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Methadone for Surgical Patients

Key Messages

What Is the Issue?

- Opioids such as morphine and hydromorphone are commonly used to treat postoperative pain; however, they are associated with serious risks such as respiratory depression.
- Methadone (a synthetic opioid) has been proposed as a potential option for preoperative or postoperative analgesia that may improve pain relief and reduce overall opioid requirements.

What Did We Do?

- We sought to identify and summarize studies of the clinical effectiveness and safety of oral methadone for preoperative or postoperative analgesia in adults as well as recommendations from evidence-based guidelines.
- We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence published since 2019.
- One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included publications, and narratively summarized the findings.

What Did We Find?

- We identified 1 randomized controlled trial (RCT) that evaluated the use of preoperative oral methadone versus placebo in adults undergoing sternotomy for isolated coronary artery bypass graft surgery. We did not identify any studies that compared oral methadone to other analgesics that met our criteria. We did not identify any evidence-based guidelines that included recommendations on the use of oral methadone for preoperative and postoperative analgesia.
- There were no differences in pain scores 24, 48, and 72 hours postoperatively in patients who received oral methadone versus placebo. Postoperative morphine requirements were lower in the methadone group than the placebo group at 24 hours; however, there were no differences between groups at 48 or 72 hours.
- There were no differences in common side effects related to opioid use (nausea, vomiting, pruritus, constipation, urinary retention, hypoventilation, or hypoxia) between patients undergoing surgery treated with oral methadone versus placebo at 24, 48, or 72 hours.

Key Messages

What Does It Mean?

- We identified very limited evidence on the use of oral methadone for preoperative or postoperative analgesia in patients undergoing surgery. There were no differences between patients undergoing surgery treated preoperatively with oral methadone versus placebo in most of the pain outcomes measured in the included RCT.
- Additional evidence may be necessary to aid decision-making around the use of oral methadone as preoperative or postoperative analgesia for adult patients undergoing surgery.

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Context and Policy Issues

What Is Current Practice?

A range of interventions can be used for analgesia (pain relief) both before and after surgery. Preoperative analgesia is treatment that is given before surgery to reduce postoperative pain and medication requirements.[1] Postoperative analgesia is treatment given after surgery to reduce or eliminate pain.[2] Ensuring adequate pain control after surgery is important as untreated acute pain can develop into chronic pain.[1] Medications used in the management and treatment of pain are known as analgesics.[3] There are many different analgesics including acetaminophen, nonsteroidal anti-inflammatory drugs, local anesthetics, and opioids.[3] Several opioids including morphine, hydromorphone, and fentanyl are commonly used in the treatment of postoperative pain.[2]

What Is Methadone?

Methadone is a long-lasting synthetic opioid.[4] Methadone is indicated for the relief of severe pain and generally should not be used in patients who have not used opioids.[5] Methadone is available as tablets, solution, and concentrate for oral administration.[5] The usual starting dose of methadone is 2.5 mg to 10 mg every 4 hours during the first 3 to 5 days, followed by a fixed dose every 8 to 12 hours depending on the patient's requirements.[5] The dosage should be titrated and adjusted according to the severity of the pain and patient response.[5] Common adverse effects of methadone include light-headedness, dizziness, sedation, nausea, vomiting, and sweating.[5] The major risks of methadone use are respiratory, central nervous system depression, and systemic hypotension (low blood pressure).[5]

Why Is It Important to Do This Review?

Opioids are commonly used for pain relief after surgery; however, they are associated with adverse events including sedation, respiratory depression, delirium, ileus (temporary lack of movement in the intestines), and the paradoxical worsening of pain with higher opioid doses.[6] Postoperative opioid-induced respiratory depression often occurs within the first 24 hours and leads to death or severe brain damage in most patients.[6] There is interest in reducing postoperative opioid use to decrease morbidity and mortality associated with adverse events related to opioid use.[6] Enhanced recovery after surgery protocols have been developed that are designed to provide superior analgesia, reduce opioid consumption, improve patient recovery, and reduce hospital length of stay.[7] These protocols use multimodal nonopioid analgesia; however, methadone has been proposed as a potential option that may offer superior, long-lasting, and stable postoperative pain relief.[7] Methadone has several properties that could be of benefit if used as analgesia for patients undergoing surgery including a mechanism of action that involves effects at several different sites; a rapid onset and long duration of action.[7,8]

Research Questions

1. What is the effectiveness of oral methadone for preoperative and postoperative analgesia in patients undergoing surgery?

2. What are the harms associated with oral methadone for preoperative and postoperative analgesia in patients undergoing surgery?
3. What are the evidence-based guidelines regarding the use of oral methadone for preoperative and postoperative analgesia in patients undergoing surgery?

Methods

Literature Search Methods

An information specialist conducted a literature search on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International Health Technology Assessment Database, the websites of health technology assessment agencies in Canada and major international health technology assessment agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevance. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (medical subject headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were methadone and perioperative pain. The search was completed on November 13, 2024, and limited to English-language documents published since January 1, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Adult patients undergoing surgery
Intervention	Oral methadone
Comparator	Other preoperative and postoperative analgesics, placebo
Outcomes	Clinical effectiveness, safety (including potential misuse or diversion), evidence-based guidelines
Study designs	Systematic reviews, randomized controlled trials, nonrandomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications or were published before 2019. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included RCT was critically appraised by 1 reviewer using the Downs and Black[9] Checklist for randomized and nonrandomized studies as a guide. Summary scores were not calculated for the included study; rather, the strengths and limitations of the included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 424 citations were identified in the literature search. Following screening of titles and abstracts, 408 citations were excluded and 16 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 19 publications were excluded for various reasons, and 1 RCT met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA[10] flow chart of the study selection.

Additional references of potential interest are provided in Appendix 2.

Summary of Study Characteristics

We identified 1 RCT[11] that evaluated the clinical effectiveness and safety of oral methadone for patients undergoing surgery. We did not identify any studies that compared oral methadone to alternative analgesics. We did not identify any evidence-based guidelines that included recommendations on the use of oral methadone as preoperative or postoperative analgesia.

Additional details regarding the characteristics of included publications are provided in Appendix 3.

Study Design

The Bolton et al. (2019)[11] study was an RCT in which patients, researchers, outcome assessors, and care providers were blind to treatment assignment.

Country of Origin

The RCT was conducted in Regina, Saskatchewan.[11]

Patient Population

The RCT included 21 adult patients (aged 18 years or older) in the hospital who were undergoing sternotomy for isolated coronary artery bypass graft surgery.[11] The average age of patients in the methadone group (n = 9) was 73 years and the average weight was 76 kg.[11] Medical comorbidities in the methadone group included previous heart surgery (n = 2), diabetes (n = 2), hypertension (n = 4), congestive heart failure (n = 1), peripheral vascular disease (n = 1), and smoking (n = 3).[11] The average age of patients in the placebo group (n = 12) was 65 years and the average weight was 91 kg.[11] Medical comorbidities in the placebo group included previous heart surgery (n = 2), diabetes (n = 4), hypertension (n = 7), congestive heart failure (n =

1), stroke (n = 2), peripheral vascular disease (n = 1), obstructive sleep apnea (n = 2), smoking (n = 5), lung disease (n = 1), and chronic pain (n = 2).[11]

Interventions and Comparators

Patients in the intervention group received a single dose of oral liquid methadone 0.3 mg/kg, to a maximum of 30 mg.[11] Patients in the placebo group received sweetened syrup.[11] Both methadone and placebo were diluted to a total volume of 5 mL in sweetened syrup diluent.[11] The 5 mL syringe containing either methadone or placebo was self-administered by the patient before entering the operating room.[11] The dose was consistently given when the patient was called to the operating room, just before transport.

Outcomes

The primary outcome was pain score at 24 hours measured using a Verbal Rating Scale with scores ranging from 0 to 10.[11,12] Secondary outcomes included pain scores over 72 hours, postoperative morphine requirements (total dose in mg of IV morphine administered by patient-controlled analgesia), time to extubation, level of sedation (level of sedation as measured by the Richmond Agitation Sedation Scale), and side effects related to opioid use (incidence of nausea, vomiting, pruritus, hypoventilation, and hypoxia).[11,12]

Summary of Critical Appraisal

The RCT by Bolton et al. (2019)[11] had both strengths and limitations. The objective, patient characteristics, intervention, and main findings were clearly described. None of the patients were lost to follow-up. The patients, researchers, outcome assessors, and care providers were all blind to intervention groups. Blinding reduces the risk of bias in the results of a study and is especially important if subjective outcomes such as pain are being assessed. Patients were randomized to intervention groups using computer generated simple randomization with a 1:1 ratio. The goal of randomization is to ensure both known and unknown confounders are balanced between treatment groups. Potential confounders were not discussed or adjusted for. There also appear to be some imbalances in baseline characteristics between the treatment groups (for example average weight is higher and average age is lower in the placebo group). If there were imbalances in variables that influence the outcomes assessed in the study, this could have led to bias in the results. A sample size calculation was conducted before the study that determined 10 patients were needed per group; however, there were only 9 patients in the intervention group. Therefore, the study may have been underpowered to detect differences between the treatment groups.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 4.

Summary of Findings

We identified 1 RCT that evaluated the clinical efficacy and safety of oral methadone versus placebo in patients undergoing sternotomy for isolated coronary artery bypass graft surgery.[11] We did not identify any studies that compared oral methadone to alternative analgesics. We did not identify any evidence-based guidelines that included recommendations on the use of oral methadone for preoperative and postoperative analgesia.

Appendix 5 presents the main study findings.

Clinical Effectiveness of Oral Methadone Versus Placebo

Primary Outcome — Pain Score at 24 Hours

There was no significant difference in pain score between the methadone and placebo groups at 24 hours postoperatively.

Secondary Outcomes

Postoperative morphine requirements were statistically significantly lower in the methadone group than the placebo group at 24 hours. There were no significant differences between groups in postoperative morphine requirements at 48 and 72 hours postoperatively.

There were no significant differences between groups in pain score measured at 48 or 72 hours postoperatively, time to extubation, or level of sedation measured at 24, 48, or 72 hours postoperatively.

Safety of Oral Methadone Versus Placebo

Common Side Effects Related to Opioid Use

There were no significant differences in the incidence of common side effects related to opioid use (nausea, vomiting, pruritus, constipation, urinary retention, hypoventilation, or hypoxia) between groups measured at 24, 48, and 72 hours postoperatively.

Limitations

This report is limited by the rapid review methodology employed (e.g., limiting the literature search to 2019) and the quantity of evidence identified. We identified 1 study comparing oral methadone to placebo in patients undergoing sternotomy for isolated coronary artery bypass graft surgery.[11] This study evaluated the use of preoperative oral methadone, and we did not identify any studies of oral methadone used postoperatively. Additionally, we did not identify any studies in patients undergoing other types of surgery or that compared oral methadone to alternative analgesics. We did not identify any evidence-based guidelines that included recommendations on the use of oral methadone as analgesia for patients undergoing surgery.

Conclusions and Implications for Decision- or Policy-Making

We included 1 RCT on the preoperative use of oral methadone versus placebo for patients undergoing sternotomy for isolated coronary artery bypass graft surgery.[11]

The RCT found no difference in pain scores measured at 24, 48, or 72 hours postoperatively between patients treated with oral methadone versus placebo. Postoperative morphine requirements were lower in the methadone group than the placebo group at 24 hours; however, there were no differences between groups at 48 or 72 hours. There were no differences between the treatment groups in the incidence of side effects related to opioid use (nausea, vomiting, pruritus, constipation, urinary retention, hypoventilation, or hypoxia) at 24, 48, or 72 hours postoperatively.

Due to the limited evidence identified in this report, it is difficult to draw conclusions on the clinical effectiveness of oral methadone used as analgesia for patients undergoing surgery. Future studies that focus on the comparative efficacy and safety of oral methadone versus alternative analgesics in patients undergoing various types of surgery would help decision-making around the use of oral methadone.

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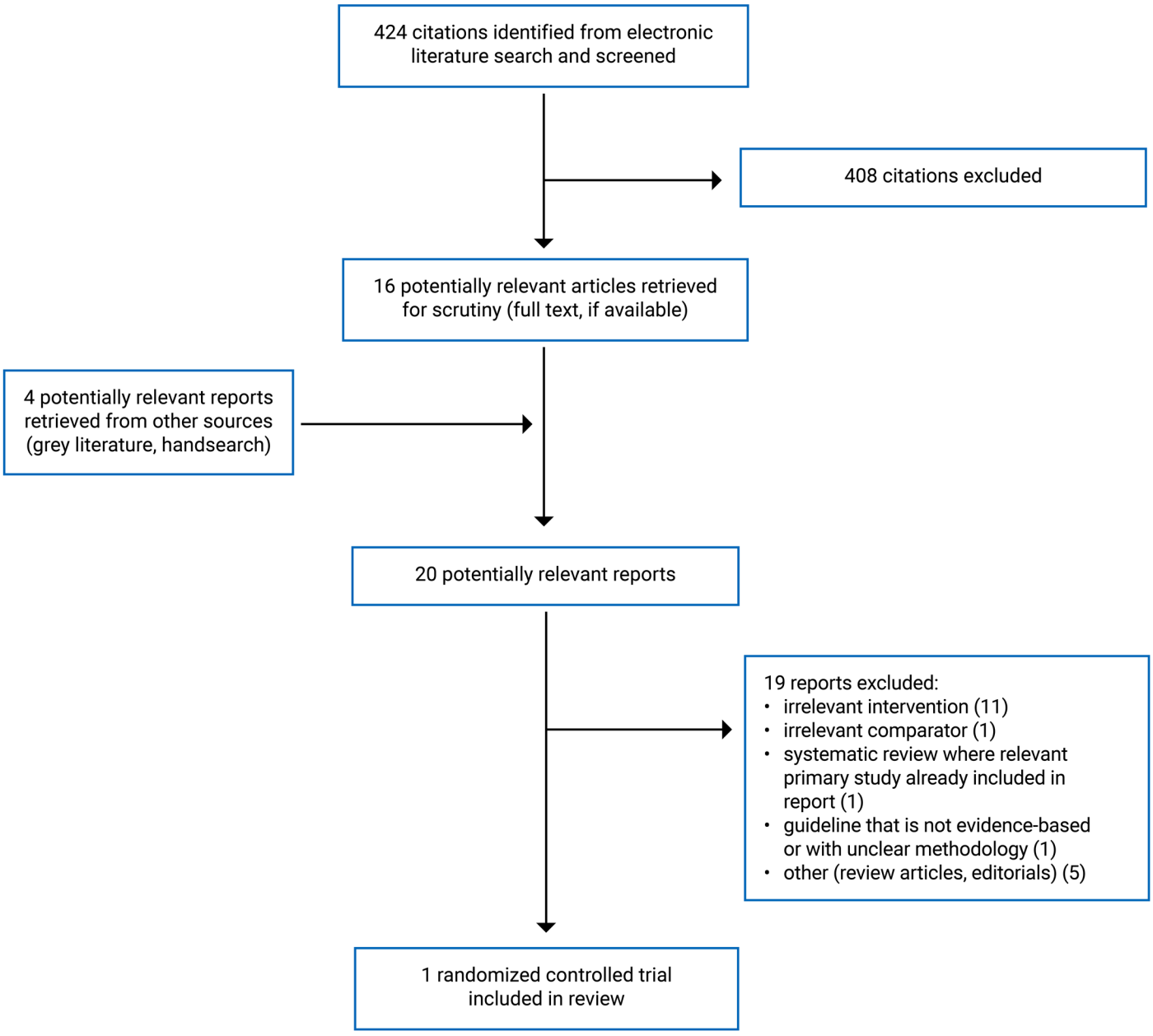
12. University of Saskatchewan. Preoperative oral methadone for patients undergoing cardiac surgery: reduction of postoperative pain. ClinicalTrials.gov. Updated January 2, 2018. Accessed December 2, 2024. https://clinicaltrials.gov/study/NCT02774499

Appendix 1: Selection of Included Studies

Figure 1: PRISMA[10] Flow Chart of Study Selection



Appendix 2: References of Potential Interest

Please note that this appendix has not been copy-edited.

Previous CDA-AMC Reports

Drug Agency. Evidence on pain management. Accessed December 4, 2024. https://www.cda-amc.ca/pain

Systematic Reviews

Nunn KP, Velazquez AA, Bebawy JF, et al. Perioperative methadone for spine surgery: a scoping review. *J Neurosurg Anesthesiol*. 2024;doi:10.1097/ANA.0000000000000966 PubMed

Rajkovic C, Vazquez S, Thomas Z, et al. Intraoperative methadone in spine surgery ERAS protocols: a systematic review of the literature. *Clin Spine Surg*. 2024;doi:10.1097/BSD.0000000000001726 PubMed

Cheriyan T, Gaber M, Glenn T, et al. Effect of intraoperative methadone vs other opioids on postoperative outcomes: a meta-analysis of randomized controlled studies. *Pain*. 2022;163(2):e153-e164. doi:10.1097/j.pain.0000000000002296 PubMed

Randomized Controlled Trials

Friesgaard KD, Brix LD, Kristensen CB, Rian O, Nikolajsen L. Clinical effectiveness and safety of intraoperative methadone in patients undergoing laparoscopic hysterectomy: a randomised, blinded clinical trial. *BJA Open*. 2023;7:100219. doi:10.1016/j.bjao.2023.100219 PubMed

Nonrandomized Studies

Esfahani K, Tennant W, Tsang S, Naik BI, Dunn LK. Comparison of oral versus intravenous methadone on postoperative pain and opioid use after adult spinal deformity surgery: a retrospective, non-inferiority analysis. *PLoS One*. 2023;18(7):e0288988. doi:10.1371/journal.pone.0288988 PubMed

Review Articles

Foglia R, 3rd, Yan J, Dizdarevic A. Methadone and buprenorphine in the perioperative setting: a review of the literature. Review. *Curr Pain Headache Rep*. 2024;28(11):1105-1111. doi:10.1007/s11916-024-01286-8 PubMed

Appendix 3: Characteristics of Included Publications

Please note that this appendix has not been copy-edited.

Table 2: Characteristics of Included RCT

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Bolton et al. (2019)[11] Canada **Funding source:** NR	RCT	Adult patients (N = 21) undergoing sternotomy for isolated coronary artery bypass graft surgery. **Baseline characteristics:** Methadone group (n = 9): • Age (years): 73 • Weight (kg): 76 Placebo group (n = 12): • Age (years): 65 • Weight (kg): 91	**Intervention:** oral methadone (0.3 mg/kg, maximum of 30 mg) **Comparator**: oral placebo	**Outcomes:** postoperative pain scores, postoperative morphine requirements, time to extubation, level of sedation, opioid-related side effects **Follow-up:** 72 hours postoperatively

NR = not reported; RCT = randomized controlled trial.

Appendix 4: Critical Appraisal of Included Publications

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Table 3: Strengths and Limitations of RCT Using the Downs and Black Checklist[9]

Strengths	Limitations
Bolton et al. (2019)[11]	
Objective, patient characteristics, intervention, and main findings clearly described Common opioid-related adverse events reported No patients were lost to follow-up Patients, care providers, and care setting were representative of the population and setting of interest Patients, researchers, outcome assessors, and care providers were all blind to intervention groups Statistical tests used to measure main outcomes were appropriate Patients in different intervention groups were recruited from the same population over the same time period Patients were randomized to intervention groups using computer generated simple randomization with a 1:1 ratio Authors reported that they had no potential conflicts of interest	Potential confounders were not discussed or adjusted for There appear to be some imbalances in patient characteristics (for example average weight is higher and average age is lower in the placebo group) A sample size calculation was done a priori that determined 10 patients were needed per group however, there were only 9 patients in the intervention group The funding source for the study was not reported

RCT = randomized controlled trial.

Appendix 5: Main Study Findings

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Table 4: Summary of Findings From Bolton et al. (2019)[11]

Outcome	24 hours		48 hours		72 hours		P-value
	Methadone	Placebo	Methadone	Placebo	Methadone	Placebo	
VRS at rest (0 to 10)	2.8	4.0	1.4	1.4	1.3	1.2	NS
VRS with cough (0 to 10)	4.8	5.0	3.3	3.5	3.6	2.6	NS
Time to extubation (min)	673	643	NA	NA	NA	NA	NS
RASS (+ 5 to −4)	−0.1	−0.1	0	0	0	0	NS
Nausea	1.6	1.7	1.8	1.8	2.0	1.8	NS
Vomiting	1.8	1.8	2.0	2.0	2.0	2.0	NS
Pruritis	2.0	2.0	1.8	2.0	1.8	2.0	NS
Constipation	2.0	2.0	2.0	2.0	1.9	1.9	NS
Urinary retention	2.0	2.0	2.0	2.0	2.0	2.0	NS
Hypoventilation (respiratory rate < 8)	2.0	2.0	2.0	2.0	2.0	2.0	NS
Hypoxia	1.3	1.3	1.3	1.5	1.6	1.7	NS

NA = not applicable; NS = not significant; RASS = Richmond Agitation Sedation Score; VRS = verbal rating scale for pain.

Table 5: Summary of Findings From Bolton et al. (2019)[11] — Postoperative Morphine Requirement

Comparison	Time point	Mean difference (99% CI), mg	P value
Methadone vs. placebo	24 hours	−23 (37 to 13)	0.003
	48 hours	NR	NS
	72 hours	NR	NS

CI = confidence interval; NR = not reported; NS = not significant; vs. = versus.

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