Title: IV Methadone

SBAR: Situation-Background-Assessment-Recommendation

Initiation and Feedback Phase

Situation:

IV methadone was never reviewed for formulary addition by the Trinty Health Pharmacy and Therapeutics Committee. It was requested to evaluate the formulary status of IV methadone in Trinity Health. The formulary monograph of IV methadone was developed in collaboration with the Surgery Multimodal Project. The objective of the formulary evaluation was to identify the role of this medication for as an opiate sparing medication and for management of surgical pain compared to currently available formulary alternatives.

Background:

Methadone is a synthetic, potent, mu-opioid receptor agonist. It predominantly acts on the central nervous system (CNS) and other organs composed of smooth muscle. Data also suggests this drug acts as a N-methyl-D-aspartate (NMDA) receptor antagonist, although it is uncertain how this impacts methadone's efficacy. Methadone is available on the Trinity Health formulary in various formulations including oral tablet and oral concentrate. Can be administered intravenously (IV), subcutaneously (SC), or intramuscularly (IM). Absorption into systemic circulation may vary depending on subcutaneous or intramuscular administration, but have not been well established at this time. Steady state concentration may take 3-5 days to achieve. Methadone has a unique pharmakinetic profile. It is used for both detoxification and pain management. It is proposed to evaluate the utility of IV methadone as a part of surgical pain management because of its mechanism on the NMDA receptor antagonist.

Assessment:

Methadone is a synthetic, multimodal, opioid analgesic that works as both potent mu-receptor agonist and NMDA receptor antagonist. Its unique NMDA receptor activity contributes to this drug's ability to provide neuropathic pain relief, of particular benefit to spinal surgery patients.
Large scale clinical trials evaluating the efficacy and safety of a single IV intraoperative methadone dose are limited. However, available literature provides evidence that utilization of a single IV intraoperative methadone dose can provide adequate analgesia while reducing patients' overall post-operative opioid requirements.
Available safety information is limited in this population. It should be noted that both opiate tolerant and opiate naïve with IV methadone experienced: 40% respiratory depression, 80% hypoxemia, and 60% prolonged QTc in an observational study with IV methadone.

FEEDBACK PROCESS:

Because of noted safety concerns with administration of IV methadone in perioperative setting, it is recommended to not add to formulary and follow pathways recommended by multimodal pain group for management of surgical patients, surgical patients on opiates prior to admission, and surgical patients with substance abuse.

Group	Initial Presentation	Formalized Council feedback
Orthopedic Clinical Excellence Council	November 15, 2018	January 17, 2019
Cardiovascular Clinical Excellence Council	November 6, 2018	December 5, 2018
Perinatal Patient Safety Group	November 14, 2018	December 13, 2018
Surgery Clinical Excellence Council	November 1, 2018	December 6, 2018

Perinatal Patient Safety (12/9/18) vote: Non-formulary-36, formulary – 2
Surgical CEC (12/6/18): Non-Formulary – 12, Formulary- 0
Orthopedic CEC: (1/17/19): Non-formulary-13, Formulary - 0
Cardiovascular CEC (1/17/19) surgeons only: Non-Formulary-2, formulary -0

Trinity Health

The initial recommendation that feedback was given on to the Surgical, Cardiovascular, Perinatal Patient Safety, and Orthopedic CEC was to establish IV methadone as non-formulary due to the low number of small studies evaluating IV methadone with a role in surgical pain as well as the safety concerns (including respiratory depression, hypoxemia and QTc prolongation).
It was noted by several sites during the pharmacy feedback process that at time patient's that are managed on methadone for detoxification or who are hyperalgesic patients need a use of methadone and it is difficult to change to alternative agents. Because of the feedback, the recommendations were changed to address patient needs for these indications.

Recommendation:

Formulary Restricted
Restrict to patients that are strict NPO (including no medications by mouth) that are admitted on chronic oral methadone
Pain management or palliative care specialists – Use in patients that are NPO (including No medications by mouth)

References/Citations:
See Complete monograph

Submitted by:	Rachael Lu, PharmD, BCPS
CEC/CLG/CSG:	Pharmacy CLG – Trinity Health Pharmacy and Therapeutics Committee
Date	2-20-19

Title: IV Methadone

Final Decision and Action Planning Phase

CEC Decision for Implementation

1. **What were final decisions? Would include any changes to the recommendations out for feedback**
2. Pharmacy and Therapeutics Committee (1-29-19) supported recommendation to:
    - **Formulary Restricted**
        - **Restrict to patients that are strict NPO (including no medications by mouth) that are admitted on chronic oral methadone**
        - **Pain management or palliative care specialists – Use in patients that are NPO (including No medications by mouth)**
3. **Who owns the next steps**?
4. ICS team in collaboration with TIS
5. **Estimated timeframe…**
6. Target implementation by September 1, 2019.
7. **Which functional groups will be involved in the implementation?**
8. Nursing, Prescribers, Pharmacists
9. **Regional ICLT to communicate to functional leads and areas.**

Teams	Actions	When
CMO	Share background and decision with medical staff for support, awareness and understanding.	Upon receipt of information

CNO	Share background and decision with nursing staff for support, awareness, and understanding.	Upon receipt of information
Pharmacy	Share background and decision with staff and coordinate efforts with ICS team to update electronic medical records to restrict IV methadone to appropriate indications.	By September 1, 2019
Informatics	Coordinate efforts with ICS team to manage change toward updating of IV methadone to restricted indications.	By September 1, 2019

Finalized by:	Rachael Lu, PharmD, BCPS
CEC/CLG/CSG:	Pharmacy CLG, Pharmacy and Therapeutics Committee
Date	2-20-19

CONFIDENTIAL

TRINITY PHARMACY & THERAPEUTICS COMMITTEE
Trinity Health Formulary Review

[METHADONE HCL (DOLOPHINE®)]

August 2018

Summary

Recommendation approved 1-29-19

Revised Recommendation to Committee:
Formulary Restricted

- **Restrict to patients that are strict NPO (including no medications by mouth) that are admitted on chronic oral methadone**
- **Pain management or palliative care specialists – Use in patients that are NPO (including No medications by mouth)**

Because of noted safety concerns with administration of IV methadone in perioperative setting, it is recommended to not add to formulary and follow pathways recommended by multimodal pain group for management of surgical patients, surgical patients on opiates prior to admission, and surgical patients with substance abuse.

FORMULARY STATUS	MO IMPLICATIONS	RESTRICTIONS REQUIRED
Non-formulary	Do Not Add	None

Key Findings Summary:
Methadone is a synthetic, multimodal, opioid analgesic that works as both potent mu-receptor agonist and NMDA receptor antagonist. Its unique NMDA receptor activity contributes to this drug's ability to provide neuropathic pain relief, of particular benefit to spinal surgery patients.
Large scale clinical trials evaluating the efficacy and safety of a single IV intraoperative methadone dose are limited. However, available literature provides evidence that utilization of a single IV intraoperative methadone dose can provide adequate analgesia while reducing patients' overall post-operative opioid requirements.
Available safety information is limited in this population. It should be noted that both opiate tolerant and opiate naïve with IV methadone experienced: 40% respiratory depression, 80% hypoxemia, and 60% prolonged QTc in an observational study with IV methadone.

Key MO Feedback:
RHM Providing Feedback – 16
Formulary – 4 RHM

- There is a pediatric surgeon that utilizes IV methadone for his Pectus Excavatum pain management protocol. He has data showing reducing length of stay from 6-8 days down to 3-4 days in over 20 patients since June 2014. Also their average pain scores are 2-4 instead of 4-8. Overall, consider keeping it on formulary with restriction
- We are NOT in support of this not being available as Opioid sparing. As you sent around IV Methadone was part of the Vanderbilt ERAS strategy. Our Providers (Mercy) have been using this for many years as standard of care with good result We often use IV Methadone for Spinal Fusion patients who are already on moderately to very high pre-op narcotics - 5-10 mg IV given intra-op, occasionally repeated in the recovery room.
- We have found it effective in the first twenty-four hours, which otherwise had been a nightmare twenty-four hours for these patients. It is always administered while the patient is monitored and under high acuity care. It would be a travesty to lose this treatment, which has been very effective for the right patients. Richard Anderson (Chief of Neurosurgery)

Non-Formulary – 12 RHM

- Although it may have promise for post-operative opioid reduction, its rate of adverse side effects causes concern at a time when we are working on reducing opioid-related respiratory depression
- Agree with monograph recommendation. non-formulary. We do not have on formulary any longer due to adverse effects with inappropriate dosing on orders not reviewed by pharmacy.Have had no requests to add back to formulary.
- Support for non-formulary status. We support the recommendations, but asks the palliative care use be further considered, as this was not addressed within the review.
- It is not used here and has not been requested. Given the safety considerations as well as cost, Wilmington agrees with the recommendation in the monograph.



methadone feedback 1-29-19.xlsx

Key Committee Feedback:

Recommendation to Clinical Excellence Council:

Because of noted safety concerns with administration of IV methadone in perioperative setting, it is recommended to not add to formulary and follow pathways recommended by multimodal pain group for management of surgical patients, surgical patients on opiates prior to admission, and surgical patients with substance abuse.

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Manufacturer: Mylan

FDA-Labeled Indications[1,2]:

1. For management of severe pain requiring opioid analgesia when alternative agents are inadequate.
2. Temporary treatment of opioid dependence in hospitalized patients unable to take oral medications

Non-FDA-Labeled Indications:

None

Proposed Use of Agent:

1. Perioperative pain management in patients on chronic opioid therapy
2. Perioperative pain management in patients taking buprenorphine for maintenance therapy for opioid dependence

Similar Agents:

- Other mu-receptor agonists typically used in the perioperative setting include morphine, hydromorphone, and oxycodone.
- Buprenorphine is a partial mu-receptor agonist that can be used for maintenance treatment in opioid dependent patients.

Clinical Pharmacology[1]:

- Methadone is a synthetic, potent, mu-opioid receptor agonist. It predominantly acts on the central nervous system (CNS) and other organs composed of smooth muscle. Data also suggests this drug acts as a N-methyl-D-aspartate (NMDA) receptor antagonist, although it is uncertain how this impacts methadone's efficacy

Pharmacokinetics/Pharmacodynamics[1,2]:

- Pharmacokinetics:
  - Absorption: Can be administered intravenously (IV), subcutaneously (SC), or intramuscularly (IM). Absorption into systemic circulation may vary depending on subcutaneous or intramuscular administration, but have not been well established at this time. Steady state concentration may take 3-5 days to achieve.
    - Oral bioavailability of methadone is 80% of the administered dose
    - Onset of action following oral administration: 30-60 mins
  - Distribution: Methadone is lipophilic in nature, and known to persist in liver and tissues. Steady state volume of distribution is documented to range between 2-6 L/kg. Noted to be plasma bound; predominantly to a1-acid glycoprotein.
  - Metabolism: Predominantly metabolized via hepatic N-demethylation to inactive metabolite 2-ethylidene-1,5 diphenylpyrrolidene (EDDP) which is excreted in the urine. Cytochrome P450 enzymes involved in metabolism include: CYP3A4, CYP2B6, CYP2C19, and to a lesser extent: CYP2C and CYP2D6.
  - Excretion: Plasma clearance of methadone following a single intravenous dose ranged from 3L/h to 10 L/h. Additionally, the terminal half-life was noted to range between 8 to 59 hours. Methadone has been noted to persist in tissues, including the liver, therefore duration of action may be prolonged despite low plasma concentrations.
- Pharmacodynamics:
  - Central Nervous System: Methadone acts directly on the brain stem to produce respiratory depression.
  - Gastrointestinal Tract and Smooth muscle: Methadone decreases motility of stomach and duodenum, therefore may be associated with delayed food digestion.
  - Cardiovascular: Methadone produces peripheral vasodilation that can lead to orthostatic hypotension or syncope
  - Endocrine System: Secretions of adrenocorticotropic hormone, cortisol, and lutenizing hormone are inhibited by opioids. Opioids also stimulate prolactin, and growth hormone secretions and pancreatic secretion of insulin and glucagon.
  - Concentration-Related Efficacy: minimum effective analgesic concentration varies widely among patients, particularly in those individuals previously treated with opioid agonist. The minimum effective analgesic concentration may increase over time due to development of analgesic tolerance.

Efficacy/Effectiveness/Comparative Trials:

Intraoperative methadone for prevention of postoperative pain A randomized, double-blinded clinical trial in cardiac surgical patients[3]

One hundred and fifty six patients undergoing cardiac surgery were randomized to receive intraoperative methadone (0.3 mg/kg) or fentanyl (12 ug/kg) for analgesia. Median time to first morphine rescue dose post-operatively was statically longer in the methadone treatment group (6.5 hours) in comparison to the fentanyl treatment group (3.75 hours). Additionally, significantly more patients in the fentanyl group required ≥20 mg of morphine in the first 24hrs compared to those in the methadone group (29.1% vs. 2.6% respectively). The requirements for morphine during the first 24 hours of ICU admission were reduced in the methadone group compared with the fentanyl group (6 mg versus 10 mg $p<0.001$)Patients treated with intraoperative methadone also had significantly lower pain scores at rest and higher overall satisfaction with pain management. No differences between groups were observed in the incidence of opioid related side effects during the first 72 hours including nausea, vomiting, hypoventilation, itching or level of sedation. No differences were noted for time to first flatus or bowel movement.

Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery[4]

A prospective study of twenty-nine patients undergoing spinal surgery randomized to receive intravenous methadone or sufentanil infusion for perioperative pain management. Patients treated with perioperative methadone required overall less post-operative opioids for analgesia. 48 hours following extubation, patients in the methadone vs sufentanil treatment group required a median of 25 mg morphine equivalents vs 63 mg morphine equivalents post-operatively. Similar trends were seen 72 hours post operatively, as patients who received intraoperative methadone required a median of 15 mg morphine equivalents compared to 34 mg morphine equivalents in the sufantanil treatment group. Side effects documented occurred hypoxemia, respiratory depression, arrhythmias, nausea, and vomiting, however no statistical difference in rate of occurrence was noted between treatment groups. The study was not powered to detect differences in side effects between groups.

Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: A randomized, double-blinded controlled trial[5]

One hundred and twenty patients undergoing posterior spinal fusion were randomized to receive intravenous methadone (0.2 mg/kg) given at induction or to 2 mg intravenous hydromorphone given at surgical closure. All patients received a hydromorphone PCIA post operatively. A total of 115 patients were included in the analysis. Differences in post-operative analgesic requirements were statistically significant between the two treatment groups. Two days post operatively, methadone patients received a median of 0.6 mg of hydromorphone in comparison to a median of 3.15 mg hydromorphone treatment group. Intraoperative methadone treatment reduced overall post-operative opioids by about 30-50%. Median visual analog pain scores (VAS) reported by patients in the methadone group were significantly lower at rest, with cough, and with movement from time of PACU admission to post-operative day 3. No patients were intubated overnight due to opioidinduced ventilatory depression. The study groups did not
differ in the incidences of nausea, vomiting, requirements for treatment of nausea or vomiting, itching, hypoventilation, or hypoxemic events from PACU admission through the afternoon of POD 3
opioid pain medication before surgery and no taking hydrocodone equivalents

Efficacy and safety of intraoperative intravenous methadone during general anaesthesia for caesarean delivery: a retrospective case-control study.

This retrospective case-control study evaluated patients undergoing elective or emergency caesarian delivery. Twenty-five women treated with intraoperative methadone were matched to two patients of similar characteristics who did not receive intraoperative methadone. Average intraoperative methadone dose ranged from 7 to 20 mg. Patients were given PCIA post-operatively to control analgesia. In the methadone treatment group, patients required an average of 73 +/- 59 mg morphine equivalents post-PACU to 24 hours following surgery while the control group required an average of 135 mg morphine equivalents (p = 0.0001). Overall, patients treated with intraoperative methadone required an average of 115 +/- 94 mg morphine equivalents of post-operative opioids, while the control group required a total of 213 +/- 104 mg morphine equivalents (p =0.0002).

Intraoperative methadone in same-day ambulatory surgery: A randomized, double-blinded, dose-finding pilot study

Sixty patients undergoing same-day ambulatory surgery were randomized to receive a single dose of IV methadone for analgesic control compared to conventional short acting opioids. Patients were started on 0.1 mg/kg IV methadone, and increased at increments of 0.05 mg/kg to find an effective dose that minimized pain. Patients treated with 0.15 mg/kg IV methadone required a median of 0.1 mg morphine equivalents post operatively compared to those treated with 0.1 mg/kg IV methadone or other short acting opioids, who required 5 mg morphine equivalents and 9.3 mg morphine equivalents respectively. 57% of patients treated with 0.15 mg/kg IV methadone required no PACU opioid administration compared to 11% of those treated with 0.1 mg/kg IV methadone and 24% of those treated with short acting opioids. No significant differences in adverse effects were noted between treatment groups.

Safety profile of intraoperative methadone for analgesia after major spine surgery: An observational study of 1,478 patients

A retrospective chart review of 1,478 patients who received intraoperative methadone for perioperative pain management was conducted to evaluate the safety profile of intravenous methadone. Intraoperative methadone dose ranged from 2 to 40 mg with a mean of 11.5 +/- 4.6 mg (or 0.14 +/- 0.07 mg/kg). Total intraoperative opioid dose ranged from 8 to 353 mg ME with a mean of 34.2 +/1 21.5 mg ME. Patients on chronic opioid therapy required greater intraoperative methadone dose, however no significant differences in adverse effects were noted when comparing opioid naïve to opioid tolerant patients. 36.8% of patients experienced respiratory depression and 79.8% experienced hypoxemia. Naloxone was required in 2.3% of patients and reintubation was required for 1.5% of patients. No significant difference between rate of adverse events was noted between opioid naïve or nonopioid naïve patients. Hypotension occurred in a total of 806 patients (54.5%), and vasopressors were used in 12.1% of patients. QTc prolongation was noted in 58.8% of patients as well.

Dosage and Administration[1]:

- Dosing should be individualized to patient
- Conversion of oral methadone to parenteral methadone is 2:1

- Dosing for analgesia in patients who are not opioid tolerant:
  - Start at 2.5 mg to 10 mg every 8-12 hours and titrate slowly to effect

Switching patients to parenteral methadone from other chronic opioids:

Total Daily Baseline Opioid Morphine Dose	Estimated Intravenous methadone dose as percent of total daily oral morphine dose
< 100 mg	10 -15%
100-300 mg	5-10%
300-600 mg	4-6%
600-1000 mg	3-5%
>1000 mg	<3%

Switching patients from intravenous morphine to intravenous methadone:

Total Daily Parenteral Morphine Dose	Estimated Daily Parenteral Methadone Dose
10-30 mg	40-60%
30-50 mg	27-66%
50-100 mg	22-50%
100-200 mg	15-34%
200-500 mg	10-20%

- Rate has not been defined for intravenous administration of methadone solution
- Concentration of injectable solution: 10 mg/mL
- Administration:
  - Methadone Hydrochloride solution can be administered intravenously, subcutaneously, or intramuscularly.

Contraindications[1]:

- Patients with significant respiratory depression, acute or severe bronchial asthma, known gastrointestinal obstruction, or noted hypersensitivity reaction to methadone or any other ingredient in the Methadone HCl injection should not use this medication

Warnings/Precautions[1]:

- Addiction, Abuse, and Misuse: This is a schedule II controlled substance. As an opioid, methadone hydrochloride injection exposes patient to increased risk of addiction, abuse and misuse; even was used appropriately. Monitor patients at risk for opioid addiction
- Life Threatening Respiratory Depression: can be serious, or life-threatening with opioid use. If not immediately treated, respiratory depression can cause death. Patients at at greatest risk for this following therapy initiation or dose change. Monitor closely for CO2 retention from opioid-induced respiratory depression. Administer with caution to patients with hypoxia, hypercapnia, or decreased respiratory reserve.
- Life-Threatening QT Prolongation: QT interval prolongation and serious arrhythmias have been observed during methadone treatment. It is observed most commonly with doses greater than 200 mg/day. Patients on lower doses, concomitant medications and /or clinical syndromes such as hypokalemia were contributing factors. Patients with risk factors to the development of prolonged QT interval should be closely monitored.
- Neonatal Opioid Withdrawal Syndrome (NOWS): expected to occur if mother is on prolonged opioid therapy. NOWS may be life threatening, neonate will require immediate treatment.

Adverse Reactions[1,2]:

- Significant adverse reactions include respiratory depression and systemic hypotension, respiratory arrest, shock, cardiac arrest, and death have occurred.
- Most frequently observed adverse reactions in ambulatory patients include lightheadedness, dizziness, sedation, nausea, vomiting and sweating.
- Intravenous methadone may be associated with pruritus, urticaria, and rarely, hemorrhagic utricaria.
  SC and IM injections may cause local tissue reactions including pain, erythema, and swelling. This is particularly common with subcutaneous infusion
- Chronic methadone therapy is associated with additional adverse effects

Drug-Drug Interactions[1]:

CYP Interactions:	
CYP Inhibitors (3A4, 2B6, 2C19, 2C9, 2D6) Co-administration of CYP inhibitors and methadone can lead to increased plasma	CYP Inducers (3A4, 2B6, 2C19, or 2C9)

concentration of methadone and result in prolonged opioid effects that may result in overdose. In the case of concomitant dosing, dose reduce methadone Examples: macrolide antibiotics, azole-antifungals, protease inhibitors, fluconazole, fluvoxamine, SSRIs	Co-administration can decrease serum concentration of methadone leading to decreased efficacy. Concomitant administration may require increased methadone dose Examples: rifampin, carbamazepine, phenytoin, St John's Wort, Phenobarbital
Benzodiazepines and other CNS depressants:	
Co-administration of benzodiazepines or other CNS depressants can increase the risk of respiratory depression, sedation, coma, and death. Limit use and decrease dosages when used concurrently. Additional Examples: sedatives, hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, opioids, alcohol	
Potential Arrhythmogenic Agents	
Concurrent use of methadone with drugs known to prolong QT interval or induce electrolyte disturbances may require additional cardiac monitoring during administration QT prolonging agents: Class I and III antiarrhythmics, neuroepileptics, tricyclic antidepressants, and calcium channel blockers Drugs that can alter electrolytes: diuretics, laxatives	
Other Interactions: <u>Serotonergic Drugs</u>: Concurrent use with methadone can result in serotonin syndrome. <u>Monoamine Oxidase Inhibitors (MAOIs):</u> MAOIs and opioids together can cause serotonin syndrome and opioid toxicity. Avoid concurrent use within 14 days of last MAOI use	

Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics : can reduce effects or precipitate withdrawal in patients using methadone

Muscle Relaxants: Methadone may enhance neuromuscular blocking action of skeletal muscle relaxants and produce increased degree of respiratory depression

Diuretics: Methadone may decrease efficacy by inducing release of ADH

Anticholinergic Drugs: concomitant use increases risk of urinary retention and/or severe constipation causing paralytic ileus

Pregnancy Category[1]:

- Pregnancy category C
- Use of parenteral methadone has not been studied in pregnancy
- Studies of oral methadone in 30 pregnant patients in 2nd and 3rd trimesters has demonstrated increased drug clearance and decreased half-life during pregnancy

Breast Feeding[1]:

- Methadone is present at low levels in breast milk, and has the ability to cause increased drowsiness or breathing difficulties in nursing infants.

Monitoring[1,2]:

- Monitor patient closely for respiratory depression, especially within the first 24-72 hours of initiation of therapy or dose increase. Routine blood pressure monitoring is also suggested. In addition, patients should obtain a baseline ECG prior to initiation of therapy, particularly if they have a history of QTc prolongation.

Medication Safety Risk Factors:

Risk	Comments
Sentinel event alerts (please refer to JCAHO standards)	None

Black box warnings	Boxed warning regarding addiction, abuse, and misuse potential, life-threatening respiratory depression, life threatening QT prolongation, neonatal opioid withdrawal syndrome, interactions with CYP450 isoenyzymes, concomitant use with benzodiazepines or other CNS depressants
High Alert medication (please refer to current ISMP recommendations)	Yes
Renal or hepatic monitoring or adjustment necessary, or contraindicated in renal or hepatic dysfunction	Intravenous methadone use has not been extensively studied in patients with hepatic or renal impairment, however methadone is metabolized by the liver therefore hepatic insufficiency may lead to accumulation. Use not recommended.
Narrow therapeutic index and/or drug level monitoring required	yes
Is special monitoring required (e.g. telemetry, frequent glucoscans, etc.)?	ECG monitoring in patients at high risk for QTc prolongation, monitoring for respiratory depression and hypoxemia
LASA (look-alike/sound-alike) risks (please refer to current ISMP recommendations)	None
New molecular entity with unique mechanism and limited post-marketing data available	No
Abuse potential (Controlled substance category)	CII
Is dosing weight-based or are calculations required to dose the medication?	Variable
Is the medication administered as an IV infusion that requires titration?	No
Code blue/emergency drug	No
Neonatal/Pediatric safety considerations	Yes

Cost:
Estimated cost impact (based on projected use, associated costs, etc.)

Drug	Route of Admin / Strength	Cost
Methadone	Intravenous 200 mg/20 ml MDV	*$279.74*
		$0.17

	Oral 10 mg tablets UD	
Hydromorphone Injection	*1 mg/1 ml*	*$1.17*
Fentanyl injection	*100 mcg/2ml*	*$1.74*

Pharmacy Informatics

Addition to Nurse Witness medications list?	No
Is Dose Range Checking required? If "yes," please specify.	No
Are Hazardous Drug precautions needed? If "yes," please specify.	No
High Alert or Black Box Warning Medication? If "yes," please specify the text that should be added to the Cerner High Alert Medication functionality.	***Functionality not currently available
Are Multum Drug-Drug Interaction Customizations needed? TH Formulary Director to verify.	Concurrent use of methadone with additional CNS depressants can increase incidence of respiratory depression
Is TALLman lettering needed for product file build? If "yes," please specify.	**No**
Is Multum product information available? TIS to verify.	No
What common order sentences are required? Please list.	No

Comments/Conclusion:

Methadone is a synthetic, multimodal, opioid analgesic that works as both potent mu-receptor agonist and NMDA receptor antagonist. Its unique NMDA receptor activity contributes to this drug's ability to provide neuropathic pain relief, of particular benefit to spinal surgery patients.
Large scale clinical trials evaluating the efficacy and safety of a single IV intraoperative methadone dose are limited. However, available literature provides evidence that utilization of a single IV intraoperative methadone dose can provide adequate analgesia while reducing patients' overall post-operative opioid requirements.
Available safety information is limited in this population. It should be noted that both opiate tolerant and opiate naïve with IV methadone experienced: 40% respiratory depression, 80% hypoxemia, and 60% prolonged QTc in an observational study with IV methadone.

Because of noted safety concerns with administration of IV methadone in perioperative setting, it is recommended to not add to formulary and follow pathways recommended by multimodal pain group for management of surgical patients, surgical patients on opiates prior to admission, and surgical patients with substance abuse.

References:

1. Methadone Hydrochloride Injection, USP. Prescribing Information. Mylan Institutional LLC.
2. Lexicomp Online®, Methadone (Lexi Drugs), Hudson, Ohio: Lexi-Comp, Inc.; Aug, 2018.
3. Murphy GS, Szokol JW, Avram MJ, et al. Intraoperative methadone for prevention of postoperative pain A Randomized, Double-blinded clinical trial in cardiac surgical patients. Anesthesiology. May 2015; 122(5): 1112-22.
4. Gottschalk A, Duriex ME, Nemergut EC. Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. Anesth Analg. 2011; 112: 218-23.
5. Murphy GS, Szokol JW, Avram MJ et al. Clinical effectiveness and safety of intraoperative methadone in patients undergoing posterior spinal fusion surgery: A randomized, double-blinded controlled trial. Anesthesiology. 2017 May; 126(5): 822-33.
6. Russell T, Mitchell C, Paech MJ et al. Efficacy and safety of intraoperative intravenous methadone during general anaesthesia for caesarean delivery: a retrospective case-control study. Int J of Obes Anaes. 2013; 22. 47-51.
7. Komen H, Brunt M, Deych E et al. Intraoperative methadone in same-day ambulatory surgery: A randomized double-blinded dose-finding pilot study. Anesth Analg. 2018 May 25; doi: 10.1213/ANE.0000000000003464
8. Dunn LK, Yerra S, Fang S et al. Safety profile of intraoperative methadone for analgesia after major spine surgery: An observational study of 1,478 patients. J of Opioid Manag. 2018; 14(2). 83-7.

EXAMPLES:

Table 1: Comparative Trials

Reference	Patients (n) Study Design	Treatment groups	Therapeutic Results	Adverse Reactions	Comments
Murphy[3]	Randomized, double-blinded clinical trial of 156 patients undergoing cardiac surgery. Primary endpoint was amount of post-operative opioid analgesics needed. Secondary endpoints included satisfaction with pain management 24 hrs following surgery.	Randomized to receive either 0.3 mg/kg of methadone or 12 ug/kg of fentanyl intraoperatively. Half the study opioid was administered via infusion over 5 mins, and the remainder was infused over the next 2 hours. Exclusion criteria: included as follows: preoperative renal failure requiring dialysis or serum creatinine greater than 2.0; significant hepatic dysfunction (liver function tests more than twice the upper limit of normal), ejection fraction less than 30%, pulmonary disease necessitating home oxygen therapy, preoperative requirement for inotopic agents or	Average time to first morphine rescue dose in methadone treatment group was 6.5 hrs, compared to 3.75 hrs in the fentanyl group, giving intraoperative methadone treatment a 2.25 hr benefit ($p < 0.001$). Pain at rest was significantly less in patients treated with methadone in comparison to the fentanyl treatment group up to 72 hrs post extubation.	More patients treated with methadone experienced itching compared to those treated with fentanyl. Other noted adverse effects included nausea, vomiting, hypoventilation, hypoxemia, and sedation; however no statistical difference in rate of occurrence was identified between the two treatment groups.	Overall, study concluded post-operative morphine requirements were reduce by about 40% in patients who received methadone in comparison to those treated with fentanyl (6 mg versus 10 mg morphine equivalents) This trial excluded high risk cardiac surgical patients

		intraaortic balloon pump to maintain hemodynamic stability, emergency surgery, allergy to methadone or fentanyl, or use of preoperative opioids or recent history of opioid abuse.			
Gottschalk[4]	Prospective study which evaluated 29 patients undergoing spinal surgery were randomized to be treated intraoperatively with methadone or sufentanil.	Randomized to receive 0.75 mg loading dose of sufentanil followed by 0.25 ug/kg/hr or 0.2 mg/kg methadone as perioperative pain management. Pts tx w sufentanil received average of 175 ug of sufentanil total while those treated with methadone received an average 14.9 mg. Exclusion criteria included preoperative methadone therapy; morbid obesity with a body mass index _36.0 kg/m2; patients with chronic renal failure defined by serum creatinine _2.0 mg/dL;	Post-operative opioid requirements were overall reduced in patients treated with perioperative methadone. Specifically, 48 hrs following extubation, patients treated with methadone vs sufentanil required a median of 25 vs 63 mg morphine equivalents respectively for proper analgesic control (p=0.023), and 15 vs 34 mg morphine equivalents respectively 72 hrs following extubation (p=0024). ~~Pts in methadone treatment group had lower average pain scores measured by VAS in the 24, 48, and 72 hrs following extubation~~. Patients in methadone group had lower VAS valuaes at 48 hr (p<0.05) 5 versus 3.	3 of 13 patients treated with methadone developed hypoxemia, while none experienced respiratory depression. Other notable side effects in the methadone treatment group included nausea (4 out of 13), and vomiting (1 out of 13). No statistical difference between rates of occurrence was noted between treatment groups.	Patients with pre-operative methadone therapy, BMI > 36 kg/m2, or patients with renal failure or liver failure were excluded. Average pre-operative morphine consumption was 8 mg morphine equivalents (ME) in the methadone treatment group and 7.5 mg ME in the sufentanil treatment group.

		or liver failure defined as a history of cirrhosis or fulminant hepatic failure. Patients with preoperative alcohol or drug abuse, patients with a history of myocardial infarction or heart failure, and patients with ASA physical status III (except patients with a history of restrictive lung disease secondary to severe scoliosis) or more were also not included in the stud			
Murphy[5]	120 Patients undergoing spinal fusion were randomized to receive either intraoperative methadone or hydromorphone; a total of 115 patients were included in analysis	Methadone treatment group was given 0.2 mg/kg intravenous methadone at induction compared to 2 mg intravenous hydromorphone given at surgical closure. Post operatively, pain was managed via PCIA in both treatment groups Exclusion criteria included preoperative chronic renal insufficiency	On post-operative day 1, postoperative PCA hydromorphone requirements were 4.56 mg vs 9.9 mg in the hydromorphone group ($p<0.001$). Results were similar on days 2 and 3 as well, as patients in the methadone treatment group continually required less analgesia.	Hypoxemia and respiratory depression were noted adverse effects in this trial, however rate of occurrence did not differ among treatment groups.	Patients given larger doses of methadone 0.2-0.4 mg/kg are not at increased risk of clinically significant respiratory depression.

		or failure (defined as a serum creatinine more than 2 mg/dl), significant liver disease (cirrhosis or hepatic failure), American Society of Anesthesiologists physical status IV or V, pulmonary disease necessitating home oxygen therapy, preoperative use of methadone or hydromorphone or allergy to either, recent history of opioid or alcohol abuse, or inability to use a PCA device or speak the English language. In addition, any patient judged by the anesthesia care team to potentially require prolonged postoperative intubation was excluded from enrollment.			
Russell[6]	Retrospective case-control study of 25 pts undergoing	Mean dose of IV methadone was 14 +/- 5.0 mg (equivalent to	Total opioid consumption was higher in the control group than methadone treatment group at	One patient treated with 10 mg IV methadone (0.19 mg/kg) and fentanyl 200 ug had respiratory	Patients excluded if given >10 mg of IV morphine equivalents. No data

	elective or emergency caesarian delivery. Pts who received intraoperative methadone were matched to two control subjects who did not for comparison.	0.17 +/- 0.06 mg/kg) with a dose range from 7 to 20 mg. Pts in methadone treatment group had average weight of 87 kg (+/- 24 kg) and an average BMI of 32. Patients were excluded if they had received preoperative neuraxial analgesia, a pre-delivery opioid dose >10 mg of intravenous morphine equivalents, were non-English speaking, or in whom a Pfannenstiel incision had not been used	PACU, PACU-24 hrs post-op, and 24-48 hrs post op. Overall mean post-op mg morphine equivalents was lower in patients treated intraoperatively with methadone compared to the control group (115 vs 213 respectively, p = 0.0002)	depression. Other noted adverse reactions included respiratory depression that occurred in 4% of pts during PACU admission who were treated with methadone compared to 2% of pts in the control group. No patients treated with methadone were noted to have dysrhythmias following perioperative administration.	regarding an appropriate methadone dose for obstetric population; as dosing ranged from 7 to 20 mg . Effects of intraoperative methadone on the infant were not assessed.
Komen[7]	Double-blind dose escalation protocol that randomized 60 pts 2:1 to receive a single intraoperative dose IV methadone for pain control in same-day ambulatory surgery.	Patients received either 0.1 mg/kg or 0.15 mg/kg IV methadone based on IBW. Media intraoperative methadone doses were 6 and 9 mg respectively. The control group received either fentanyl or fentanyl and hydromorphone	Patients who received 0.1 mg/kg or 0.15 mg/kg IBW methadone intraoperatively required a median of 5 and 0.1 mg morphine equivalents during their PACU stay, while patients in the control group received 9.3 mg morphine equivalents. Post discharge opioid consumption between groups was also analyzed. Pts who received 0.15 mg/kg methadone reported using a	33% of the control group, 33% of the methadone 0.1 mg/kg treatment group, and 48% of the methadone 0.15 mg/kg methadone group experienced nausea. 71% of the control group, 67% of the 0.1 mg/kg methadone treatment group, and 67% of the 0.15 mg/kg treatment group noted fatigue as a same-say surgery adverse effect. Other noted adverse effects included itchiness,	Authors concluded 0.15 mg/kg IV methadone at induction significantly reduced need for post-operative PACU opioids.

			total of 5 post-discharge opioid pills while pts who received 0.1 mg/kg methadone used 7 pills. In comparison pts in the control group consumed a total of 10 pills.	dry mouth, headache, and lightheadedness.	

Table 2: Safety Studies

Reference	Patients (n) Study Design	Treatment groups	Therapeutic Results	Adverse Reactions	Comments
Dunn[8]	Records of 1478 adult pts undergoing elective spinal fusion of two or more levels received perioperative analgesia w/ IV methadone. Primary outcome was incidence of postoperative respiratory depression. Secondary outcomes were time to extubation, incidence of hypotension, MAP < 60, or hypoxemia.	Included both opioid naïve and chronic opioid users. Intraoperative methadone dose ranged from 2 to 40 mg with a mean of 11.5 +/- 4.6 mg (or 0.14 +/- 0.07 mg/kg).	Total intraoperative opioid dose ranged from 8 to 353 mg ME with a mean of 34.2 +/1 21.5 mg ME. Patients on chronic opioid therapy required greater intraoperative methadone dose, however no significant differences in adverse effects were noted when comparing opioid naïve to opioid tolerant patients.	The most common adverse reaction was hypoxemia, which occurred in 79.8% of patients. 36.8% of patients experienced post-op respiratory depression, and naloxone was administered to 2.3% of patients. Reintubation was required in 1.5% of patients Of the 968 patients who received post-operative ECGs, 289 patients (29.9%) experienced new cardiac arrhythmias, the most common being sinus tachycardia (76.1%). 58.8% of these patients demonstrated prolonged QTc.	Low reintubation rates and naloxone administrations compared to high incidence of respiratory depression and hypoxemia suggest while these side effects may be common in patients given IV methadone, they are also easily managed. Side effects of opioid naïve patients and chronic opioid users did not significantly differ. Limitations of this study include its observational nature and non-standardized intraoperative methadone doses.