METHADONE BASICS FOR HOSPICE PROVIDERS

Ellen Fulp, PharmD, MSPC, BCGP
Director of Pharmacy Education, AvaCare, Inc.
March 17, 2020
OBJECTIVES

- Discuss the history of methadone
- Review types of pain and basic pain assessment
- Discuss the risks and benefits
- Describe the appropriate use of methadone in the hospice population
- Review dosing and monitoring strategies
HISTORY

- Developed by German scientists in the 1930s
  - Used in Europe in WWII
- Marketed by Eli Lilly in the U.S. as Dolophine
  - Claims methadone is a “safe” alternative to morphine due to reduction in sedation or nausea
- 1990s: growing evidence for neuropathic pain control
  - Resurgence of use for chronic and malignant pain
- 2006: FDA Public Health Advisory
TYPES OF PAIN

- **Acute**
  - Duration = brief
    - Hours, days, weeks, or a few months
    - Tissue damage, inflammation, brief disease process, procedural

- **Chronic**
  - Duration = extended period
    - Months, years, lifetime
  - Chronic malignant pain
  - Chronic nonmalignant pain
TYPES OF PAIN

- Nociceptive pain
  - Visceral
  - Somatic
- Neuropathic pain
- Mixed, unspecified pain
- Pain resulting from psychological disorders
PAIN SCREENING & ASSESSMENT

- **NQF #1634 Pain Screening**
  - Measure Description: Percentage of patient stays during which the patient was screened for pain during the initial nursing assessment.

- **NQF #1637 Pain Assessment**
  - Measure Description: Percentage of patient stays during which the patient screened positive for pain and received a comprehensive assessment of pain within 1 day of the screening.
    - Location, severity, character, duration, frequency, what relieves or worsens that pain, and the effect on function or quality of life
METHADONE AND NEUROPATHIC PAIN

- Most effective opioid for neuropathic pain
- Active N-methyl-D-aspartate (NMDA) receptor antagonist
  - Reduces CNS sensitization to pain/hyperalgesia
  - Reduces CNS amplification of pain sensation
- Few other known NMDA receptor antagonists:
  - Dextromethorphan
  - Ketamine
  - Memantine
PHARMACOKINETICS
ABSORPTION

- Variety of routes for administration
  - Oral, Rectal, Intravenous (IV), Subcutaneous (SQ), Epidural
    - Oral tablets (5mg, 10mg, 40mg), liquid (10 mg/5 mL), liquid intensol (10 mg/mL)
    - Intramuscular (IM): Should generally be avoided in pain management
    - Intrathecal: Not FDA approved
- Basic, Lipophilic
- Peaks 2-4 hours after oral dosing
- Oral, rectal and IV routes of administration yield a mean bioavailability of 70-80%
DOSING PEARL: IV ROUTE

- Danger: QT prolongation and lack of data
- Given IV or Subcutaneous via PCA, continuous or intermittent bolus infusion
  - Subcutaneous infusions may result in localized reactions; rotate site
- Total Daily Dose (TDD) parenteral methadone dose is 50% of the oral TDD
- PCA is the preferred method
  - Calculate basal rate
    - Not to be increased for AT LEAST 12 hours
    - Continuous basal rate or intermittent doses Q6-8H
DISTRIBUTION

- Lipophilic = fat soluble
  - Distributed throughout the body and slowly released back into the plasma
- Extremely long half-life
- Protein binding
  - Free/unbound drug results in pharmacologic effect
  - Results in a wide variance of response among patients
METABOLISM

- Primarily metabolized in the liver
  - CYP3A4, 2B6, 2C8, 2C9, 2C19, 2D6
  - Auto-Inducer

- CYP3A4 and/or 2B6 INHIBITORS: methadone toxicity
  - Examples: Verapamil, Fluconazole, Paroxetine, Doxycycline, Clarithromycin

- CYP3A4 and/or 2B6 INDUCERS
  - Examples: Carbamazepine, Phenytoin, Phenobarbital
ELIMINATION

- Inactive metabolites eliminated in urine and feces
  - Useful medication in renal disease
- Average elimination half-life of 20-35 hours
  - Result = potential toxicity
- Four to ten days to reach steady state
  - Steady state = the rate of the drug in equals the rate of the drug out.
  - Do I only have to worry about reaching steady state once?
HEPATIC & RENAL CONSIDERATIONS

- Safe in renal failure → No active metabolites
  - Dose should still be reduced in severe renal impairment
- Does undergo hepatic metabolism → should be avoided in severe liver disease

<table>
<thead>
<tr>
<th>Estimated Renal Function</th>
<th>Preferred Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 40 mL/min</td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Oxycodone</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td>CrCl = 30-40 mL/min</td>
<td>Oxycodone</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>Oxycodone</td>
</tr>
<tr>
<td></td>
<td>Methadone</td>
</tr>
</tbody>
</table>
QT PROLONGATION
QT PROLONGATION & METHADONE

QT Prolongation

Torsades de Pointes (TdP)

Ventricular tachycardia
QT PROLONGATION & METHADONE

- Risk Factors
  - Female
  - Impaired liver function
  - Heart disease: arrhythmias, CAD, history of MI, CHF
  - QT prolonging medications
    - Examples: amiodarone, quetiapine, haloperidol, chlorpromazine, citalopram, paroxetine, fluoxetine, sotalol, trazodone, ranolazine, and ondansetron
  - Electrolyte imbalances
    - Examples: hypokalemia, hypomagnesemia
    - May be caused by diuretics, laxatives, vomiting and diarrhea
  - Methadone doses >200 mg per day
QT PROLONGATION: CLINICAL CONSIDERATIONS

- Avoid in multiple risk factors
- Reduce controllable risk factors
  - Example: dehydration, nausea/vomiting/diarrhea, medications
- Arrhythmia alone is not a contraindication
- Risk vs benefit discussion with patient and caregivers
- Monitor for new or increased tachycardia, syncope, palpitations, diaphoresis
- Consider baseline and periodic EKG in patients with longer prognoses
QT PROLONGATION: MONITORING

- EKG Monitoring Guidelines
  - Center for Substance Abuse Treatment Expert Panel
  - U.S. Consensus Guideline
    • *Palliat Support Care.* 2008; 6(2): 165-176.
  - American Pain Society (APS)

- General Guidelines
- Not written specifically for hospice patients
- New Hospice and Palliative Care Consensus White Paper
SUMMARY: RISKS VS BENEFITS

RISKS
- QT Prolongation
- Time to steady-state
- Clinician discomfort
- Patient discomfort
- Respiratory depression
- Drug-drug interactions

BENEFITS
- Neuropathic Pain
- Long half-life
- Multiple formulations
- Bioavailability
- Morphine allergy
- ESRD
- Cost
HOSPICE CONSIDERATIONS
REMS

- Monitoring includes therapeutic response, adverse reactions, environment oversight, and REMS
- Risk Evaluation and Mitigation Strategy (REMS)
  - Patient, family, and caregiver education
  - Locked medication storage boxes
  - Designated caregivers to assist with administration
  - Alternate routes of administration
  - Limited prescription quantities
  - Adjusted basal regimens when appropriate
  - Alternate suggestions: treatment agreements and urine drug testing (UDT)
METHADONE IN HOSPICE

Medication appropriateness refers to whether a medication is useful in an individual clinical situation based on both the attributes of the medication and its recipient.

Important factors to consider:

- Remaining life expectancy of patient
- Time until therapeutic benefit of medication
- Goals of care
- Treatment target

IS MY PATIENT A METHADONE CANDIDATE?

- Patient A is a 53-year-old male with esophageal cancer recently admitted to the hospital after a pain crisis.

- Home Regimen:
  - Morphine ER 200 mg po q8h
  - Morphine IR 60 mg po q2h PRN breakthrough pain

- Dysphagia secondary to disease progression

- Hospital Regimen:
  - Hydromorphone 1.2 mg/hour continuous subcutaneous infusion with 0.5 mg bolus q20 minutes PRN breakthrough pain
IS MY PATIENT A METHADONE CANDIDATE?

- Patient B is a 52-year-old female on hospice for 10 days with a primary diagnosis of metastatic melanoma.
  - Palpable tumors
  - Significant pain with minimal movement
- History of substance use disorder and diversion
- Home Medications:
  - Hydroxyzine HCl, Hydrocodone/Acetaminophen, Lyrica, MiraLax OTC, Oxycodone ER, Promethazine, Senna-S
  - Analgesics:
    - Oxycodone ER 160 mg po q6h
    - Hydrocodone/Acetaminophen 10/325 mg 2 tabs po q4h PRN
    - Pregabalin 200 mg po bid
METHADONE IN HOSPICE

- Opioid Rotation
  - Switching to a different opioid due to inadequate analgesic response or intolerable adverse effects
- Incomplete cross tolerance
  - Improved pain control
  - Decreased intensity of adverse effects
- Failure to respond to one opioid does not represent a class response
METHADONE IN HOSPICE: CONSIDERATIONS

- Patients with rapidly escalating opioid requirements (greater than 200 mg of morphine equivalents a day)
  - Full conversion
  - Adjunct dosing

- Patients with dose-limiting adverse effects from other opioids
  - Nausea, constipation, hallucinations, myoclonus

- Dysphagia

- Patients or caregivers with a history of substance use disorders
DOSING
METHADONE DOSING

1. Calculate total daily opioid dose in oral morphine equivalents (OME)
2. Use oral morphine: oral methadone ratio
3. Establish methadone dose schedule
   (total daily methadone dose divided into 2-3 doses per day)
4. Use a traditional opioid for breakthrough pain
   (10-15% of basal opioid requirement)
5. Monitor pain and adverse effects
   • Increase methadone total daily dose no more frequently than every 5 days
   • Patients with higher OME requirements may require a cross-taper (rule of thirds)
METHADONE DOSING: CONVERSION RATIO

- Methadone is dosed using a non-linear conversion
  - The higher the dose of oral morphine equivalents, the less methadone per oral morphine equivalents required.
- Methadone (NMDA blockade) reverses tolerance — increases sensitivity to opioids
- Increased opioid sensitivity results in a lower methadone requirement
# METHADONE DOSING: CONVERSION RATIO

## OPIOID NAÏVE
Consider 2 to 7.5 mg oral methadone per day, in divided doses

## OPIOID TOLERANT

<table>
<thead>
<tr>
<th>ORAL MORPHINE EQUIVALENTS (OME) PER DAY</th>
<th>PATIENT AGE</th>
<th>OME: ORAL METHADONE RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 mg</td>
<td></td>
<td>Use opioid naïve dosing</td>
</tr>
<tr>
<td>60-199 mg</td>
<td>&lt;65 years-old</td>
<td>10:1</td>
</tr>
<tr>
<td>60-199 mg</td>
<td>&gt;65 years-old</td>
<td>20:1</td>
</tr>
<tr>
<td>&gt;200 mg</td>
<td></td>
<td>20:1</td>
</tr>
</tbody>
</table>

# Methadone Dosing: Conversion Ratio

<table>
<thead>
<tr>
<th>24 Hour Oral Morphine Equivalent</th>
<th>Morphine : Methadone (per 24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg /24 h</td>
<td>2 : 1</td>
</tr>
<tr>
<td>30 – 99 mg /24 h</td>
<td>4 : 1</td>
</tr>
<tr>
<td>100 – 299 mg /24 h</td>
<td>8 : 1</td>
</tr>
<tr>
<td>300 – 499 mg /24 h</td>
<td>10 : 1</td>
</tr>
<tr>
<td>500 – 999 mg /24 h</td>
<td>15 : 1</td>
</tr>
<tr>
<td>&gt;1000 mg /24 h</td>
<td>20 : 1</td>
</tr>
</tbody>
</table>

# Methadone Dosing Data

**Appendix Table A1. End of Life/Palliative Education Resource Center and Friedman Morphine-to-Methadone Conversion Ratios**

<table>
<thead>
<tr>
<th>MEDD (mg)</th>
<th>Morphine:Methadone (EPERC)</th>
<th>Morphine:Methadone (Friedman)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>3:1</td>
<td>and &lt;65 years old, 10:1</td>
</tr>
<tr>
<td>101–300</td>
<td>5:1</td>
<td></td>
</tr>
<tr>
<td>301–600</td>
<td>10:1</td>
<td></td>
</tr>
<tr>
<td>601–800</td>
<td>12:1</td>
<td></td>
</tr>
<tr>
<td>801–1000</td>
<td>15:1</td>
<td></td>
</tr>
<tr>
<td>&gt;1001</td>
<td>20:1</td>
<td>and/or &gt;65 years old, 20:1</td>
</tr>
<tr>
<td>&gt;2000</td>
<td>40:1 and confirm with Pain or Palliative PharmD</td>
<td>40:1 and confirm with Pain or Palliative PharmD</td>
</tr>
</tbody>
</table>

EPERC, end of life/palliative education resource center; MEDD, morphine equivalent daily dose.

*JPM.2017;20(12):1385-1388.*
# METHADONE DOSING DATA

## AAHPM Methadone Dose Conversion Guidelines

<table>
<thead>
<tr>
<th>Steps:</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1: Calculate total daily morphine dose</td>
<td>Convert all current opioid therapy to PO Morphine</td>
</tr>
<tr>
<td>Step 2: Convert to Methadone</td>
<td>PO Morphine: PO Methadone ration; Non-linear</td>
</tr>
<tr>
<td>Step 3: Account for incomplete cross-tolerance</td>
<td>50% dose reduction; opioid rotation</td>
</tr>
<tr>
<td>Step 4: Determine dosing schedule</td>
<td>Divided doses; typically TID (q8h)</td>
</tr>
<tr>
<td>Step 5: Choose a PRN medication</td>
<td>Traditional opioid; short half-life</td>
</tr>
<tr>
<td>Step 6: Determine PRN dose</td>
<td>10-15% of the total opioid dose</td>
</tr>
<tr>
<td>Step 7: Make adjustments to regimen</td>
<td>No more frequently than steady-state achieved</td>
</tr>
</tbody>
</table>

AAHPM Dosing Conversion Guidelines; 2017.
BREAKTHROUGH PAIN

- Especially important during initial titration
- Utilize traditional immediate-release opioid
  - Morphine IR, oxycodone IR, hydromorphone IR
    - Dosed q2-4h PRN breakthrough pain
    - One breakthrough dose = 10% - 15% of total daily dose of oral morphine equivalents (OME)
- If methadone must be used for breakthrough pain, start low and limit to 3 PRN doses per day.
- Be conservative with daily methadone dose and more aggressive with breakthrough pain regimen.
METHADONE DOSING: CLINICAL CONSIDERATIONS

- If more than 3 breakthrough doses are needed per day to treat baseline pain, contact prescriber with recommendation to increase methadone.
- If breakthrough pain is caused by movement or is episodic, pre-treat with short acting opioids.
- Hold methadone for lethargy, respirations < 9/min, decreased responsiveness, or other signs of opioid toxicity.
- Although it is as effective as other opioids, do not use methadone PRN for shortness of breath.
  - Use short-acting, traditional opioid
EXAMPLE
MRS. C

- 64-year-old female admitted to hospice
  - Primary Dx: breast cancer with mets
  - Complains of increasing back pain
    - Intensity: 10/10
    - Describes as stabbing and burning
  - PMH: Diabetes, Non-smoker

- Current analgesic regimen:
  - Morphine ER 45 mg PO q12h
  - Morphine IR 7.5 mg PO q2h PRN BTP (using 6 doses/day)
  - Total Oral Morphine/day: 135 mg
**MRS. C**

| OPIOID NAÏVE |  |
|--------------|  |
| Consider 2 to 7.5 mg oral methadone per day, in divided doses |  |

<table>
<thead>
<tr>
<th>OPIOID TOLERANT</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORAL MORPHINE EQUIVALENTS (OME) PER DAY</td>
<td>PATIENT AGE</td>
<td>OME: ORAL METHADONE RATIO</td>
</tr>
<tr>
<td>&lt;60 mg</td>
<td></td>
<td>Use opioid naïve dosing</td>
</tr>
<tr>
<td>60-199 mg</td>
<td>&lt;65 years-old</td>
<td>10:1</td>
</tr>
<tr>
<td>60-199 mg</td>
<td>&gt;65 years-old</td>
<td>20:1</td>
</tr>
<tr>
<td>&gt;200 mg</td>
<td></td>
<td>20:1</td>
</tr>
</tbody>
</table>
MRS. C

- Methadone Equianalgesic dosing ratio: 10:1
- $135 \div 10 = 13.5$ mg methadone per day
- Consider dose reduction
  - 25% = 10 mg methadone
  - 50% = 7 mg methadone
- Round up or down based on pain severity and individual patient factors.

Mrs. C’s Plan:

- Discontinue Morphine ER
- Begin Methadone 5mg po q12h
- Increase Morphine
  - 20 mg/mL: Take 0.5 mL (10 mg) to 1 mL (20 mg) po q2h PRN pain
- Monitor analgesic response and methadone toxicity
- No changes for 5-7 days!
MRS. C: CONTINUED

- Today is methadone day 3
  - Current regimen: Methadone 5 mg PO q12h
- Reports pain intensity: 9/10
- Has taken two morphine 10 mg doses in the last 24 hours
- Patient insists the methadone dose should be increased
- What do we do?
ADVERSE EFFECTS
# MANAGEMENT OF ADVERSE EFFECTS

<table>
<thead>
<tr>
<th>Common Adverse Effects</th>
<th>First Line Medication(s)</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Opioid-induced constipation (stasis)   | Senna-S                  | Induces motility  
Avoid “all mush, no push!”  
Less severe/frequent with methadone |
|                                        | Metoclopramide           |          |
| Opioid-induced nausea/vomiting         | Haloperidol              | Dopamine-mediated  
Less severe/frequent with methadone |
|                                        | Prochlorperazine         |          |
|                                        | Metoclopramide           |          |
| Sedation                               | Oral steroid             | Reduces with continued use  
Less severe/frequent with methadone |
|                                        | Methylphenidate          |          |
| Opioid-induced itching/rash            | Oral diphenhydramine     | Uncomplicated itching/rash is a  
common side effect, not an allergy.  
Switching opioids may or may not be effective |
|                                        | *Hydroxyzine              |          |
TOXICITY

- Signs and symptoms:
  - Extreme somnolence
  - Stupor
  - Muscular flaccidity
  - Cold, clammy skin
  - Constricted pupils
  - Respiratory depression

- Synergistic toxicity: benzodiazepines
  - Examples: lorazepam, diazepam
Counseling and Monitoring:
- Drowsiness
- Decreased level of arousal
- Apnea/loud snoring
- Decreased respirations
- Slurred speech
- Pinpoint pupils

Clinicians Should Consider:
- EKG
- Counseling
- High starting dose
- Interacting medications
- Co-administration of medications that may also decrease the respiratory rate
ADJUVANT DOSING
ADJUVANT DOSING

- Patients may be unable or unwilling to switch completely to methadone.
- Consider adding a smaller dose of methadone to a patient’s existing pain regimen:
  - Improves pain control
  - Reduces side effects
  - Cost
- Current regimen is usually decreased
- Evaluate adjunct medication regimen:
  - Steroids
  - Gabapentin
MR. P

- 42-year-old male with pancreatic cancer and significant metastases
- Still able to swallow pills whole
- Currently taking: Morphine IV via continuous infusion
  - 25 mg per hour continuous
  - 10 mg bolus q 10 min PRN breakthrough pain
  - Has used 39 breakthrough doses with 51 attempts in the last 24 hours
- Pain is still 10/10 and he states: “Everything hurts! Even the blanket!”
- Refuses to switch outright to methadone
SUMMARY
SUMMARY: HOSPICE

Good Methadone Candidate
- True morphine allergy
- Intolerable opioid adverse effects
- Renal disease
- Neuropathic pain
- Refractory pain
- Cost burden
- Dysphagia

Poor Methadone Candidate
- Limited prognosis
- Numerous drug-drug interactions
- History of arrhythmia
- Lives alone
- Cognitively impaired
- Adherence issues
QUESTIONS?
THANK YOU!
REFERENCES

- Story P. Primer of Palliative Care, 3rd Ed. AANPM 2004.
REFERENCES

- Lexi-Comp Online™, Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; July 2014
REFERENCES

• AAHPM Methadone Dose Conversion Guidelines 2017.