IV Methadone: When All Else Fails

Annas Aljassem, MD
Levi M. Hall, PharmD, BCPS

Disclosure

- Nothing to disclose
Objectives

- Summarize current evidence based recommendations on indicated uses of parenteral methadone
- Describe the pharmacokinetic and pharmacodynamics properties of methadone
- Identify medical staff and patient/family education needs and implementation strategy
- Evaluate case series and outcomes of opioid-tolerate patients receiving parenteral methadone
- Explore logistics of adding parenteral methadone to your health system formulary, establishing medication prescribing guidelines, development of an order set in electronic health record, and identifying a list of approved prescribers

Patient Case: RF 67-Year-Old Man

- CC: Admitted to hospital in with 10/10 pain, dysphagia and 30 pound weight loss
- HPI:
  - Increasing dysphagia resulting in NPO x 3 months
  - Headache in temporal region radiating to left jaw and neck
- PMH: Stage IIIC squamous cell cancer of mid and distal esophagus
- Medication
  - Hydromorphone PCA, 0.6 mg Q 6 minutes + 1 mg/hour
  - Oral morphine equivalent ~700 mg/day
  - Previous failed attempts to transition off the PCA included
    • Fentanyl patch 150 mcg/hr + hydromorphone 2 mg IV (9 doses/day) + morphine 20 mg + methocarbamol Q8H + guaifenesin w/codeine
  - After 4 week of failed pain regimens, you receive the consult to save the day and manage RF’s pain
The Situation…

- Pharmacologic treatment of acute pain for opioid-tolerant patients requiring high doses of opioids (>300 mg OME per day) can be challenging, suboptimal, and is often based on expert opinions and consensus.
- Patients with high OME requirements are uniquely challenging when they are admitted to the hospital due to a pain crisis because increases in traditional opioids, such as hydromorphone and fentanyl, mainly result in increased adverse side effects.
- Clinicians who are experienced in pain management may consider a rotation to methadone, but are met with large differences in dosing guidelines when OME requirements reach >300 mg per day.

Breaking the Pain Cycle

Our Process…

*blow up your current plan*
Breaking the Pain Cycle

- What is the cause of the pain?
  - Did you prescribe the correct class of pain medicine?
- Evaluate complete pain history
  - What medication was tried in past?
  - What worked in the past/now?
- Streamline current opioids
  - One long-acting and one short-acting plus IV push opioid for BTP
  - Titrate doses based on monitoring outcome
- Optimize nonopioids/adjuvant agents
  - Schedule APAP
  - Order adjunctive medication ATC with HOLD parameters (aka “RN must offer, patient may refuse”)

Pain Pearls: Total Pain Syndrome

- If anxiety, depression or insomnia is documented in the problem list, is each being addressed with medical management?
  - Anxiety:
    • PRN: buspirone >> BZDs (try to avoid opioids + BZD combo)
    • Constant: SSRI >> SNRI/TCA
  - Depression:
    • First line: SNRI >> TCA
    • Second line: SSRI (no benefit to pain outcomes)
  - Insomnia:
    • First line: melatonin 9 mg (OTC)
    • Second line (w/muscle spasm): tizanidine 4mg QHS
    • Third line: trazodone 50 mg
    • Third line: zolpidem 5 mg or temazepam 15 mg
Opioids: Side Effects

**Common side effects**
- Constipation
- Nausea
- Sedation
- Confusion
- Hallucination
- Sweats
- Dry mouth

**Uncommon side effects**
- Urinary retention
- Pruritus
- Delirium
- Myoclonus
- Hyperalgesia
- Seizures
- Respiratory depression

---

Opioids in Kidney & Liver Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Failure</th>
<th>Dialysis</th>
<th>Stable Cirrhosis</th>
<th>Severe Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Do NOT use</td>
<td>Do NOT use</td>
<td>Caution (reduce dose and frequency)</td>
<td>Do NOT use</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Caution (reduce dose and frequency)</td>
<td>Caution</td>
<td>Caution (reduce dose and frequency)</td>
<td>Caution (reduce dose and frequency)</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Preferred reduce dose and frequency</td>
<td>Preferred not dialyzed but minimal toxicity</td>
<td>Caution (reduce dose and frequency)</td>
<td>Caution (reduce dose and frequency)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Preferred</td>
<td>Preferred not dialyzed but minimal toxicity</td>
<td>Preferred</td>
<td>Preferred</td>
</tr>
<tr>
<td>Methadone</td>
<td>Preferred (with consultation only)</td>
<td>Preferred not dialyzed but minimal toxicity (with consult only)</td>
<td>Preferred (with consult only)</td>
<td>Preferred (with consult only)</td>
</tr>
</tbody>
</table>

Adapted from Meridian Health System, New Jersey

Levy MH. NCCN Clinical Practice Guidelines in Oncology™ Palliative Care, v.1, 2008.
**Types of Pain**

- Physical
- Emotional
- Total pain
- Pseudoaddiction
- Addiction

**Assessment**

- Recognize patients at **HIGH RISK** for opioid induced respiratory failure:
  - Opioid-naïve patients in acute pain
  - Obese
  - Elderly
  - History of sleep apnea
  - Impaired renal, hepatic, pulmonary, or cardiac function
    *Polypharmacy: benzodiazepines, certain antiemetics, sedatives, hypnotics or other CNS depressants*
Methadone can be useful...

- Component of neuropathic pain
- Poorly controlled pain despite appropriate use of other opioids (either due to refractory pain or intolerance of side effects)
- Patients requiring high doses of opioids (>300 mg OME)
- Patient with true morphine intolerance/allergy


Poor Methadone Candidate

- Risk of respiratory compromise in unmonitored setting
- Paralytic ileus
- History of syncope or arrhythmias
- QTc >500 msec
- Cardiac impairment
- Very limited prognosis (less than week to live)
- Multiple drug interactions
- Poor cognitive function with limited home support
- History of unpredictable adherence or misuse

**N-methyl-D-aspartate (NMDA) Receptor**

- Play a role in opioid tolerance, neuropathic pain, hyperalgesic states
- NMDA receptor blockers
  - Methadone
  - Ketamine
- Limited well-controlled trials have restricted their recognition and use
  - Hospice/palliative care teams have extensive use
Methadone…

- Racemic mixture of R- and S-methadone
- Synthetic opioid receptor agonists (μ,κ,δ)
- Inhibits reuptake of serotonin and norepinephrine
- Antagonists at NMDA (N-methyl-D-aspartate)
  - Prevent central sensitization
  - Reduce opioid tolerance
  - Increase effectiveness in treating neuropathic pain compared to other opioids

Bechwith SK, Wellman C. Weiner's Pain Management. ©2007

---

Methadone: Reasons for Resurgence

- Useful in different types of pain syndromes
- No active metabolites
- Positive pharmacoeconomics
  - Methadone 10 mg, #120: $12.20
  - Fentanyl transdermal patch 25 mcg/hr, #5: $31.19
  - Morphine ER 30 mg, #60: $50.80
  - Oxycodone ER 20 mg, #60: $138.43
- Multiple routes and dosage forms
- Oral and rectal absorption
- Favorable dosing schedule with long half-life
Pharmacokinetics

- **Absorption**
  - Almost completely absorbed by the GI tract (3x higher than other opioids)
  - Bioavailability approaching 70%-80%

- **Distribution**
  - Rapid and extensive distribution phase
  - Tissue stores slowly release back into plasma during redistribution → long half-life
  - Binds to alpha 1-acid glycoprotein (free fraction varies 4-fold)
  - Competition for protein binding sites → increased free fraction
    - TCA and neuroleptic medications

- **Metabolism/elimination**
  - N-demethylation to inactive metabolite
  - Slow elimination phase (range 4.2-130 hours)
  - Eliminated mostly by the fecal route


Don’t start methadone and walk away!

**Methadone: Oral**

- Oral bioavailability 70%-80% (range 36%-100%)
- Onset 15-45 minutes after oral, peak in 2.5-4 hours
- Duration from single dose 4-8 hours

**How supplied**
- Oral solution:
  - 5 mg/5 mL
  - 10 mg/5 mL
  - 10 mg/1 mL
- Oral tablet:
  - 5 mg
  - 10 mg

**Sublingual**
- Lipophilic
- 34% absorbed

---

**Methadone: Parenteral (IV/SQ)**

**Intravenous**
- Chlorobutanol, preservative increase risk of QT prolongation and Torsades
  - Prefer PF for patients with risk factors for arrhythmia
- Duration of action is 4-8 hours in single dose studies
  - Shorter than its elimination half-life

**Subcutaneous**
- Racemic mixture available is not always well tolerated
- Local reaction as site of injection
  - Erythema
  - Induration
- May add dexamethasone 1-2 mg per day or hyaluronidase 150 IU injection

---

Signs of Methadone Overdose

- Methadone-associated mortality is higher shortly after initiating (3-5 days)
- Acute intoxication
  - Euphoria
  - Slurred speech
- Late signs of accumulation
  - Loud snoring
  - Slow or shallow respirations or apnea
  - Extreme tiredness or sleepiness
  - Inability to think, talk, or walk normally
  - Pinpoint pupils


Methadone Drug Interactions

<table>
<thead>
<tr>
<th>CYP-mediated drug interactions</th>
<th>Metabolized by 3A4, 2B6, 2C19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction Description</td>
<td>CYP 3A4 inhibitors&lt;br&gt;Increased methadone levels&lt;br&gt;1-2 days for inhibition (FAST)</td>
</tr>
<tr>
<td>Examples of interacting medications</td>
<td>Macrolides&lt;br&gt;Imidazoles&lt;br&gt;Fluoroquinolones&lt;br&gt;Antidepressants (SSRIs, TCAs)</td>
</tr>
<tr>
<td>Therapeutic Recommendations</td>
<td>Decrease dose empirically by 25% or more, encourage rescue medication</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Concurrent CNS depressants</th>
<th>QT-prolonging medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction Description</td>
<td>Increased risk of CNS depression</td>
</tr>
<tr>
<td>Examples of interacting medications</td>
<td>Alcohol&lt;br&gt;Neuroleptics&lt;br&gt;Benzodiazepines&lt;br&gt;Antidepressants</td>
</tr>
<tr>
<td>Therapeutic Recommendations</td>
<td>Evaluate and recommend discontinuation of interacting medications if clinically appropriate</td>
</tr>
</tbody>
</table>


[Image of Painweek logo]
Parenteral Administration

- Intermittent IV administration
  - IV push
  - IV piggyback
- Continuous IV infusion
  - PCA
  - PCA + CIV ± RN bolus
  - CIV only
- Continuous SQ infusion

Parenteral Methadone

- Methadone PCA 50 mg/50 mL in 60 mL syringe
- Only compatible in 0.9% sodium chloride
- On formulary of accepted drugs
  - Pharmacist must place initial order
- Alaris Guardrail: methadone PCA
PCA Medication Order Format

- PCA Demand Dose: _______ mg
- Lockout Interval: _______ minutes
- Continuous Infusion: ______ mg/hour
- Max Limit: _________ mg/hour

- RN Bolus: ____ mg (ONCE) Q____H PRN BTP

Parenteral Methadone: Dosing

1. Convert opioid to oral methadone dose equivalent
2. TDD of IV methadone is 50% of the TDD of PO methadone
3. Divide by 24 to determine an hourly infusion rate
   or divide into intermittent doses to be administered every 6-8 hours

Methadone PCA Dosing Pearls

- Patient controlled analgesia (PCA) is preferred method
- Calculate a conservative initial basal rate based on current opioid use
- **Do NOT increase the basal rate for the first 12 hours after starting IV PCA therapy** (with infusion initiation or dose increase)
- PCA demand dose equivalent to the hourly infusion rate during the titration phase, offered every 15-30 minutes (20 minutes)
- Clinician-activated boluses at twice the hourly infusion rate may be given every hour


Example: Morphine PO to Methadone IV PCA

Patient JS is taking MS Contin 120 mg PO Q12H + morphINE IR 30 mg every 4 hours PRN (approximately 4 doses/day). He is no longer able to swallow oral medications, and his physician states that he thinks the patient is experiencing significant neuropathic pain not adequately treated with morphine. Therefore, the physician would like to start an IV methadONE PCA to quickly establish a therapeutic regimen.

1. Calculate total daily dose of opioids in morphINE equivalents: long-acting (120 mg x 2) + short-acting (30 mg x 6) = 360 mg per day (TDD in morphINE equivalents)
2. Utilize conversion chart to determine appropriate morphINE: methadONE conversion ratio, and convert to ORAL methadONE
   a. Patient falls into the 301-600 mg morphINE mg/day category ⇒ use 10:1 ratio for morphINE: methadONE
   b. 360 mg PO morphINE x 10 = 36 mg per day PO methadONE
3. Convert PO methadONE to IV methadONE (2:1 ratio): 36 mg divided by 2 = 18 mg IV methadONE per day
4. Divide total daily IV methadONE requirement by 24 hours to obtain hourly infusion rate = 18 mg/24 hours = 0.75 mg/hour
   a. CIF = 0.75 mg per hour
   b. PCA Demand dose = 0.75 mg
   c. Lockout: 15-30 minutes
   d. RN bolus: 1.5 mg QL-4 hours PRN

<table>
<thead>
<tr>
<th>Morphine dose (mg/day)</th>
<th>&lt;100</th>
<th>101-300</th>
<th>301-600</th>
<th>601-800</th>
<th>801-1000</th>
<th>&gt;1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine: methadONE</td>
<td>3:1</td>
<td>5:1</td>
<td>10:1</td>
<td>12:1</td>
<td>15:1</td>
<td>20:1</td>
</tr>
<tr>
<td>Ripamonti, 1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>----------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine dose (mg/day)</td>
<td>30-90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>90-300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Greater than 300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine: methadone</td>
<td>4:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8:1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mercadente, 2001</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine dose (mg/day)</td>
<td>30-90</td>
</tr>
<tr>
<td></td>
<td>90-300</td>
</tr>
<tr>
<td></td>
<td>&gt;300</td>
</tr>
<tr>
<td>Morphine: methadone</td>
<td>4:1</td>
</tr>
<tr>
<td></td>
<td>8:1</td>
</tr>
<tr>
<td></td>
<td>12:1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ayonrinde, 2000</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine dose (mg/day)</td>
<td>&lt;100</td>
</tr>
<tr>
<td></td>
<td>101-300</td>
</tr>
<tr>
<td></td>
<td>301-600</td>
</tr>
<tr>
<td></td>
<td>601-800</td>
</tr>
<tr>
<td></td>
<td>801-1000</td>
</tr>
<tr>
<td></td>
<td>≥1001</td>
</tr>
<tr>
<td>Morphine: methadone</td>
<td>3:1</td>
</tr>
<tr>
<td></td>
<td>5:1</td>
</tr>
<tr>
<td></td>
<td>10:1</td>
</tr>
<tr>
<td></td>
<td>12:1</td>
</tr>
<tr>
<td></td>
<td>15:1</td>
</tr>
<tr>
<td></td>
<td>20:1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Friedman, 2004</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine dose (mg/day)</td>
<td>&lt;1,000 mg</td>
</tr>
<tr>
<td></td>
<td>&lt;1,000 mg</td>
</tr>
<tr>
<td></td>
<td>&gt;1,000-&lt;2,000 mg</td>
</tr>
<tr>
<td></td>
<td>&gt;2,000 mg</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;65 years</td>
</tr>
<tr>
<td></td>
<td>≥65 years</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Morphine: methadone</td>
<td>10:1</td>
</tr>
<tr>
<td></td>
<td>20:1</td>
</tr>
<tr>
<td></td>
<td>20:1</td>
</tr>
<tr>
<td></td>
<td>30:1</td>
</tr>
</tbody>
</table>

---

**Loading Dose**

- Loading doses are appropriate for patients who meet the following criteria
  - Pain score >5
  - RASS ≥ -1
  - Respiratory rate >10 breaths per minute and no respiratory compromise

- If pain is not controlled when starting PCA, choosing to not give a loading dose will result in treatment failure!
Pharmacokinetic Properties

Pitfalls of Opioid Rotation...

- Continuous IV infusion or too rapid oral titration may be dangerous (respiratory depression)—will need frequent dose adjustment (usually downward), if IV continuous infusion given
- Rotation from high dose morphine (eg, 300 mg/24 hrs) should be done with caution using equianalgesic tables
- This makes conversion to methadone (and other opioids) potentially quite dangerous when rotating from high dose opioid therapy
- Such rotations should generally be done in the inpatient setting
- Beware of methadone in equianalgesic; tables can be misleading

...Pitfalls of Opioid Rotation

- Be aware of the potential for inducing withdrawal with some rotations (e.g., from morphine to fentanyl)
- Account for incomplete cross tolerance and underestimates of actual potency of new opioid due to individual variation when using equianalgesic tables; typically adjust the calculated dose downward by 25%-50%
- Also adjust for individual patient characteristics (psychosocial needs, prior opioid history, substance abuse history, etc)

Parenteral Methadone: IV → PO

- DO NOT use IV dose equal to 50% of the PO dose equivalency
- Methadone bioavailability is 70%-80%
- The 1:2 ratio assumes bioavailability of 50%
  - This low estimate of bioavailability would cause an increase in sedation and confusion
- Study of 8 cancer patients found most accurate conversion oral:parenteral methadone of 1:0.7 with good pain control
- Multiply TDD of IV methadone by 1.3 to determine TDD of oral methadone

Example: Methadone IV to PO

One week after admission, JG’s pain is very well controlled on IV PCA methadone infusion at 1.5 mg/hour with a 1.5 mg bolus. His physician would like to discharge the patient on oral methadone solution. (Note: in the setting of well-controlled pain, would only include continuous infusion dose to convert to oral methadone in order to decrease risk of overdose)

1. Calculate total daily dose of IV methadone: 1.5 mg/hour x 24 hours = 36 mg per day
2. Convert IV methadone to PO methadone (IV dose x 1.3 = PO dose): 36 mg per day x 1.3 = 46.8 mg PO methadone per day
3. Divide total daily PO methadone dose to schedule Q8 regimen: methadone 15 mg suq PO Q8h, first dose to be given when infusion D/C’d
4. Calculate breakthrough regimen: 10-15% of total daily dose
   a. 46.5 x 0.10 - 0.15 = 4.5 - 6.8 mg
   b. Breakthrough regimen: methadone 5 mg PO suq PO Q8H PRN

**Methadone PCA Initiation Guidelines**
- PCA Demand dose = hourly infusion rate
- Length: 15-30 minutes
- CIW: hourly infusion rate
- RN order: 2x hourly infusion rate

**PO to IV and IV to PO (see picture above)**
- Total daily dose of IV methadone x 50% is PO methadone, however, you should double the IV dose to obtain the PO dose due to incomplete bioavailability.
- The IV methadone dose should be multiplied by 1.3 to obtain the equivalent PO methadone dose based on an accepted bioavailability of 75%.
Electrocardiogram Monitoring

Misconception:
Ondansetron is a benign antiemetic.
Medication Prescribing Guidelines

- List of approved prescribers
- List of units approved for medication administration
- Dosing guidelines—multiple methods creates a challenge for your clinical pharmacists for order verification
- Pharmacist verification process
- Limitation on dose escalations/timing
- Pharmacy compounding/dispensing

Development of Methadone Order Set Within your EMR

- Developing a standardized order set for IV methadone is preferred to ensure the following:
  - Uniform dosing for all patients following EBM guidelines
  - Preparation of one medication concentration
  - Limiting prescribing ability to those credentialed to use IV methadone
Patient Case: Conclusion

- He was requiring: 720 mg oral morphine equivalent (via hydromorphone PCA + CIV)
- Was started on the following methadone IV PCA
  - PCA demand: 1.25 mg → 2.5 mg
  - LO: 20 minutes
  - CIV: 1.25 mg/hr → 2.25 mg/hr
  - RN Bolus: 1.25 mg per PCA pump Q4H PRN BTP → 2.5
- Final oral methadone 20 mg PO Q8H
- Outpatient follow-up regimen: methadone 5 mg PO TID PRN pain (no longer requiring scheduled methadone regimen)

Challenges

- PCA interrogation & documentation
  - PCA demands
  - PCA delivered
- Pain reassessment
- Delay in pump programming and medication procurement
- Patients chasing euphoria as experienced with previous ineffective opioid regimens
- Nursing compliance with policy and fear of patient harm
Lack of Robust EBM

- Several conversions have been published for rotating to methadone create false or misleading dose design for prescribers that are less familiar with methadone
- Numerous studies suggest that equianalgesic dose depends on the previous opioid treatment but there are few studies on the use of IV methadone for management of severe or refractory pain
- Essentially no dosing recommendations for oral morphine equivalents >2,000 mg oral morphine/day
- Must of this has been based on clinical experience (or a lack there of)
- More research is needed on dose recommendations for patients with high OME (>1,000-5,000 OME)

When all else fails...

...Call the Bearded Bandits
References


IV Methadone: When All Else Fails

Annas Aljassem, MD