The Place for Methadone Therapy in the Hospice Setting

Esther Liu, PharmD, MSIA, BCGP
Clinical Pharmacist
Hospice Pharmacy Solutions
Methadone Background

1940s
- Antispasmodic
- Analgesic

1960s
- Opioid Addiction
- Heroin Addiction

2000s
- Chronic Pain
Methadone Pharmacology

- Potent μ-opioid receptor agonist
  - Similar to Morphine, greater efficacy

- Non-opioid analgesic mechanisms of action
  - N-methyl-D-aspartate (NMDA) antagonism
  - Inhibits reuptake of serotonin

- Extremely lipophilic
  - Good bioavailability & offers a variety of administration routes

- Metabolized in liver

- Minimum renal excretion (<10%)
Advantages of Methadone

- Long-acting (8-12hrs)$^2$
- Good absorption$^{4,5}$
  - Both oral and sublingual administration
- Hospice favorable dosage forms:
  - Liquid and crushable tablets
- Relatively safe in patients with renal/liver impairment $^2$
- Synthetic opioid with distinct chemical structure$^1$
  - Great for opioid rotation
- Efficacy toward neuropathic pain
- Very inexpensive
Favorable Methadone Dosage Forms

- Oral Tablets:
  - 5mg, 10mg (may be crushed)
  - 40mg dispersible tablet (restricted usage methadone maintenance detox clinics, hospitals only)
- Oral solution: 5mg/5ml, 10mg/5ml, 10mg/ml
- Sterile solution for injection 10mg/ml (IV, SC)
- Suppository (compounded)
### Great Choice for Renal Impairment

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Renal Dysfunction</th>
<th>Liver Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meperidine</td>
<td>NOT recommended</td>
<td>NOT recommended</td>
</tr>
<tr>
<td>Codeine</td>
<td>NOT recommended</td>
<td>NOT recommended</td>
</tr>
<tr>
<td>Morphine</td>
<td>Use cautiously</td>
<td>Use cautiously</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Use cautiously</td>
<td>Use cautiously</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Use cautiously</td>
<td>Use cautiously</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>Use cautiously</td>
<td>Use cautiously</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Use cautiously</td>
<td>Use cautiously</td>
</tr>
<tr>
<td><strong>Methadone</strong></td>
<td><strong>Safe</strong></td>
<td><strong>Use cautiously</strong></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Safe</td>
<td>Safe</td>
</tr>
</tbody>
</table>
Great Choice for Opioid Rotation

- Tolerance develops to other opioids
- Intolerable side effects
  - Neurotoxicity of Morphine and Hydromorphone in renal impairment
  - Morphine’s “pseudo-allergy” related to histamine release

- Methadone is a good alternative
  - Synthetic opioid
  - Different structural class vs. Morphine vs. Fentanyl
Great Choice for Neuropathic Pain

- Neuropathic pain occurs in 40% of cancer patients\textsuperscript{7}
- More effective for neuropathic pain than other opioids.
- Additional non-opioid analgesic activity:
  - Inhibition of the NMDA receptor
  - Inhibition of serotonin re-uptake (SSRI)
# Cost Effective Long-Acting Opioid

Approximate cost of a 15 day supply of equivalent doses (based upon AWP)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>5mg q12h</td>
<td>$8</td>
</tr>
<tr>
<td>Fentanyl Patch</td>
<td>50mcg Q72h</td>
<td>$132</td>
</tr>
<tr>
<td>Morphine ER tablet</td>
<td>60mg Q12h</td>
<td>$186</td>
</tr>
<tr>
<td>Oxymorphone (Opana ER)*</td>
<td>20mg Q12h</td>
<td>$255</td>
</tr>
<tr>
<td>Morphine capsule (Kadian, Avinza)*</td>
<td>100mg q24h</td>
<td>$296</td>
</tr>
<tr>
<td>Oxycodone ER (Oxycontin)*</td>
<td>40mg Q12h</td>
<td>$300</td>
</tr>
<tr>
<td>Zohydro ER</td>
<td>60mg q12h</td>
<td>$552</td>
</tr>
<tr>
<td>Exalgo</td>
<td>32mg Daily</td>
<td>$915</td>
</tr>
</tbody>
</table>

* Only some select strengths have become generically available, still relatively high cost
Concerns about Methadone

- Negative connotation
  Opioid detox. use, drug addicts

- Respiratory depression
  May persist longer than the analgesic effects during initial dosage period

- Cardiac effects with high doses
  QT prolongation

- Drug interactions
  CYP substrate

- No high strength tablets available
  5mg and 10MG

- Unfamiliar Kinetics
  Biphasic analgesic duration
♠ Require More Patient Educations

- Emphasize severe pain is the indication
- Provide rationale of using Methadone
- Educate on monitoring parameters to ensure successful Methadone therapy
Methadone Side Effects

- Constipation
- Sedation
- Nausea/vomiting
- Confusion, delirium (reported to be less with Methadone)
- Hypotension
- Respiratory depression (more prolonged with Methadone)

♦ Take the same precautions as you use any other opioids
Opioid Respiratory Depression

- General risk factors for all opioids:
  - Opioid naïve patient
  - Rapid escalation of the opioid dosage (especially long-acting opioids)
  - Presence of sleep apnea
  - Frail elderly and severely debilitated patients
  - Combination with other drugs that contribute to respiratory depression (benzodiazepines, phenobarbital, sedative-hypnotic drugs, alcohol, muscle relaxant)

- Little difference in risk among opioids w/ equi-analgesic doses
  - Less common with oral opioid therapy

- Tolerance to respiratory depression develops rapidly

♠ Methadone should be used as long-acting opioid
Potential Methadone Cardiac Side Effects

- **EKG changes:** possible prolonged QT interval
  - Potential for serious arrhythmia (torsade de pointes). Rare.
  - Not usually associated with low dose methadone (< 200mg/day)
  - No clinical confirmation of this effect with oral methadone; only IV

- **Patient Risk Factors for prolonged QT interval:**
  - Cardiac hypertrophy or conduction disorder
  - Methadone doses > 200mg/day (Warning – methadone package insert labeling)
  - Low potassium & or magnesium levels (use caution with diuretic therapy)
  - Combination with other drugs that prolong QT interval
    - Tricyclic antidepressants, Anti-arrhythmics, Antipsychotics, Macrolide
    - some 35 other drugs have FDA approved warnings for this

♠ **QT Prolongation is not usually a concern at low methadone dose when treating pain**
Methadone Drug Interactions

- Primary means of metabolism: demethylation by CYP-3A4
- CYP-3A4 activity varies considerably among patients
  - Methadone bioavailability varies and difficult to predict interactions
- Generally of a delayed onset, and of moderate severity \(^6\)
- Short-term changes in methadone blood levels not often associated with clinically significant changes
  - Due to large volume of distribution

♠ Start Methadone at low dose and titrate to effect slowly base on clinical response
Some drugs that may increase activity of Methadone
(by decreasing the metabolism of Methadone)

- SSRI’s
  - Prozac (Fluoxetine), Paxil (Paroxetine), Luvox (Fluvoxamine).
  - Newer SSRI’s not as significant (Citalopram, Escitalopram)
- Elavil (Amitriptyline)
- Antifungals
  - Fluconazole, Ketoconazole
- Antibiotics:
  - Ciprofloxacin, Erythromycin, Clarithromycin
- Chronic alcohol consumption
Some drugs that Decrease activity of Methadone (by increasing the metabolism of Methadone)

- Rifampin
- Carbamazepine (Tegretol)
- Phenytoin (Dilantin)
- Phenobarbital
- Risperidone (Risperdal)
- Protease Inhibitors
- Acute high dose alcohol use
Methadone Kinetics

- Time until detected in plasma after oral dose: 30 min.
- Time to reach maximum plasma conc. (Tmax): 2.5 – 4.5 hr
- Plasma protein binding: 60 – 90%
  - Only unbound drug is active
- Lipid solubility:
  - 98% of drug that reaches central compartment is rapidly transferred to tissues
  - 2% remains in blood compartment
- Plasma half-life (T 1/2) is bi-phasic:
  - Initial or alpha phase: 2 – 4 hr (distribution phase – about 5 days)
  - Maintenance or beta phase: 10 – 40 hrs (big differences b/w individuals)
Methadone Distribution & Biphasic Analgesic Duration

- Extensive tissue distribution
  - High degree of drug-tissue binding (only “unbound” drug is active)
- Reservoir of drug is created during distribution phase
  - Steady-state reached in 5 days on average (distribution phase complete)
- Duration of analgesic effect is biphasic – correlates w/ above
  - 4 - 6 hours when therapy initiated
  - 8 - 12 hours after repeated routine dosing
    (average of 5 days to reach steady-state level, longer for liver impairment)
Avoid starting any LA opioid in an opioid naïve patient
  - Including Methadone
Initial opioid responses may be unpredictable and vary from patient to patient
Risk of toxicity may be magnified and extended if using a LA opioid to initiate therapy
Patient may be considered as “no longer opioid naïve” after 5 days of opioid therapy with 60mg/day of morphine or equivalent opioid.
When to Consider Methadone in Hospice

- Long-acting opioid is required to manage pain
  - > 4 breakthrough doses for > 5 days
- Severe neuropathic pain
- Poor pain relief/tolerance to other opioids
  - > 200mg oral Morphine/day
- Unacceptable side effects that could be signs of opioid neurotoxicity or pseudo-allergy
  - Hyperalgesia, myoclonus, allodynia
- Chronic Renal Failure -- may be the opioid of choice
  - No toxic metabolites as there is with Morphine and Hydromorphone
- When a low cost, long-acting opioid is indicated
Implications for Methadone Dosing

- Duration of analgesic effect:
  - Before distribution phase complete: 4 - 6hrs
  - After distribution phase complete: 8 – 12hrs

- Recognize the initial increased risk of Methadone accumulation\(^{11}\)
  - First week – avoid frequent dosage intervals if possible\(^{12}\)

- Prefer fixed routine methadone dose: **Q8h or Q12h interval**\(^{12}\)

- Avoid Methadone dose increases more frequently than q 5 days

- Anticipate need for PRN analgesic for BTP during first 5 days
  - Use short-acting opioid (Morphine, Oxycodone, etc) PRN for BTP
  - Methadone is generally not recommended for BTP\(^{12}\)
Typical Methadone Regimen for Pain

Methadone 5mg PO Q12h routine
Morphine (solution or IR tab) PO 10 or 20mg Q2 – 4h prn BTP

- Reassess PRN usage after 5 days & increase Methadone dose if indicated
- Increase Methadone dose base on PRN morphine required during 24h period on day 5 of distribution phase
- Monitor daily during initial week of therapy
  - Respiratory depression
  - Signs of over sedation
  - Breakthrough pain
Several Published Methadone Conversion Methods

- MD Anderson Med Cntr Guidelines (Ayonrinde & Bridge)
- United Kingdom Model (Morely & Makin)
- Edmonton Model aka Canadian Model (Bruera)
- Italian Method (Ripamonti)
- CDC Guideline for Prescribing Opioids for Chronic Pain (Dowell, etc)

All except MD Anderson guidelines use Q4h dosing initially, then gradually lengthen dosage interval

- High risk for accumulation/toxicity

Most methods are based on “Oral Morphine Equivalents”

- Some do not account for differences in cross tolerance among opioids at higher doses
HPS Methadone Conversion Guideline

- Based on MD Anderson Cancer Center guidelines
- Fix dose at long routine interval (8 -12h) from day 1
- Does NOT rely on PRN Methadone usage
- Use of a short-acting opioid for BTP (i.e. Morphine)
- Sliding scale equivalency ratios
- Works well for patients on low or high dose opioid therapy
- Less risk of Methadone accumulation/toxicity
Step 1: Calculate the total daily Oral Morphine Equivalent (OME) from all opioids
# Morphine Conversion Factor Chart (Step 1)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Multiply current dose by this factor to equal oral Morphine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone oral</td>
<td>4</td>
</tr>
<tr>
<td>Hydromorphone IV</td>
<td>20</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Morphine IV, SC</td>
<td>3</td>
</tr>
<tr>
<td>Methadone</td>
<td>See methadone guidelines</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>25mcg/hr patch roughly = 50mg Oral Morphine/day (ratio of 1:100)</td>
</tr>
</tbody>
</table>
HPS Methadone Conversion Guideline

Step 1: Calculate the total daily Oral Morphine Equivalent (OME) from all opioids

Step 2: Convert total daily OME to total daily oral Methadone dose
## “Sliding Scale” Methadone Conversion (Step 2)

<table>
<thead>
<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Morphine to Methadone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100mg</td>
<td>5:1</td>
</tr>
<tr>
<td>101-750mg</td>
<td>10:1</td>
</tr>
<tr>
<td>751-1500mg</td>
<td>12:1</td>
</tr>
<tr>
<td>&gt;1500mg</td>
<td>15:1</td>
</tr>
</tbody>
</table>

Adapted from MD Anderson Cancer Center guidelines, Ayonrinde and Bridge (Med J Aust 2000), and Ripamonti (Cancer Pain & Palliative Care 1999)
HPS Methadone Conversion Guideline

Step 1: Determine the total daily Oral Morphine Equivalent (OME) from all opioids

Step 2: Convert total daily OME to total daily oral Methadone dose

Step 3: Divide total daily Methadone dose into 2 to 3 divided doses

Step 4: Provide a PRN short-acting opioid at 10% to 20% of OME and used q2-4h prn

Step 5: Monitor for 5 days and adjust Methadone dose according to PRN opioid usage
Conversion we have described here is **ONLY** for conversion of other opioids TO Methadone.

Conversion FROM Methadone to another opioid must take into account the extensive half-life of Methadone (related to tissue binding and wide distribution).
Case Study

Ima Payne:

- 71 year old female with lung cancer, mets to the bone, and painful diabetic neuropathy
- Current pain meds:
  - Fentanyl patch 150mcg Q72h
  - PRN Hydrocodone/Acetaminophen 5/325 (14 tabs daily)
- Has persistent c/o severe burning, shooting pains in her legs, despite current pain meds
Decision to convert

A decision is made to convert from fentanyl to methadone to try and achieve a better response to her pain.

Rationale:
- Neuropathic pain is not responding to current meds
- She can swallow tablets
- Fentanyl is used at high dose and is expensive
- She is receiving 4550mg acetaminophen/day
- May not be a candidate for TCA therapy due to age
### Oral Morphine Conversion Factor Chart:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Multiply current dose by this factor to equal oral Morphine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydromorphone oral</td>
<td>4</td>
</tr>
<tr>
<td>Hydromorphone IV</td>
<td>20</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
</tr>
<tr>
<td>Morphine IV, SC</td>
<td>3</td>
</tr>
<tr>
<td>Methadone</td>
<td>See Methadone Guidelines</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>1</td>
</tr>
<tr>
<td>Codeine</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Fentanyl patch</strong></td>
<td><strong>25mcg/hr patch roughly = 50mg Oral Morphine/day (ratio of 1:100)</strong></td>
</tr>
</tbody>
</table>
Step 1: Determine Total Daily Oral Morphine Equivalent

**From the morphine conversion factor chart:**

- **Fentanyl**
  - $150\text{mcg/hr} = 150\text{mcg}/25\text{mcg} = 6$
  - $6 \times 50\text{mg oral morphine/day} = 300\text{mg oral morphine/day}$

- **Hydrocodone/APAP 5mg/325mg**
  - $14\text{ tabs} = 70\text{mg hydrocodone} \times 1 = 70\text{mg oral morphine/day}$

- **Total daily oral morphine equivalent = 370mg**
Step 2: Convert OME to Daily Methadone Dose

Using the oral morphine equivalent, determine the appropriate conversion ratio from the table:

<table>
<thead>
<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Morphine to Methadone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100mg</td>
<td>5:1</td>
</tr>
<tr>
<td>101-750mg</td>
<td>10:1</td>
</tr>
<tr>
<td>751-1500mg</td>
<td>12:1</td>
</tr>
<tr>
<td>&gt;1500mg</td>
<td>15:1</td>
</tr>
</tbody>
</table>
Methadone Conversion Continued

Step 2: Convert oral Morphine equivalent to methadone:

*From the oral Morphine to Methadone conversion chart:*

- Ratio is **10:1** for this patient’s current dose of 570mg/day
- $370mg / 10 = 37mg$ total daily Methadone dose

Step 3: Divide total daily dose by 2 = 18.5mg Q12h

- Round down to nearest 5mg increment = Methadone 15mg Q12h
- Initiate methadone **12 hours after** fentanyl patch removed\(^\text{15}\)
Methadone Conversion Continued

Step 4: Provide PRN opioid for breakthrough pain
- Morphine IR tablet 30mg q2h prn
- Oxycodone IR tablet 20mg q2h prn, if morphine allergy

Step 5: Titrate Methadone dose based on PRN opioid use on day 5. Example:
- 5 doses of Oxycodone IR used in 24 hours on day 5
- Total 100mg Oxycodone daily = 150 OME
- 150 OME = 15mg add’l Methadone per day (45mg total)
- Increase Methadone dose to 20mg q12h
Methadone is an analgesic of indisputable value that continues to gain acceptance for chronic severe pain management.

Methadone has no active metabolites

Methadone is an inexpensive long-acting opioid with a rapid onset of action available in various dosage forms.

Methadone is an excellent long-acting opioid alternative from both a clinical and economic perspective.
References

2. Goodman & Gilman’s  The Pharmacological Basis of Therapeutics, 11th edition (McGraw-Hill)
Partnering with you to help your patients