Magical, Mystical, Mischievous Methadone!

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Objectives

- At the conclusion of this lecture, the participant will be able to:
  - Describe the pharmacokinetic and pharmacodynamic properties of methadone.
  - Given a simulated opioid-naïve patient, identify an appropriate starting dose of oral methadone.
  - Given a simulated patient receiving an opioid, identify an appropriate equivalent dose of oral methadone.

Pharmacodynamics of Methadone

- Synthetic opioid developed 50 years ago
- Used to treat opioid dependent patients
- Many characteristics making it ideal for chronic pain patients
  - Long duration of action, efficacy, low cost
- Racemic mixture of R- and S-methadone
  - R-methadone is 8-50 times more potent than S-methadone
- Mu, kappa, delta agonist
- NMDA receptor antagonist

Pharmacokinetics of Methadone

- Absorption
  - PO, PR, IV, IM, SQ, epidural*, intrathecal *
  - Basic, lipophilic drug
  - Onset 15-45 minutes after oral, peak in 2.5-4 hours
  - Oral bioavailability 70-80% (range 36-100%)

*spinal methadone not FDA-approved
### Pharmacokinetics of Methadone

**Distribution**
- Widely and quickly distributed throughout
  - Brain, gut, kidney, liver, muscle, lung
- Retained in tissues and slowly released back into plasma during redistribution and elimination; contributes to long half-life
- Binds to alpha 1-acid glycoprotein; less so to albumin and globulin
  - Free fraction varies four-fold among patients

**Metabolism**
- Extensively metabolized
  - N-demethylation
  - Pharmacologically-inactive metabolites, eliminated in urine and feces
  - Primarily by liver, also in gut
  - Cytochrome P450 – 3A4, 2B6, 2C8, 2C9, 2C19, 2D6
  - Involved in numerous drug interactions

**Elimination**
- Inactive metabolites are eliminated in urine and feces
- Elimination half-life 5-130 hours, average is 20-35 hours
- Takes 4-10 days to achieve steady-state
  - When initiating therapy
  - With dosage changes

### Drug Interactions with Methadone

**Drug interaction**
- A clinical scenario where one drug alters the pharmacologic effect of another drug given at the same time (e.g., in the same drug regimen)
  - Drug interactions can alter the pharmacokinetics or pharmacodynamics of a drug
  - Altered pharmacodynamic effects includes increased or decreased therapeutic effectiveness or or adverse effects of either drug
Pharmacodynamic Drug Interactions with Methadone

- Methadone and other opioids
  - Increased analgesia
  - Additive toxicities – increased risk respiratory depression and sedation
- Methadone and alcohol, neuroleptics, benzodiazepines, antidepressants, etc.
  - Increased CNS depression
- Methadone and other medications that prolong QT interval (antiarrhythmics, antipsychotics, antidepressants, etc.)

Pharmacokinetic Drug Interactions with Methadone

- Distribution
  - Competition for protein binding sites
  - May increase methadone free fraction
  - TCA and neuroleptic medications compete with methadone for binding on alpha 1-acid glycoprotein

Pharmacokinetic Drug Interactions with Methadone

- Metabolism
  - Extensively metabolized in intestines and liver
  - Primarily by 3A4 enzyme system
  - 30 fold difference in liver 3A4 enzymes among individuals
  - 11 fold difference in intestinal 3A4 enzymes among individuals

- Metabolism
  - Other medications can *induce* (increase) activity of enzymes
  - Other medications can *inhibit* (reduce) activity of enzymes
  - These other medications affect the serum level of the object drug being metabolized – methadone – known as the *substrate*
Pharmacokinetic Drug Interactions with Methadone

- **Metabolism**
  - Enzyme *induction* usually takes 1-2 weeks
    - May take 1-2 weeks to see a reduction in methadone serum levels and increase in pain
  - Enzyme *inhibition* occurs much more quickly (a day or two)
    - See an increase in methadone serum levels and possibly adverse effects within one or two days

Effect of Enzyme Inhibitors/Inducers

<table>
<thead>
<tr>
<th>What's the situation?</th>
<th>What happens in this situation?</th>
<th>What does this mean for my patient?</th>
<th>What should I do about it?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taking methadone with medications known to be enzyme inhibitors</td>
<td>Slowed metabolism of methadone, resulting in increased methadone serum level</td>
<td>The patient may become toxic from a methadone overdose</td>
<td>Reduce calculated methadone dose by 25% or more. Encourage use of rescue opioid.</td>
</tr>
<tr>
<td>Taking methadone with medications known to be enzyme inducers</td>
<td>Increased metabolism of methadone, resulting in decreased methadone serum level</td>
<td>Dose of methadone may be insufficient and patient can experience increased pain</td>
<td>Use calculated methadone dose but strongly encourage use of rescue opioid. Increase methadone if appropriate once at steady-state.</td>
</tr>
</tbody>
</table>

Enzyme Inhibitors/Inducers

<table>
<thead>
<tr>
<th>Enzyme Inducers</th>
<th>Enzyme Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin / rifampin</td>
<td>Ketoconazole</td>
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<tr>
<td>Rifabutin</td>
<td>Erythromycin</td>
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<tr>
<td>Phenobarbital</td>
<td>Troleandomycin</td>
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<tr>
<td>Phenytoin</td>
<td>Clarithromycin</td>
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<tr>
<td>Spironolactone</td>
<td>Telithromycin</td>
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<td>Nevirapine</td>
<td>Itraconazole</td>
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<td>Efavirenz</td>
<td>Despiramine</td>
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<td>Clarithromycin</td>
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<td>Nelfinavir</td>
<td>Triazolam</td>
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<td>Ritonavir</td>
<td>Ciprofloxacin</td>
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<tr>
<td>Carbamazepine</td>
<td>Citalopram</td>
</tr>
<tr>
<td>St. John's Wort</td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>

Audience Response

- JR is a 72 year old man with end-stage lung cancer, maintained on methadone 7.5 mg po q12h with good effect. He has developed oral thrush and his prescriber added fluconazole 150 mg po qd for 7 days. How quickly will this drug interaction be apparent, and what will the outcome be?
  - A. Fluconazole will induce methadone metabolism, effect seen in about a week resulting in lower methadone serum level
  - B. Fluconazole will inhibit methadone metabolism, effect seen in a day or two resulting in higher methadone serum level
  - C. Fluconazole will induce methadone metabolism, effect seen in a day or two resulting in lower methadone serum level
  - D. Fluconazole will inhibit methadone metabolism, effect seen in about a week resulting in lower methadone serum level
Appropriate Methadone Candidates

- True morphine allergic (or other mu agonist)
- Significant renal impairment
- Neuropathic pain
- Opioid-induced adverse effects
- Pain refractory to other opioids or uncontrolled pain
- Cost is an issue
- Long-acting opioid preferred (especially oral solution)
- Any opioid-requiring patient

Inappropriate Methadone Candidates

- Very limited prognosis (less than a week)
- Numerous drug interactions with methadone
- History of syncope or arrhythmias
- Lives alone, poor cognitive functioning, unreliable, noncomprehending instruction
- History of nonadherence to therapy

Methadone in Opioid-Naïve Patients

- Dolophine Hydrochloride (Roxane)
  - 2.5 to 10 mg every 8-12 hours, titrate to effect
- College of Physicians and Surgeons of Ontario (nonmalignant pain guidelines)
  - 2.5 mg every 8 hours
  - 2.5 mg once or twice daily in frail older adults or those taking enzyme inhibitors

Case 1

- FA is an 89 year old man admitted to hospice with a diagnosis of failure to thrive, c/o generalized aches and pains.
- Patient is ambulatory and frail.
- Has a history of bleeding ulcer, PCP does not want to prescribe a NSAID. Did not respond to acetaminophen.
- PCP would like you to recommend a methadone dose.
- No interacting medications.
Case 1

- No interacting medications, but he is elderly and frail.
- Possible recommendations:
  - 1 mg po qam or qhs
  - 2.5 mg po qam or qhs
- Rescue opioid?
  - Morphine or oxycodone 2.5 to 5 mg q2-4h prn

Case 2

- BL is a 54 year old woman with a 20 year history of T2DM.
- Complained of diabetic neuropathy in feet for the past 5 years.
  - Did not respond to acetaminophen, NSAID
  - Adverse effects to gabapentin and duloxetine
- Not taking any medications that interact with methadone, and is opioid-naïve.
- PCP asks for dosing recommendation.

Case 2

- No interacting medications, and she is younger (54 yo)
- Possible recommendations:
  - 2.5 mg po q12h
  - 2.5 mg po q8h (possibly switch to q12h dosing later)
- Rescue opioid?
  - Morphine or oxycodone 5 mg q2-4h prn

Prescribing information states...

- "Respiratory depression is the chief hazard associated with methadone hydrochloride administration.
- Methadone's peak respiratory depressant effects typically occur later, and persist longer than its peak analgesic effects, particularly in the early dosing period.
- These characteristics can contribute to cases of iatrogenic overdose, particularly during treatment initiation and dose titration."
The road to steady-state

Signs and symptoms of overdose

- Signs and symptoms of acute intoxication
  - Evident euphoria
  - Ataxia, slurred speech

- Signs and symptoms of accumulation
  - Excessive drowsiness / level of arousal
  - Slowed respiration or periods of apnea, more rapid respiration, shallow breathing
  - Slurring of speech
  - Loud snoring
  - Pinpoint pupil size

Cardiac Safety Monitoring Recommendations

1. Clinicians should inform patients of arrhythmia risk when they prescribe methadone.
2. Clinicians should ask patients about any history of structural heart disease, arrhythmia, and syncope.
3. Obtain a pretreatment ECG for all patients to measure the QTc interval and a follow-up ECG within 30 days and annually. Additional ECG is recommended if the methadone dosage exceeds 100 mg/d or if patients have unexplained syncope or seizures.

Cardiac Safety Monitoring Recommendations

4. If the QTc interval is > 450 ms but < 500 ms, discuss the potential risks and benefits with patients and monitor them more frequently. If the QTc interval > 500 ms, consider discontinuing or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy.
5. Clinicians should be aware of interactions between methadone and other drugs that possess QT interval-prolonging properties or slow the elimination of methadone.

Converting to methadone from other opioids

- Question of the day:
  - How can we best convert a patient from a different opioid to methadone;
  - Achieve pain relief as quickly as possible;
  - And NOT increase the risk of immediate or delayed toxicity?
- Conversion from other opioids to methadone is NOT linear!

Converting to methadone from other opioids

- The higher the opioid dose a patient is receiving, the more “potent” methadone is
- “More potent” doesn’t mean “more effective” – potency refers to an equivalent dose to achieve equivalent pain control
- Why does methadone become more powerful with increasing prior exposure to other opioids?

Steps to convert to oral methadone

1. Globally assess the patient’s pain complaint to determine if pain is due to worsening pain or development of a new type of pain.
2. Determine the total daily dose of the current opioid (LA and SA opioid).
3. Convert to methadone (more on this!)
4. Individualize dose based on assessment information gathered in step 1. Ensure adequate access to breakthrough medication. Consider interacting medications. Decide on “rapid switch” (known as "stop-start") or gradual switch.
5. Close patient follow-up and continued reassessment.

Converting to methadone from other opioids

1. Molecular structure and chemical characteristics of methadone may alter binding to the opioid receptors, possibly resulting in less cross-tolerance to methadone (patient more sensitive to methadone).
2. Methadone has additional mechanisms of action – NMDA receptor antagonism.
3. More traditional opioids such as morphine and hydromorphone are metabolized to pharmacologically active products that may be “proalgesic” (e.g., M3G, normorphine)
Case 3

- AO is a 64 year old man with chronic low back pain. He is taking extended-release morphine 80 mg po q12h with morphine oral solution 20 mg po q2h prn breakthrough pain (using about 2 doses qd).
- He is not a surgical candidate, and his physician would like to switch him to methadone. AO not taking any interacting medications.
- Step 1 - PQRST
  - Pain is nociceptive and neuropathic
  - Pain in sacral area, with occasional shooting down leg and numbness in left leg with prolonged standing

Case 3 – Step 2 (TDD Opioid)

- He is taking extended-release morphine 80 mg po q12h with morphine oral solution 20 mg po q2h prn breakthrough pain (using about 2 doses qd).
- TDD = 80 mg x 2 = 160 mg PLUS 20 x 2 = 40 mg for a TDD of 200 mg oral morphine

Case 3 – Step 3 (Conversion to Methadone)

- If patient is not already taking oral morphine, convert to oral morphine
  - Refer to equianalgesic dosing chart
  - Consider LA and SA opioid use
  - Do not reduce for lack of complete cross-tolerance
- Conversion is NOT linear; what ratio(s) do we use?

<table>
<thead>
<tr>
<th>Ripamonti, 1998</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MS Dose (mg/day)</td>
<td>30-90</td>
</tr>
<tr>
<td>M:ME EDR</td>
<td>4:1</td>
</tr>
</tbody>
</table>

| Mercadente, 2001 |
| --------------- | --------------- |
| MS Dose (mg/day) | 30-90 | 90-300 | > 300 |
| M:ME EDR | 4:1 | 8:1 | 12:1 |

| Ayenmire, 2000 |
| --------------- | --------------- |
| MS Dose (mg/day) | < 100 | 101-300 | 301-600 | 601-800 | 801-1000 | > 1000 |
| M:ME EDR | 3:1 | 5:1 | 10:1 | 12:1 | 15:1 | 20:1 |
Case 3 – Step 3 – Conversion

**EPERC Fast Facts**
- Ayonrinde method; reduce by 50%

**Dolophine Hydrochloride prescribing info**
- < 100 mg MS (20-30% ME)
- 101-300 mg MS (10-20% ME)
- 300 – 600 mg MS (8-12% ME)
- 600-1000 mg MS (5-10% ME)
- > 1000 mg MS (< 5% ME)

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**Case 3 – Step 3 – Conversion**

- “One important distinction that needs to be made is between methadone rotations as a care process as opposed to a dose calculation.
- It may be less important to determine an exact opioid ratio when performing a methadone conversion than it is to assure that the patient is an appropriate candidate for methadone conversion, the switch is carried out over a time period consistent with the therapeutic goals, and that the patient is monitored closely by medical staff throughout the process.”


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**Case 3 – Step 3 – Conversion**

Modified Morley-Makin UK Model (Friedman)

- Patient’s TDD oral morphine is 200 mg
- Patient less than 65 years old
- Use 10:1 conversion
  - Methadone 20 mg TDD
  - Recommendation: 10 mg po q12h
Case 3 – Step 4
Individualization
- No interacting medications
  - No need to reduce methadone dose
- What to do for rescue medication?
  - Methadone
  - Morphone or oxycodone – 10-15% TDD
    - MSIR 20 mg po q2h prn breakthrough pain
- Rapid switch or gradual?

Case 3 – Step 5
Patient Monitoring
- Ask AO’s wife to observe AO several times a day for changes in his respirations (depth, rhythm, rate), difficulty awakening him, snoring, and other signs of opioid overdose.
- We will see or speak to AO/wife daily over the next week.
- Do not adjust therapy before 5-7 days.

Case 4
- SM is a 63 year old woman with significant OA pain in both knees, both hips and the sacral area of her spine.
- Referred to your clinic for conversion to methadone from her current regimen of extended-release morphine 45 mg po q8h and morphone oral solution 20 mg q4h prn, taking three doses per day. She is taking no interacting medications. Methadone is appropriate.
- Calculate an appropriate dose of methadone using ALL 5 methods discussed.

Case 4
- TDD oral morphine = 195 mg
- Ripamonti – 90-300 mg oral MS is 6:1 conversion = 32.5 mg oral methadone qd
- Mercadente – 90-300 mg oral MS is 8:1 conversion = 24.4 mg oral methadone qd
- Ayonrinde – 101-300 mg oral MS is 5:1 conversion = 39 mg oral methadone qd
- Fast Facts – Ayonrinde reduce by 50% = 19.5 mg oral methadone qd
- Friedman – 10:1 conversion = 19.5 mg oral methadone qd
### Case 4
- Calculated range is 19.5 – 39 mg per day
- Recommendation: methadone 10 mg po q12h
- DC extended-release morphine, begin methadone 8-12 hours after last XL MS dose
- Continue morphine for breakthrough pain; 10% TDD morphine = 19.5 mg, 15% = 29.25 mg; recommend morphine solution 20 mg po q4h prn.

### Case 5
- JK is a 54 year old man referred to hospice with end-stage lung cancer, taking:
  - Transdermal fentanyl 75 mcg/h q72 hours
  - Oxycodone LA 20 mg po q12h
  - Morphine 10 mg po q2h prn (takes 5 qd)
- Rates his pain as a worst of 8, best of 4, average of 5.
- No interacting medications.

### Case 5 – Friedman Method
- < 1000 mg qd oral morphine; < 65 years old
- 10:1 = 26 mg oral morphine TDD
- Patient’s pain control not optimal
- Recommendation: methadone 10 mg po q8h
- Lung cancer, therefore recommend morphine oral solution 30 mg q2h prn dyspnea or breakthrough pain

### Case 5
- Calculate TDD oral morphine equivalent
- Transdermal fentanyl 75 mcg/h q72 hours
  - TDF 75 mcg ~ 150 mg oral morphine per day
- Oxycodone LA 20 mg po q12h
  - 40 mg TDD oral oxycodone
  - 20 mg oral oxycodone ~ 30 mg oral morphine
  - ~ 60 mg TDD oral morphine
- Morphine 10 mg po q2h prn (takes 5 qd) = 50 mg oral morphine
- **TDD oral morphine = 260 mg**
- What dose of methadone do you recommend?
Case 6 – Adjusting Methadone

• AZ is a 48 year old man with end-stage AIDS, referred to hospice.
• He experienced itching from morphine, therefore he was switched to methadone.
  – Methadone 5 mg po q12h
  – Methadone 5 mg q3h prn breakthrough pan.

<table>
<thead>
<tr>
<th>Day</th>
<th>Scheduled Methadone Dose</th>
<th># prn Methadone Doses Taken</th>
<th>Average Pain Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methadone 5 mg po q12h</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Methadone 5 mg po q12h</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Methadone 5 mg po q12h</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Methadone 5 mg po q12h</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Methadone 5 mg po q12h</td>
<td>2</td>
<td>2-3</td>
</tr>
<tr>
<td>6</td>
<td>Methadone 5 mg po q12h</td>
<td>2</td>
<td>2-3</td>
</tr>
</tbody>
</table>

It's now day 7; do you adjust his regimen? Why or why not? If yes, what is your recommendation?

Audience Response Question

• How would you adjust AZ’s methadone at this time (if at all)?
  – A. Keep regimen as is (methadone 5 mg po q12h plus methadone 5 mg po q3h prn)
  – B. Increase to methadone 10 mg po q12h plus methadone 5 mg po q3h prn
  – C. Increase to methadone 10 mg po q12h plus methadone 10 mg po q3h prn

Case 6 – Adjusting Methadone

• Current regimen:
  – Methadone 5 mg po q12h
  – Methadone 5 mg po q3h prn
• Recommendation:
  – Methadone 10 mg po q12h
  – Methadone 5 mg po q3h prn
Converting FROM Methadone

- Very poor data
- Many clinicians use a 1:3 ratio (ME:M)
- Walker et al. found a ratio of 1:4.7 (ME:M)
- Carefully monitor for opioid withdrawal, pain ratings and oversedation

Case 7

- GW is a 62 year old woman with a history of OA pain in both knees and hips.
- She was started on methadone and titrated to 7.5 mg po q12h.
- Her pain is well-controlled, but she continues to complain of a “hung-over” type feeling that she’s had the whole time while taking methadone.
- She tells you today she wants to stop taking methadone and is agreeable to switching to oral morphine. What dose do you recommend?

TDD methadone is 15 mg

- Using ME:M 1:4.7, which would be 70.5 mg oral morphine per day
- Using more conservative ME:M 1:3, this is 45 mg oral morphine per day
- Recommendation: Get prescription filled for morphine. Stop methadone, 12 hours later start morphine 7.5 mg every 4 hours; have 5 mg oral morphine available every 2 hours for additional pain.

Notes