Methadone Dosing for Analgesia
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Why this Presentation?

- Over 50% of methadone prescribed in the US is for analgesia
- Methadone has toxicities and pharmacokinetics unique to opioids
- Mortality associated with increased use of methadone is increasing

Increase in Methadone-related Deaths

SOURCE: CDC/NCHS, data from the National Vital Statistics System.
Increase in Opioid-related Deaths

- Narcotic-related deaths have played the largest role in the increase in all poisoning deaths from 1999 to 2005.
- They accounted for 56 percent of all poisoning deaths in 2005, increasing from 50 percent in 1999.
- Their absolute numbers increased 84 percent over the 7 years.
- Methadone-related deaths have increased more than other narcotic-related deaths.

Why do we use Methadone?

- A mu-opioid receptor agonist
  - Hence, an opioid analgesic
  - A phenylheptylamine, unlike morphine
- in vitro evidence of antagonism of the NMDA receptor
  - Argues for the use of methadone for the treatment of pain with neuropathic component
  - Limited clinical data to support this use.

Why do we use Methadone?

- Its long elimination half life (1-3 days) allows every 8-12 hour dosing
- It is available as a liquid (and tablets, IV)
- It is metabolized to inactive metabolites, so is useful in patients with poor kidney function
- It is relatively inexpensive
Methadone Pharmacology

- Methadone is currently administered as a racemic mixture
- R-isomer is the mu-opioid agonist
  - Metabolized by CYPs 3A4, 2C19, 2D6
- S-isomer is the NMDA antagonist
  - A CYP2B6 substrate
  - Primary cause of QTc prolongation

- Both isomers have a very high tissue distribution (4 L/kg) and a modest clearance of ~ 5 L/hr
  - Elimination half life is long and variable
  - Steady state requires patience and caution
    - Concentration plateau takes 5 – 14 days
  - Renal elimination is slowed by an alkaline urine pH, but isn’t major elimination route

- Concentration plateau takes 5 – 14 days
- Renal elimination is slowed by an alkaline urine pH, but isn’t major elimination route

Who are our Candidates for Methadone Treatment?

- True allergy to other pure mu-opioids
- Patients with mod-severe renal impairment
- Adverse effects from other opioids
  - Hallucinations, myoclonic jerks, dysphoria
- Pain refractory to other opioids
- Cases where cost is an issue
- Benefit from long-acting opioid
  - Especially those with G/J-tube access (liquid)
Methadone has advantages in patients with renal dysfunction

- Other opioid glucuronide metabolites are renally excreted, but not all are active:
  - Inactive glucuronides are found with:
    - Oxycodone
    - Hydrocodone
    - Tapentadol
  - Active glucuronides are found with:
    - Morphine (M3G: neuroexcitatory; M6G: analgesia)
    - Hydromorphone (H3G: likely neuroexcitatory)

Methadone has characteristics of an extended-release formulation

- Extended Release Formulations
  - Tablets
    - Morphine, Oxycodone, Oxymorphone, Hydromorphone
  - Controlled-release granules
    - Morphine
  - Patches
    - Fentanyl, Buprenorphine, Hydromorphone
- Extended Effect (due to pharmacokinetics)
  - Methadone

Why shouldn’t we Start ALL Patients on Methadone?

- Highly variable elimination half-life and time to steady state
  - Impairs speed of titration
- Variable conversion ratio from other opioids
- Prolongation of QTc, risk of Torsades
- Multiple drug interactions
- Social stigma
Relative Contraindications for Considering Methadone Treatment

- Patients with very limited prognosis (hours to days)
- Other medications that would affect P450 enzyme activity or increase risk of QTc prolongation
- Pts with history of arrhythmias or syncope
- Poor adherence, poor cognition, unreliable

McPherson L. Demystifying opioid conversion calculations

What are our options for extended effect, chronic pain control in a patient unable to swallow meds?

- IV or SubQ infusion
  - Morphine, hydromorphone, fentanyl, methadone
- Per G- or J-tube
  - Methadone solution
    - CAUTION! (1mg/ml, 2mg/ml, and 10mg/ml solutions are available. Be careful and check!)
  - Kadian® controlled release granules
    - Can clog small bore tubes
- Fentanyl and other patches

The Economies of Methadone

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Oral Dose</th>
<th>Daily Dosage</th>
<th>Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine Sulfate ER</td>
<td>600 mg</td>
<td>6 X 100mg</td>
<td>$682</td>
</tr>
<tr>
<td>Oxycodone ER</td>
<td>400 mg</td>
<td>5 x 80mg</td>
<td>$1960</td>
</tr>
<tr>
<td>Fentanyl TTS</td>
<td>300 mcg/hr</td>
<td>100mcg/hr</td>
<td>$545</td>
</tr>
<tr>
<td>Methadone</td>
<td>60 mg</td>
<td>6 x 10mg</td>
<td>$102</td>
</tr>
</tbody>
</table>
Can we start Methadone in an Opioid-naïve Patient?

- Yes
- 2.5 mg methadone PO 1 – 3x daily
  - Once daily usually best for frail elderly
  - 2.5 mg Q12H or Q8H for others
  - 5-7.5mg methadone approximates 15-40mg oral morphine
- Breakthrough (Rescue) med?
  - Some use methadone
  - Most use morphine, oxycodone, hydromorphone

Starting Methadone

- Non-naïve patients
  - The equianalgesic ratio of methadone to morphine IS NOT LINEAR, but VARIES
  - You will see ratios of 4:1 – 40:1, depending upon the dose
  - As a rule, the larger the equivalent morphine dose, the higher the conversion ratio

QUICK...Which is methadone (Q8H) and which is the morphine IR for Q2Hr dosing for breakthrough pain?
Recommended Reading


FDA-Approved Dolophine® Label

<table>
<thead>
<tr>
<th>Total Daily MEDD*</th>
<th>Estimated Daily Oral Methadone Dose as % of MEDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 100mg</td>
<td>20 – 30% (3.3:1 – 5:1 ratio)</td>
</tr>
<tr>
<td>100 - 300mg</td>
<td>10 – 20% (5:1 – 10:1 ratio)</td>
</tr>
<tr>
<td>300 - 600mg</td>
<td>8 – 12% (8:1 – 12:1 ratio)</td>
</tr>
<tr>
<td>600 - 1000mg</td>
<td>5 – 10% (10:1 – 20:1 ratio)</td>
</tr>
<tr>
<td>&gt;1000mg</td>
<td>&lt; 5% (&gt; 20:1 ratio (?))</td>
</tr>
</tbody>
</table>

MEDD: Morphine Equivalent Daily Dose

Ripamonti and Mercadente Models

<table>
<thead>
<tr>
<th>Oral MEDD</th>
<th>30 – 90mg</th>
<th>90 - 300mg</th>
<th>&gt;300mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ripamonti (1998)</td>
<td>4:1</td>
<td>6:1</td>
<td>8:1</td>
</tr>
<tr>
<td>Mercadente (2001)</td>
<td>4:1</td>
<td>8:1</td>
<td>12:1</td>
</tr>
</tbody>
</table>

MEDD = Morphine Equivalent Daily Dose (Oral)
Friedman Methadone Conversion

- Less than 1000 mg MEDD and < 65 years:
  - Use a 10:1 oral morphine / methadone ratio
- Less than 1000 mg MEDD and ≥ 65 yrs OR 1000-2000 mg MEDD:
  - Use a 20:1 oral morphine / methadone ratio
- More than 2000 mg MEDD:
  - Consider 30:1 oral morphine/methadone
  - High MEDD may represent hyperalgesia
  - High MEDD may affect Pgp opioid transport

Modified Friedman (Hutson)

<table>
<thead>
<tr>
<th>Morphine Equivalent Daily Dose (mg)</th>
<th>Morphine to Methadone Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At or Under 65 yr and Not frail</td>
</tr>
<tr>
<td>&lt; 300 mg/day</td>
<td>5:1</td>
</tr>
<tr>
<td>300 – 1000 mg/day</td>
<td>10:1</td>
</tr>
<tr>
<td>1001 – 2000 mg/day</td>
<td>20:1</td>
</tr>
<tr>
<td>2001 -</td>
<td>30:1</td>
</tr>
</tbody>
</table>

The starting dose of methadone for inpatients or closely monitored patients should not exceed 90mg/day. For most outpatients, the starting dose should not exceed 45 mg/day.

Methadone TO Morphine

- VERY LITTLE information on this
- DO NOT use 1:10 ratio (or higher)
- Recommendation:
  **1:3 ratio to be conservative**

eg. From 15mg Q8H methadone go to 45mg q8H extended release morphine
Timing of Conversions

• Rapid method (with close observation)
  – Stop infusion; Start methadone 3 hours later
  – or, Give first dose of methadone instead of next dose of CR morphine or oxycodone
• Tapered method (gentler, better for outpatient)
  – More often used with high MEDD conversions
  – Give 1/3 of equivalent dose of methadone and drop MEDD by 1/3
  – Repeat daily x3, dropping original drug by 1/3 of original dose daily, replacing with methadone

Methadone Conversion: Case 1

Example: A patient is to be converted from 600mg Morphine SR (200mg Q8H)
Scheduled Dose:
  Methadone 20mg Q8H (10:1 ratio)
Rapid Taper:
  No need to taper morphine, just switch
Rescue Dose:
  Methadone 10mg PO Q4H PRN, or
  Morphine 60-120mg PO Q2H PRN

Methadone Conversion

Example: A patient is to be converted from 600mg Morphine SR (200mg Q8H)
Scheduled Dose (10:1) = Methadone 20mg Q8H
Slow Taper (better for Outpatient Transition):
Day 1: 120mg Morphine SR & 5mg Methadone, Q8H
Day 2: 60mg Morphine SR & 10mg Methadone, Q8H
Day 3: 30mg Morphine SR & 15mg Methadone, Q8H
Day 4: Stop Morphine SR, Give 20mg Methadone Q8H
  Rescue: 60-120mg Morphine IR, Q2H PRN
  [OR: Methadone 5mg Q3-4H, PRN]
Case 2

- Patient BR is receiving a basal SC hydromorphone infusion at a rate of 2.5 mg/hr, and has had an average of an additional 30mg over 24hrs from patient or RN boluses. We are asked to convert him to oral methadone for a neuropathic pain component and for cost considerations. What should his initial regimen be?

Converting between Opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV/SC (mg)</th>
<th>Oral (mg)</th>
<th>Topical (mcg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>-</td>
<td>20-30</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1.5</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>1</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>50% of Oral</td>
<td>~3</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.015</td>
<td>-3</td>
<td>15 (0.015 mg/h)</td>
</tr>
</tbody>
</table>

After determining conversion dose, reduce by 25-33% for incomplete cross-tolerance, EXCEPT for conversion of morphine to methadone or fentanyl.

Case 2:

- What is the daily oral morphine equivalent of the hydromorphone IV?
  - 2.5 mg/hr x 24hr = 60mg basal
  - + 30mg from PID & RN = 90mg IV hydromorphone
  - Using a 1:20 ratio, this would equal 1800mg oral morphine per day.
    - Lower by 25-33% for incomplete cross-tolerance to 1200mg/day MEDD
Case #2 - Methadone

- Calculating an daily morphine equivalent dose of 1800 mg, the methadone regimen should be (with appropriate rescue dosing):
  
a) 210mg, as 70mg PO every 8 hours  
b) 150 mg, as 50mg PO every 8 hours  
c) 90 mg, as 30mg PO every 8 hours  
d) 30 mg, as 10mg PO every 8 hours

Comparison of Methadone  
Conversions from 1800mg MEDD

<table>
<thead>
<tr>
<th>Method</th>
<th>Ratio</th>
<th>Daily Methadone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ripamonti</td>
<td>8:1</td>
<td>225 mg</td>
</tr>
<tr>
<td>Mercadente</td>
<td>12:1</td>
<td>150 mg</td>
</tr>
<tr>
<td>FDA-approved PI</td>
<td>20:1</td>
<td>90 mg</td>
</tr>
<tr>
<td>Friedman</td>
<td>20:1</td>
<td>90 mg</td>
</tr>
</tbody>
</table>

Many clinicians will limit the initial daily methadone dose to 90mg (30mg TID) if calculations suggest a higher initial dose.

Question #2 - Methadone

- Calculating an daily morphine equivalent dose of 1800 mg, the methadone regimen should be (with appropriate rescue dosing):
  
a) 210mg, as 70mg PO every 8 hours  
b) 150 mg, as 50mg PO every 8 hours  
c) 90 mg, as 30mg PO every 8 hours  
d) 30 mg, as 10mg PO every 8 hours
Methadone Caveats

- Conversions from other opioids are NOT proportional
- Reaching steady state takes ~ 1 week
- Clearance will vary with adding/removing other drugs that affect its P450 enzymes (3A4, 2B6)
- QTc interval will likely increase with higher doses
  - Avoid use with other QTc prolonging drugs
  - Some MDs will get an ECG before/during Tx

Timing of Conversions

- Rapid method (with close observation)
  - Stop infusion, start methadone 3 hours later
  - or, give first dose of methadone instead of next dose of CR morphine or oxycodone
- Tapered method (gentler, better for outpatient)
  - More often used with high MEDD conversions
  - Give 1/3 of equivalent dose of methadone and drop MEDD by 1/3
  - Repeat daily x3, dropping original drug by 1/3 of original dose daily, replacing with methadone

Rapid Conversion

- Stop IV hydromorphone infusion
- Wait 3 hours, and give first dose of 30mg methadone
- Continue through the rest of the day at 30mg q8h
- Rescue / Breakthrough: Most convenient will be IV PID doses of hydromorphone (2.5 mg q10min)
  - Could also give 15mg methadone q4h
Tapered Conversion

• Day 1
  – Decrease hydromorphone infusion from 2.5 to 1.6mg/hr
  – 3 hours later start 10mg methadone q8 hours

• Day 2
  – Decrease hydromorphone infusion from 1.6 to 0.8mg/hr
  – 3 hours later start 20mg methadone q8 hours

Tapered Method (continued)

• Day 3
  – Stop hydromorphone infusion
  – 3 hours later start 30mg methadone q8 hours

• Rescue/Breakthrough
  – Hydromorphone 2.5mg q10 min IV PID
  – Morphine 120-240 mg PO Q2 hours
  – Methadone 50% of Scheduled dose, given orally Q3-4 hours

• Cognition? Caregiver helping with PRNs?

Can we Give Methadone IV?

• Yes, bioavailability is 30-100%
• Use 100% bioavailability when transitioning from IV to PO methadone
  – 36 mg IV/day >> 36 (45) mg PO/day
• Use a more conservative 2:1 ratio when converting from PO to IV methadone
  – 45 mg PO/day >> 24 mg IV/day
Opioid Respiratory Depression

• Treatment
  – Ventilate
  – Stop infusion / remove patch, if present
  – Administer 50-100 mcg boluses naloxone Q5 min
    • Naloxone is a pure mu antagonist
      – Higher doses (400 mcg) are more likely to reverse BOTH respiratory depression AND pain control

Opioid Respiratory Depression

• For sustained-release products, a continuous infusion of naloxone is indicated
  – Dilute 2 mg in 500 ml NS
  – Initial rate (mcg/hr) is approximately 67% of the bolus size needed for initial resuscitation
  – Titrate rate to clinical effect; may require additional boluses as the infusion rate is increased.

Opioid Respiratory Depression

• Example
  – If we needed to administer 200mcg of naloxone to reverse apparent opioid-induced respiratory depression
  – We should immediately start a naloxone infusion of about 120mcg/hr.
  – Duration of infusion will depend on the half-life of the opioid causing the toxicity
Methadone Association with Prolonged QTc Interval

- Prolonged QT wave intervals are associated with an increased risk of ventricular fibrillation (VF) and torsade de points (TdP)
  - Although VF and TdP may spontaneously resolve, they are commonly associated with sudden cardiac death
  - Prolongation of the QT interval is considered a serious cardiac risk
  - Most common reason for restriction or removal of drugs from the US market

When is a QTc Interval ‘Prolonged’?

- Borderline QTc (Strauss)
  - Males: 431-450ms
  - Females: 451-470ms
- Long QT:
  - Males: > 450 ms
  - Females: > 470 ms
  - CTCAE 3 used 450-470 ms for Grade 1, 470-500 for Grade 2
- Substantial variability in healthy adults
  - Mean diurnal variation in QTc was 95ms
  - Average maximal QTc was 495 +/- 21ms
Torsade de pointes
“Twisting of Points”

Risk Factors for TdP:
- QT-prolonging drugs
- Type I and III antiarrhythmics
- Other drugs
  - Hypokalemia
  - Structural heart disease
  - Prolonged baseline QTc
  - Bradycardia
  - Female
  - Prior history of LQTS


Of 249 incidents of Torsades, virtually all patients had at least one risk factor, and 71% had multiple risks

Treatment of Torsades
- IV Magnesium Sulfate (2gms of 50%)
  - May repeat in 10 minutes PRN
  - An IV infusion of Mg may also be needed
    - (3-20mg/min)
- Overdrive pacing: HR > 100
- Isoproterenol
- Potassium replacement as possible
- IV naloxone seems reasonable for opioid-related Torsades

Other Risk Factors for LQTS (and by inference Torsades)
- Genetic polymorphisms found in some patients with medication-induced LQTS and arrhythmias:
  - CYP2D6 Poor metabolizer genotype
  - LQT6 6 affects I_Na beta subunit
  - S1103Y affects sodium channel gene SCNSA
- In addition to drugs that increase QTc, drugs that slow their metabolism and/or increase their blood concentration can increase QTc
Drugs Implicated in TdP

- Antiarrhythmics
  - Class IA and III
- Promotility agents
  - Cisapride*
  - Erythromycin
- Antibiotics
  - Erythromycin
  - Clarithromycin
  - Pentamidine
- Antimalarials
- Antidepressants
  - TCA > SSRIs
- Antipsychotics
  - Phenothiazines
  - Butyrophenones
    - Haloperidol
    - Droperidol
  - Ziprasidone (GEODON)
- Supplements
  - Licorice
- Opioids
  - Methadone
  - Oxycodone?

Methadone and LQTS/TdP

- Multiple series reporting prolonged QTc and some cases of Torsades in patients receiving methadone
  - Most were opioid replacement patients or IV
    - Doses tend to be higher than for pain
  - Few cases were for pain treatment
- Quality and generalizability of reports varies
  - Case report/series
  - Cross-Sectional, Retrospective, or Prospective

Other Possible Risk factors for Methadone LQTS

- Exposure to cardiotoxic chemotherapy
  - Taxanes, anthracyclines, high dose cyclophosphamide
- Hypokalemia
  - NG suction
  - Chronic diarrhea
  - History of Cisplatin treatment
- Bradycardia (perhaps drug-induced)
What about other opioid effects?

- No evidence of clinically significant QTc prolongation:
  - Morphine
  - Codeine
  - Fentanyl
  - Tramadol
- Dose-dependent QTc prolongation with
  - Oxycodone

Expert Panel Recommendations

- Disclosure
  Clinicians should inform patients of the arrhythmia risk when they prescribe methadone

- Clinical History
  Clinicians should ask patients about any history of structural heart disease, arrhythmias, or syncope

Expert Panel Recommendations

- Screening
  Obtain a pretreatment ECG for ALL patients to measure QTc interval, and a follow-up ECG within 30 days and annually.

  Additional ECGs are recommended if the methadone dosage exceeds 100mg/day, OR if patients have unexplained syncope
Expert Panel Recommendations
Krantz 2009

• Risk Stratification
  If the QTc is > 450ms but < 500ms, discuss the potential risk and benefits with patients and monitor them more frequently. If the QTc interval exceeds 500ms, consider stopping or reducing the methadone dose; eliminating contributing factors, such as drugs that promote hypokalemia; or using an alternative therapy

Expert Panel Recommendations
Krantz 2009

• Drug Interactions
  – Clinicians should be aware of interactions between methadone and other drugs that possess QTc-interval prolonging effects, or that slow the elimination of methadone

Methadone Drug Interactions

• CYP3A4 Inhibitors
  – Fluconazole
  – Fluoxetine
  – Fluvoxamine
  – Nefazodone
  – Paroxetine
  – Venlafaxine
  – Erythromycin/Clarithro
  – Ciprofloxacin

• CYP2B6 Inhibitors
  – Fluoxetine
  – Fluvoxamine
  – Haloperidol
  – Nefazodone
  – Paroxetine
  – Sertraline
  – Ticlopidine
  – Clopidogrel
Methadone Drug Interactions

- **CYP2D6 Inhibitors**
  - Bupropion
  - Cinacalcet
  - Fluoxetine
  - Paroxetine
  - Duloxetine
  - Sertraline
  - Terbinafine
  - Amiodarone
  - ...

- **CYP3A4 Inducers**
  - Carbamazepine
  - Glucocorticoids
  - Phenytoin
  - Rifampin

Adding or removing inducers or inhibitors can change the clearance of methadone, and the effects at steady state will not be known for days to weeks, even on stable methadone doses

Modifiable Concerns

- **Avoid or Correct Concurrent**
  - Hypokalemia
  - Medications
    - Erythromycin / Clarithromycin
    - Ondansetron
    - Haloperidol
    - Ziprasidone (Geodon)
    - Tricyclic antidepressants, perhaps SSRI's
    - Enzyme inhibitors (CYP3A4 and 2D6)
    - Cardiac Chronotrophs

Indications for Considering Methadone Treatment

- True allergy to other pure mu-opioids
- Patients with renal impairment
- Opioid-induced adverse effects
  - Hallucinations, myoclonic jerks
- Pain refractory to other opioids
- Cases where cost is an issue
- Benefit from long-acting opioid
  - Especially those with G/J-tube access
Relative Contraindications for Considering Methadone Treatment

- Patients with very limited prognosis (hours to days)
- Other medications that would affect P450 enzyme activity or increase risk of QTc prolongation
- Pts with history of arrhythmias or syncope
- Poor adherence, poor cognition, unreliable

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References and Suggested Readings

- Cruciani AR. Methadone: To ECG or not to ECG. That is still the question. J Pain Symptom Manage 2008; 36: 545-52.

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Thank You

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  – 608.263.2496