1, 3, 6, and 12 months after surgery to assess the patients' weekly frequency and intensity of pain. Of the 115 patients in the study, 75 (65%), 66 (57%), 74 (64%), and 66 (57%) patients at 1, 3, 6, and 12 months, respectively, responded to the survey. There were no demographical differences between the methadone and hydromorphone groups. Postsurgical pain frequency at three months was significantly lower in the methadone group (median less than once a week) compared to the hydromorphone group (median daily), but no differences were found after six months. Pain scores with movement were lower at 1 and 3 months in the methadone group. Pain scores at rest were lower at 1, 3, and 6 months after surgery in the methadone group, but the data was not statistically significant. The percentage of patients that required opioids was lower in the methadone group at three months post-surgery (10% of methadone patients vs. 41% of hydromorphone patients). The highest incidence of chronic postsurgical pain occurs in patients undergoing complex spine surgery; therefore, it is essential to implement an effective opioid-sparing analgesic regimen to improve quality of life [12].

Bariatric Surgery

Up to 42% of patients undergoing laparoscopic bariatric surgery experience significant postoperative pain. Respiratory function, hemodynamic status, bowel function, mobility, length of hospital stay, and patient satisfaction are adversely affected. Providers are hesitant to prescribe narcotics in the obese population due to the risk of respiratory depression, leading to inadequately managed acute postsurgical pain. Poorly treated postsurgical acute pain is a significant risk factor for chronic pain, which can affect 50% of patients after bariatric surgery [17].

The first study to target the effect of methadone on morbidly obese patients was conducted at the University of São Paulo with patients undergoing open bariatric surgery. Patients were to receive either intravenous methadone (0.15 mg/kg) or fentanyl (6µg/kg) at induction with dosing based on ideal body weight (IBW) plus 20%. Bolus doses of the same induction opioid were administered to treat hypertension: methadone (0.05 mg/kg IBW + 20%) or fentanyl (2µg/kg IBW + 20%) every 10 minutes. Patients were given a morphine PCA postoperatively, and morphine consumption was recorded at hours 2, 6, 24, 48, and 72. Fifty-six patients were initially enrolled in the study, but due to statistically significant differences in postoperative morphine consumption favoring the methadone group versus fentanyl, recruitment for the study was stopped. Thirty-two patients were analyzed for the study, with 16 in each group. The mean postoperative morphine consumption in the fentanyl group at 2, 2-6, 6-24, 24-48, and 48-72 hours after surgery were 6.5mg, 12.5mg, 13.5mg, 16.6mg, and 4.2mg, respectively. In the same time intervals, morphine consumption in the methadone group was 0.1mg, 0.9mg, 3.1mg, 2.1mg, and 0.2mg. The differences were statistically significant at all-time intervals except at 48-72 hours. The fentanyl group had higher pain scores up until 24 hours post-surgery, a higher incidence of nausea and vomiting, and lower patient satisfaction scores than the methadone group. No differences were found regarding other opioid-related side effects (pruritus, sedation, need for supplementary oxygen, and urinary retention). The researchers completed a three-month follow-up and found no statistical differences concerning spontaneous pain and dysesthesia symptoms between the two groups, but lower evoked pain scores after mechanical stimulus at the surgical scar location were observed in the methadone group [18].

Pontes, et al. [17] conducted a study to evaluate the effect of intraoperative intravenous methadone on postoperative quality of recovery in patients undergoing laparoscopic gastroplasty. One hundred thirty-seven patients were randomized to receive intravenously either 0.1mg/kg of methadone or 0.1mg/kg of morphine 20 minutes before the end of surgery

based on lean body weight. Quality of recovery (QoR) assessment was conducted through a questionnaire 24 hours after surgery. The questionnaire consisted of 40 questions covering five fields of patient recovery: physical comfort, physical independence, emotional status, psychological support, and pain. Each question scored from 1 through 5, and the total score ranges from 40 to 200, indicating extremely poor QoR at low scores to excellent QoR at high scores. The methadone group scored 194, whereas the morphine group 181. Statistically significant differences were observed in all data points, except psychological support favoring the methadone group.

Additional secondary assessments were performed up to 48 hours after surgery. The researchers observed that the methadone group had a shorter postanesthesia care unit (PACU) stay, lower pain burden, lower cumulative rescue morphine administration, and lower incidence of supplemental oxygen use and nausea and vomiting. No significant respiratory or cardiovascular adverse events were observed in either group.

The researchers in the previous study conducted a post-discharge follow-up with the patients to assess the effects of intraoperative methadone on quality of life three months after laparoscopic gastroplasty. Of the 137 initial patients, 123 participated in the follow-up. Of the various categories assessed, only 'General Health Perception' was statistically significant, favoring the methadone group. The researchers hypothesized that the study population's lack of substantial differences in the other data points could be due to lower methadone dosage administration (0.1mg/kg) than other studies administering higher doses (0.2mg/kg). In addition, the authors suggested methadone is more beneficial for patients undergoing surgeries with high chronic postsurgical pain potential (spinal or cardiac surgery) compared to lower chronic pain potential with laparoscopic gastroplasty [19].

Ambulatory Surgery

Only one study has been conducted on the clinical effectiveness of intraoperative methadone in reducing postoperative opioid consumption among patients undergoing same-day discharge ambulatory surgery. Komen, et al. [20] enrolled 60 patients in a randomized, double-blind, dose-escalation, dose-finding pilot study undergoing laparoscopic cholecystectomy, tubal ligation, salpingectomy, oophorectomy, or salpingectomy with oophorectomy. Forty patients were assigned to the methadone group, and the first cohort of 20 patients received intravenously 0.1mg/kg IBW and the second cohort received 0.15mg/kg IBW at induction of anesthesia. The remaining 20 patients were administered standard short-acting opioids. The dose-escalation method for methadone dosing was utilized to identify the minimal effective dose that was statistically significant in reducing postoperative opioid

consumption. Postoperative opioid consumption, pain intensity, and opioid side effects were evaluated after surgery prior to discharge, and for 30 days postoperatively through a patient home diary. Results indicated 0.15mg/kg IBW of methadone at induction significantly reduced intraoperative and postoperative opioid requirements compared to 0.10mg/kg IBW of methadone and short-acting opioids. Patients who received 0.15mg/kg of methadone reported less pain at rest over 30 days postoperatively, and cumulative opioid consumption was significantly less than the control group. No difference in opioid-related side effects was observed between the groups.

Ketamine as a Synergistic Adjunct

Ketamine, a potent NMDA antagonist, is often administered intraoperatively as a preemptive analgesic. Two studies have been conducted assessing the clinical effects of administering ketamine in addition to methadone on decreasing postoperative opioid consumption. Pacreu, et al. [21] enrolled 22 patients undergoing multilevel lumbar arthrodesis. In the methadone only (ME) group, 11 patients received intraoperative methadone with saline infusion and a postoperative methadone PCA. In the methadone and ketamine (MK) group, 11 patients received a ketamine bolus (0.5mg/kg) after tracheal intubation, followed by an infusion of 2.5µg/kg/min intraoperatively and a postoperative methadone plus ketamine PCA. Opioid consumption in the MK group was reduced by 70 to 80% on the first two postoperative days compared to the ME group.

Murphy, et al. [22] conducted the second study assessing the synergistic effects of ketamine and methadone. One hundred twenty-seven patients undergoing elective spinal fusion surgery were randomly assigned to one of two groups: intraoperative methadone only group (0.2mg/kg of IBW at induction intravenously) or an intraoperative methadone/ketamine group (0.2mg/kg of IBW methadone at induction plus ketamine infusion at 0.3mg/kg/hour intravenously). The maximum dosage of methadone in either group was 2mg. In the methadone/ketamine group, the ketamine infusion rate was reduced to 0.1mg/kg/hour during surgical closure and maintained for 48 hours postoperatively. All patients received a hydromorphone PCA for postoperative pain management. Cumulative hydromorphone consumption, pain scores, patient satisfaction with pain management, and any potential side effects of either methadone or ketamine were evaluated. The researchers observed that patients in the methadone/ketamine group required 57% less hydromorphone on the first postoperative day than the methadone group. During the first three days postoperatively, cumulative hydromorphone consumption in the methadone/ketamine group was reduced by 53%, and total oral

opioid (hydrocodone 5mg/acetaminophen 325mg tablets) requirements were reduced by 45%. Pain scores at rest, with coughing, and with movement were significantly lower in the methadone/ketamine group, and patient satisfaction was high in both groups. No differences in side effects related to opioids or ketamine were found between the two groups, and the length of PACU or hospital stay did not differ. Few studies exist on the boosting effects of ketamine combined with methadone. The limited data indicate ketamine plus methadone is superior to ketamine plus short-acting opioids (fentanyl, hydromorphone) in reducing postoperative opioid requirements. The synergistic mechanism of ketamine with methadone has not been elucidated and necessitates further exploration.

Methadone Safety

Concerns with the use of perioperative methadone include prolonged respiratory depression, opioid-related side effects, serotonin syndrome, QT prolongation, and cardiac arrhythmias. A multitude of randomized trials found no differences in the incidence of respiratory depression (respiratory rates less than 8 to 12 breaths/min) or hypoxemic events (oxygen saturations less than 90 to 92%) between methadone and control groups during PACU or in-hospital stay. One retrospective review of perioperative adverse events in 1,478 patients administered intraoperative methadone for major spine surgery found respiratory depression (fewer than 8 breaths/min) was observed in 37% of patients. Hypoxemic events (oxygen saturation less than 90% or the need for more than 2 liters of oxygen to maintain oxygen saturation at greater than 96%) were noted in 80% of patients. A major limitation in this study was the lack of a control group given short-acting opioids [8].

Clinical trials suggest the incidence of other opioid-related side effects (nausea, vomiting, impaired bowel function, pruritis, and sedation) were not increased in patients that received intraoperative methadone. Serotonin syndrome is a concern because methadone inhibits the reuptake of serotonin. Serotonin syndrome has not been reported in patients administered intravenous methadone perioperatively. Serotonin syndrome has been reported in patients concurrently on chronic methadone maintenance therapy and serotonergic medications, including monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants [8].

The risk of QT prolongation, torsade de pointes, and cardiac death are notable concerns with methadone administration. These risks are increased in patients on chronic methadone maintenance therapy as the risk is directly related to dose and chronicity of use. Randomized trials have not been conducted evaluating the effect of a single intraoperative dose of

methadone on the QT interval and risk of arrhythmias. However, clinical studies on intraoperative methadone administration have not reported an increased incidence of adverse cardiac events. Conclusions regarding cardiac safety cannot be definitively made due to the small size of the majority of clinical trials [8].

Future Research

Limited investigations on intraoperative methadone administration restrict the adoptability of routine methadone use. Large-scale, randomized controlled trials are needed to assess the benefits and risks of methadone across various patient populations. Only four studies involved a sample size greater than 100, with many studies enrolling less than 50 subjects. Small sample sizes can lead to false positives and exaggerate the magnitude of an association. Many of these studies also excluded high-risk patients. The safety of methadone in high-risk populations (elderly, severe cardiovascular disease, or multiple significant comorbidities) has not been evaluated. Limited data indicate risks of methadone do not exceed standard short-acting opioids, and further studies are warranted [8].

The optimal dosage of intraoperative methadone that will provide prolonged analgesia without respiratory depression has not been established across various surgical populations. Surgeries with higher postsurgical pain (major spine or cardiac operations) will require higher dosing than surgeries with low potential for high postsurgical pain. Dosing in opioid-tolerant patients has also not been assessed and will require additional exploration [8]. Furthermore, most studies evaluated patients up to 72 hours postoperatively and did not perform long-term follow-ups at 1, 3, 6, or 12 months, which can be beneficial in establishing whether methadone is effective in reducing chronic postsurgical pain and cumulative opioid consumption.

Literature on the opioid-sparing effects of methadone has not been compared to a perioperative multimodal, opioid-sparing approach (acetaminophen, magnesium, dexmedetomidine, ketamine, gabapentinoids, or regional anesthesia). Does methadone have a role in Enhanced Recovery After Surgery Protocols? Can adding methadone to other opioid-sparing agents lead to better patient outcomes? These topics require further inquiry.

Conclusion

Methadone is a long-acting opioid, NMDA antagonist, and serotonin and norepinephrine inhibitor, making it a unique pharmacological agent. These properties can attenuate the development of chronic postsurgical pain and reduce postoperative analgesic requirements compared to short-acting opioids without increasing the risk of opioid-related side effects. A study by Porter et al. [23] demonstrated that methadone administration at induction of anesthesia was more effective in reducing

postoperative analgesic requirements compared to surgical closure. The respiratory depressant effects of methadone peak at 8 to 10 minutes after administration. This notion favors early administration to avoid delayed anesthesia emergence [9].

Machado, et al. [24] conducted a meta-analysis utilizing 13 studies. After performing a Trial Sequential Analysis, the researchers concluded no further clinical trials were required to validate pain reduction at rest until 48 hours post-surgery. However, large-scale, randomized investigations across various surgical patient populations are necessary to make definitive conclusions regarding the safety, efficacy, and dosing of perioperative methadone administration. Research comparing multimodal, opioid-sparing approaches to perioperative methadone administration is needed. Investigations examining these topics are required before routine use of methadone perioperatively can be recommended.

Data Sources

The research information was gathered via an extensive literature review on Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar, EBSCOhost, and PubMed.

Disclosure

I have no conflicts of interest.

Financial support and sponsorship

None.

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