Methadone for Chronic Pain in Palliative Care

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Outcome Resources
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Goals of the presentation

1. Understand the role of Methadone in the treatment of chronic pain
2. Be able to describe appropriate dosage for initiation of methadone in the opioid naïve patient
3. Be able to identify advantages and pitfalls of methadone analgesic therapy
4. Be able to recognize potential side effects of methadone
5. Become familiar with an algorithm or plan for introducing or converting to methadone
6. Be able to work through case studies on conversion of patients from other opioids to methadone

Methadone Background

• Developed originally as an antispasmodic and later used as an analgesic, starting in late 1940’s

• Used extensively as a treatment for opioid addiction starting in the 1960’s

• Increased use for treatment of chronic pain starting in 2000
Methadone Uses

- Acute Pain …………. every 4 hours PRN
- Chronic Pain ……….. every 6 or 8 hours ATC
- Maintenance ………… every 24 hours
  (Addiction Program)

Methadone Pharmacology

- Potent mu-opioid receptor agonist (similar to morphine, greater efficacy)
- Has non-opioid analgesic mechanisms of action:
  - N-methyl-D-aspartate (NMDA) antagonism
  - Inhibits reuptake of serotonin
- Extremely lipid soluble (good bioavailability & offers a variety of administration routes)
- Metabolized in liver to inactive metabolites
- Renal/hepatic impairment has no significant influence on clearance

Hospice Indications

- When unusually large doses of Morphine are being required.
- As an alternative to other opioids due to unwanted side effects or adverse reactions.
- When absorption issues are suspected.
- When additional activity as NMDA inhibitor is desired.
- In the presence of renal insufficiency
Positive Aspects

- Well absorbed (PO, SL)
- Fast onset
- Long duration
- Potent
- Effective
- Low cost orally
- Less adverse effects
- Great alternative opioid
- No active metabolites
- Low Tolerance

- No ceiling dose?
- Variety of routes
- Tabs/Liquid rectally
- Compound transderm gel or supp
- Long acting liquid
- Long acting tablet that can be cut or crushed
- Neuropathic pain activity
- Use w/ renal insufficiency

Morphine “pseudo-allergy”

Symptoms:
- itching, flushing, sweating, bronchoconstriction
- related to histamine release (mast cells in skin) \(^{(6)}\)
- not mediated by IgE or T-cell \(^{(7)}\)

Methadone is a good alternative (no histamine release)
- a synthetic opioid
- from a different structural class than
  morphine
- does not trigger or exacerbate asthmatic attacks like
  morphine can \(^{(2)}\)

Neurotoxicity Risk of Morphine & Hydromorphone in Renal Impairment

- Morphine -3 glucuronide
  - myoclonus
  - hyperalgesia
  - allodynia

- Hydromorphone -3 glucuronide
  - agitation
  - myoclonus
  - seizures
**Advantage in neuropathic pain**

- More effective for neuropathic pain than other opioids.
- Additional non-opioid analgesic activity:
  - Inhibition of the NMDA receptor
  - Inhibition of serotonin re-uptake (SSRI)

**Negative Aspects**

- Unfamiliar
- Negative connotation
- Opioid phobia
- Difficult to convert doses
- Difficult to titrate
- Accumulation
- No high strength tablets
- No commercial supps
- Drug interactions
- Different acute vs chronic
- Protracted withdrawal
- Cardiac effects w/high doses
- Adjust w/ liver impairment?
- Irritating to skin SC
- Bitter taste

**METHADONE BLACK BOX WARNINGS**

- Respiratory Depression - occurs later and lasts longer.
- Cardiac Effects – QT interval prolongation 
  – serious arrhythmia (torsades de pointes)
- Limitations on use of Methadone for treatment of opioid addiction.
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, transdermal gel (compounded)

Pharmacodynamics of Methadone

• Rapid absorption from the stomach (onset in 30 - 40 min)
• Duration of analgesic effect is bi-phasic:
  - 4 hours when therapy initiated
  - 12 hours after repeated routine dosing
• Methadone pharmacokinetics are patient-specific and may be highly variable

Methadone Pharmacokinetics

• Extensive tissue distribution (brain, lungs, liver, muscle, adipose tissue)
• High degree of tissue binding
• A reservoir of methadone is created during initial therapy
• Re-absorption from the tissues back into the circulation results in maintenance of steady-state serum levels
• Extensive tissue distribution, drug binding, and re-absorption result in extended duration of methadone
“filling the bucket”

Steady – state blood level:
Routine oral dose + re-absorption from tissues
= amount of drug metabolized via liver

Methadone Distribution Phase

• 5 days required for equilibration of distribution/re-absorption phase (steady-state drug levels)
• Duration of analgesic effect during initial titration may only be 4 hours
• Expect to use PRN analgesic doses during the distribution phase (oral morphine solution or methadone)
• Do not increase routine dose prior to completion of distribution phase
• Duration of effect after distribution phase: 12 hrs in most patients

Picture of Methadone

Onset – 15 to 30 min
Peak Analgesia – 1 hour
Peak Conc – 4 hrs
Duration – 6 to 12 hrs
Single dose 4 to 5 hrs
Half Life – 22.4 hrs
Drugs that may increase activity of Methadone
(by decreasing the metabolism of Methadone)

- SSRI's - Prozac (fluoxetine), Paxil (paroxetine),
  Luvox (fluvoxamine), Celexa (Citalopram), etc.
  as well as tricyclics like Elavil (Amitriptyline)
- Antifungals eg. Diflucan (fluconazole)
- Tagamet (cimetidine)
- Antibiotics: Ciprofloxacin, erythromycin
- Chronic alcohol consumption

Drugs that Decrease activity of Methadone
(by increasing the metabolism of Methadone)

- Rifampin
- Carbamazepine (Tegretol)
- Phenytoin (Dilantin)
- Phenobarbital
- Risperidone (Risperdal)
- Protease Inhibitors
- Acute alcohol use
- Zidovudine (reverse transcriptase inhib.)

Other Methadone Drug Interactions

- Methadone increases Zidovudine (reverse transcriptase inhib.) plasma levels
- Additive neuromuscular blocking and respiratory depression with sed/hyp.
  psyche, anticonvulsants, muscle relaxants, alcohol & other opioids
- Additive chance of QT interval prolongation with other meds that have that effect –
  chloroquine, Cipro, antiarrhythmics, antipsychotics, antihistamines,
- Opioid agonist-antagonists can precipitate withdrawal
### Cost Comparison Long Acting Opioids

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

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Dose</th>
<th>BID</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone ER (OxyContin) 60mg</td>
<td>60</td>
<td>BID</td>
<td>315.00</td>
</tr>
<tr>
<td>Oxymorphone ER (Opana ER) 30mg</td>
<td>30</td>
<td>BID</td>
<td>290.00</td>
</tr>
<tr>
<td>Fentanyl Patch 100mcg Q72h</td>
<td></td>
<td></td>
<td>265.00</td>
</tr>
<tr>
<td>Morphine ER 100mg BID</td>
<td>100</td>
<td>BID</td>
<td>140.00</td>
</tr>
<tr>
<td>Methadone 10mg BID</td>
<td>10</td>
<td>BID</td>
<td>8.00</td>
</tr>
</tbody>
</table>

### Cost comparison: Morphine / Methadone Oral Concentrate

Based upon AWP:

- Oral Morphine Solution 20mg/ml (Roxanol) 30ml = $25.00
- Methadone oral concentrate 10mg/ml 30ml = $25.00

### Starting Methadone in a Patient NOT on Strong Opioids

Start low, often at 2.5mg to 5mg po q12 hrs

Use oral morphine solution (roxanol) for breakthrough pain (starting with 5mg -10mg up to Q2h prn)

Reassess on day 6 & increase methadone if needed

Increase routine methadone dosage if necessary based on prn morphine use in the previous 24 hr

Divide Roxanol dose by 10 to get the total daily methadone equivalent, then split evenly into the two Q12h routine doses
Clinical rationale for opioid conversion to Methadone

- Premise: To improve analgesia & reduce side effects

- Rationale: Differences in opioid receptor binding, metabolites, kinetics, & incomplete cross tolerance

- Good clinical evidence for reduced sedation and confusion w/ opioid rotation - DeStouz 1995 (9)

- Rotation to methadone found to reduce adverse effects by 70% - Breura 1996 (10)

Converting to Methadone

Outcomes Resources Conversion Guide (11,12)

<table>
<thead>
<tr>
<th>Total Daily Oral Morphine Dose</th>
<th>Morphine to Methadone Ratio</th>
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<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>
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</table>

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

Opioid Equivalent Dosage Chart

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral Dose</th>
<th>Parenteral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>30mg</td>
<td>10mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>7.5mg</td>
<td>1.5mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>20mg</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>See methadone guidelines</td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>30mg</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>200mg</td>
<td></td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>180mg</td>
<td></td>
</tr>
<tr>
<td>Meperidine</td>
<td>300mg</td>
<td>75mg</td>
</tr>
<tr>
<td>Fentanyl Patch</td>
<td>0.3mg/24h topical (12.5mcg/hr)</td>
<td></td>
</tr>
</tbody>
</table>
Morphine Conversion Factor Chart

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

Conversion Charts Are Approximations!

Conversion dose decisions should be tempered by:

- Current level of pain control
- Compliance history
- Co-morbid conditions
- Patient age
- Renal/hepatic function
- Potential drug interactions

Conversion Case Study #1

- Ima Payne: 71 year old female with lung cancer, mets to the bone, and painful diabetic neuropathy.
- Current pain meds: Fentanyl patch 250mcg Q72h & PRN Vicodin ES 10/750 (7 tabs daily)
- Has persistent c/o severe burning, shooting pains in her legs, despite current pain meds ……

What’s can we do to improve pain control?
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 expensive
- She is receiving 5250mg Acetaminophen/day
- May not be a candidate for TCA therapy due to age

Determine Total Daily Oral Morphine Equivalent

*From the morphine conversion factor chart:*

Fentanyl 250mcg/hr = Oral morphine ? mg/day
Hydrocodone/Apap 10/750; 7 tabs = Oral morphine ? mg/day

Total daily oral morphine equivalent = ?

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<td>Fentanyl patch</td>
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**Oral morphine equivalent**

*From the morphine conversion factor chart:*
- Fentanyl 250mcg/hr = 250mcg/25mcg = 10
  - 10 x 50mg Oral morphine/day = 500mg Oral morphine/day
- Hydrocodone/Apap 10/750; 7 tabs = 70mg hydrocodone x 1 = 70mg Oral morphine/day
- Total daily oral morphine equivalent = 570mg

**Methadone conversion**

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

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**Case Study Continued**

Convert oral morphine equivalent to methadone:

*From the morphine to methadone conversion chart:*
- Ratio is 10:1 for this patient’s current dose of 570mg/day
- 570mg/10 = 57mg total daily methadone dose
- Divide total daily dose by 2 = 28.5mg Q12h
- Round off to nearest 5mg increment = methadone 30mg Q12h
- Initiate methadone 12 hours after fentanyl patch removed

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12
Case study #2

Adam Able, a 68 year old man with severe cancer pain.
Dx: Pancreatic CA, CHF, Renal insufficiency
Currently on MS-Contin 130mg Q8hr,
- since his last morphine dose increase has experienced
  myoclonic tremors & mental status changes
  (hallucinations, confusion)
- pain fairly well managed on this dose
- Roxanol 30mg PRN (using 1-2 doses per day)

Patient and family are concerned about recent changes in his
mental status and the tremors …… ???

Conversion process

Opioid rotation to methadone is considered so that he can avoid
possible morphine neurotoxicity.

• First determine the total daily oral morphine equivalent
  for MS Contin 130mg Q8hr

• Determine the equivalent ratio of oral morphine equivalent to
  methadone from the Methadone Conversion Chart
  (5:1, 10:1, 12:1, or 15:1)

Conversion process continued

• Determine total daily Methadone conversion dose by
dividing OME by the appropriate ratio number

• Divide total daily methadone dose by 2 (round off):
  ____ mg Q12h
Conversion dose

OME for Mr. Able:
(\text{MS Contin} 130mg Q8h)
OME = 390mg/day

Appropriate ratio:
from Methadone Conversion Chart = 10:1

Methadone total daily dose:
390mg/10 = 39mg total daily methadone dose

Divide total daily methadone dose by 2: 19.5mg

Round off for ease of measurement: 20mg Q12h

Case study #3

Bert B., a 54 year old male with pancreatic cancer
Meds: Fentanyl 250mcg q72hr
      Oxycontin 80mg Q12h
      Oxyfast 20mg Q2h prn BTP

Pain was controlled initially, but…
Pain control has been steadily deteriorating over the past 2 weeks. He is taking 6 doses per day of the PRN med and rates his pain at 8 of 10.

What’s next for pain control?

The next step for Mr B.

A decision is made to rotate to Methadone since this patient is likely exhibiting tolerance to current therapy.

First determine the total daily \textbf{oral} morphine equivalent
- Fentanyl 250mcg patch = ___mg oral morphine
- Oxycontin 160mg = ___mg oral morphine
- Oxyfast 120mg = ___mg oral morphine

Total daily OME: _____mg
Methadone conversion dose for Mr B.

OME:
- Fentanyl 250mcg patch = 500mg oral morphine
- Oxycontin 160mg = 240mg oral morphine
- Oxyfast 120mg = 180mg
Total daily OME: = 920mg

Appropriate ratio:
from Methadone Conversion Chart = 12:1
Methadone total daily dose:
920mg/12 = 76.7mg total daily methadone dose

Divide total methadone dose by 2 & round off: 40mg Q12h

Converting back from methadone

- 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)

Methadone Side Effects
Common to All Opioids

- Constipation
- Sedation
- Nausea/vomiting
- Confusion, delirium
- Hypotension
- Respiratory depression
Opioid Respiratory Depression

- General risk factors:
  - opioid naïve patient
  - introduction of fentanyl patch in opioid naïve pt.
  - rapid escalation of the opioid dosage (especially long-acting opioids)
  - frail elderly and severely debilitated patients
  - combination with other drugs that contribute to respiratory depression

- No difference in risk among opioids w/ equianalgesic doses

- Relatively uncommon with oral opioid therapy

- Tolerance to respiratory depression develops rapidly

Potential Cardiac Side Effects

- EKG changes: prolonged QT interval
- Potential for serious arrhythmia (torsades de pointes)
- Not associated with low dose methadone (<200mg/day)


- Risk factors:
  - rapid escalation of the methadone dose
  - doses > 200mg/day (FDA boxed warning – methadone labeling)
  - HIV infection
  - other drugs that prolong QT interval (tricyclic antidepressants, antiarrhythmic drugs, Biaxin, erythromycin)

Methadone Experience for one California Hospice

<table>
<thead>
<tr>
<th>Meds</th>
<th># Rxs</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>65</td>
<td>$7639</td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td>42</td>
<td>3376</td>
</tr>
<tr>
<td>Morphine ER</td>
<td>61</td>
<td>2131</td>
</tr>
<tr>
<td>Methadone</td>
<td>12</td>
<td>522</td>
</tr>
</tbody>
</table>

Long-acting opioid cost: $13,668

- Hospice goal:
  Methadone as a primary choice when a L.A. opioid is indicated

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<th># Rxs</th>
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<tr>
<td>Fentanyl</td>
<td>58</td>
<td>$6233</td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td>13</td>
<td>508</td>
</tr>
<tr>
<td>Morphine ER</td>
<td>29</td>
<td>947</td>
</tr>
<tr>
<td>Methadone</td>
<td>131</td>
<td>704</td>
</tr>
</tbody>
</table>

Long-acting opioid cost: $8,392

* Average daily census = 280 patients
Changes in long-acting opioid usage over 1 year

- **Drug**
  - Oxycodone ER: 70%
  - Morphine ER: 52%
  - Fentanyl patch: 11%

- Methadone prescription volume: increased from 7% of long-acting opioid category to 57%

- Overall Long Acting Opioid expense decreased by 39%

- Monthly cost savings to this hospice: $5276.00

When is methadone the right choice?

- Severe neuropathic pain
- Poor pain relief/tolerance to other opioids (> 600mg oral morphine/day)
- Unacceptable side effects that could be signs of opioid neurotoxicity or pseudo-allergy (hyperalgesia, myoclonus, allodynia)
- Liver disease (no active metabolites)
- Chronic Renal Failure—may be the opioid of choice (no toxic metabolites as there is with MS, hydromorphone)
- When a low cost, long-acting opioid is indicated.

Methadone Bottom Line

- Methadone is an analgesic of indisputable value that continues to gain acceptance in chronic 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 alternative from both a clinical and economic perspective.
References

12. Cancer Pain and Palliative Care JASP, 1999