The Methadone Safety Guidelines: A Live Webinar

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CONFLICT OF INTEREST DISCLOSURE

Drs. Weimer and Chou: No financial disclosures

Intellectual disclosure: Dr. Weimer is Medical Director of a substance abuse treatment program that prescribes methadone for treatment of opioid dependence; Drs. Weimer and Chou were authors of a systematic review and guideline on methadone safety funded by the American Pain Society
DISCLAIMER

The content and recommendations included in this webinar are based on recently published evidence-based Methadone Safety clinical practice guidelines. Clinical practice guidelines are “guides” only and may not apply to all patients and all clinical situations. Variations in practice, which take into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments and/or procedures that differ from the recommendations outlined in this guideline. These recommendations should not be construed as dictating an exclusive course of management, nor does the use of such recommendations guarantee a particular outcome.
LEARNING OBJECTIVES

• Discuss the epidemiology of methadone associated harms
• Discuss the unique properties of methadone
• Develop strategies to reduce the risk of overdose and other serious harms associated with methadone use.
Chronic Pain Case

• 45 yo man with history of multiple sclerosis maintained on methadone 30mg every 8 hours for chronic pain presents with altered mental status and torsades in the setting of a week long history of nausea and vomiting. He is found to have profound hypokalemia (K 1.4) and a QTc of 694ms. His QTc corrects to 500ms with potassium replacement.

• Should he continue on methadone for pain treatment?
Opioid Use Disorder Case

• 23 yo man with a history of IV heroin use is successfully treated in the hospital for endocarditis. He presents to an opioid treatment center for methadone maintenance therapy. His baseline QTc is 480ms. His electrolytes and liver function are normal.

• What do you recommend?
FDA Public Health Advisory, November 2006

“Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat”

http://www.fda.gov/Drugs/DrugSafety/PublicHealthAdvisories/ucm124346.htm
Methadone

• Synthetic opioid use for treatment of opioid dependence and treatment of *chronic* pain

• Large increase in number of methadone associated deaths
  • 1999: 800
  • 2007: 5,500
  • 2008: 4,900

• Part of larger trend regarding prescription opioids
  • Rate of increase in methadone-associate deaths larger than for any other opioids
Figure 4. Number of drug poisoning deaths involving opioid analgesic by opioid analgesic category: United States, 1999–2008

Source: NCHS Data Brief, December 2011
Since 2008, 15,000 deaths per year. This exceeds MVA deaths in 30 states.

Methadone prescribing patterns

- Methadone accounted for 1.7% of opioid prescriptions in 2009 and 9.0% of morphine equivalents in 2010\(^a\)
- Methadone was associated with 31% of opioid-related deaths and 40% of single-drug deaths\(^a\)
- For chronic non-cancer pain, methadone evaluated in a single, small, poor-quality trial of neuropathic pain\(^b\)

\(^a\)MMWR 2012;61:493-7
\(^b\)Morley et al. Palliative Med 2003
## Costs of long-acting opioids

<table>
<thead>
<tr>
<th>Generic name and strength</th>
<th>Brand name</th>
<th>Total daily dose</th>
<th>Average monthly cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine patch 5 mcg/hr</td>
<td>Butrans</td>
<td>120 mcg</td>
<td>$189</td>
</tr>
<tr>
<td>Buprenorphine patch 20 mcg/hr</td>
<td>Butrans</td>
<td>480 mcg</td>
<td>$495</td>
</tr>
<tr>
<td>Fentanyl patch 25 mcg/hr</td>
<td>Duragesic/generic</td>
<td>600 mcg</td>
<td>$303/$126</td>
</tr>
<tr>
<td>Fentanyl patch 50 mcg/hr</td>
<td>Duragesic/generic</td>
<td>1200 mcg</td>
<td>$666/$205</td>
</tr>
<tr>
<td>Methadone 5 mg</td>
<td>Generic</td>
<td>15 mg</td>
<td>$17</td>
</tr>
<tr>
<td>Methadone 10 mg</td>
<td>Generic</td>
<td>30 mg</td>
<td>$20</td>
</tr>
<tr>
<td>Morphine SR 15 mg</td>
<td>Generic</td>
<td>30 mg</td>
<td>$48</td>
</tr>
<tr>
<td>Morphine ER 30 mg</td>
<td>Avinza/Kadian</td>
<td>30 mg</td>
<td>$177/$247</td>
</tr>
<tr>
<td>Morphine SR 30 mg</td>
<td>Generic</td>
<td>60 mg</td>
<td>$72</td>
</tr>
<tr>
<td>Morphine ER 60 mg</td>
<td>Avinza/Kadian</td>
<td>60 mg</td>
<td>$313/$433</td>
</tr>
<tr>
<td>Oxycodone SR 10 mg</td>
<td>Oxycontin</td>
<td>20 mg</td>
<td>$164</td>
</tr>
<tr>
<td>Oxycodone SR 20 mg</td>
<td>Oxycontin</td>
<td>40 mg</td>
<td>$306</td>
</tr>
</tbody>
</table>
Methadone Maintenance Therapy

- Only licensed methadone clinics are permitted to *dispense* methadone
- Reduces euphoria of subsequent opioid abuse
- Typical effective dose range 60-90mg/day
- Effective to
  - Increase retention in treatment
  - Reduce use of opioids
  - Reduce human immunodeficiency virus (HIV)

Methadone deaths in patients in opioid treatment programs

<table>
<thead>
<tr>
<th>Study</th>
<th>State (years of study)</th>
<th>Number of deaths in patients prescribed methadone</th>
<th>Number of deaths in patients receiving methadone from opioid treatment program (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballesteros et al</td>
<td>North Carolina (1997-2001)</td>
<td>73</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Gagajewski et al</td>
<td>Minnesota (1992-2002)</td>
<td>15</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>Madden et al</td>
<td>Vermont (2001-2006)</td>
<td>25</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Oregon Dept of Human Services</td>
<td>Oregon (1999-2002)</td>
<td>226/152*</td>
<td>83 (37%/55%*)</td>
</tr>
<tr>
<td>Paulozzi et al</td>
<td>West Virginia (2006)</td>
<td>32</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>Shah et al</td>
<td>New Mexico (1998-2002)</td>
<td>68/17**</td>
<td>31 (45%)/3 (18%)</td>
</tr>
<tr>
<td>Weimer et al</td>
<td>Virginia (2004)</td>
<td>20</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>

*Excluding patients with unknown source of methadone

**Excluding cases of methadone co-intoxication
Challenges in interpreting epidemiological data

• Uncertainty regarding the degree to which increases in deaths are proportionate to increased prescribing
• Increased surveillance
• Differentiating prescribed versus non-prescribed use
• Separating effects of other potential contributing factors
• Ascribing cause of methadone-associated death
  • Generally not possible to determine whether death occurred as a result of overdose due to respiratory depression or other factors, such as cardiac arrhythmias
Question: What is the approximate half life of methadone?

- A: 4-6 hours
- B: 12 hours
- C: 15-60 hours
- D: >100 hours
Unique properties of methadone

- Long and variable half-life
- Potential interactions with multiple medications
- Variability in equianalgesic dose ratios depending on dose
- Association with prolongation of the electrocardiographic corrected QT (QTc) interval
  - Prolonged QTc predisposes to torsades de pointes
  - Proportion of methadone-associated deaths due to arrhythmia thought to be relatively low relative to proportion related to accidental overdose, but reliable estimates not available
  - Recent data suggest that methadone is the most common drug-related cause of ventricular arrhythmia
Guidelines on methadone safety

• Three guidelines published between 2008 and 2011
• Two not fully endorsed by a professional society or government entity; third endorsed by the Substance Abuse and Mental Health Services Administration
• Systematic review conducted, but strength of recommendation or quality of evidence supporting recommendations not graded
• Focused on prevention of cardiac arrhythmias
APS/CPDD guideline on methadone safety

• Purpose: Develop a clinical practice guideline on safer prescribing of methadone
  • Risks related to overdose and cardiac arrhythmia potential
• Target audience: Clinicians prescribing methadone for chronic pain or for treatment of addiction
  • Partnership between APS and CPDD
  • Funding from APS
  • Heart Rhythm Society invited to join after co-chair and initial panel selection had taken place
  • Does not address methadone for acute or postoperative pain
Methadone Safety Guidelines

Methadone Safety: A Clinical Practice Guideline From the American Pain Society and College on Problems of Drug Dependence, in Collaboration With the Heart Rhythm Society

Methadone Overdose and Cardiac Arrhythmia Potential: Findings From a Review of the Evidence for an American Pain Society and College on Problems of Drug Dependence Clinical Practice Guideline

# GRADE Recommendation Grid

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td>High, Moderate, Low, Very Low</td>
</tr>
<tr>
<td><strong>Weak</strong></td>
<td>High, Moderate, Low, Very Low</td>
</tr>
</tbody>
</table>
Patient assessment and selection

Patient education and counseling

Recommendations

- Perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone (*strong recommendation, low-quality evidence*)

- Educate and counsel patients regarding risks and benefits prior to first prescription and periodically while taking methadone (*strong recommendation, low-quality evidence*)
Prolonged QTc and torsades de pointes
Question: Elevated risk for torsades de pointes starts at what QTc?

- A: 450ms
- B: 450ms for men; 470ms for women
- C: 480ms
- D: 500ms
Baseline ECG

- Obtain a baseline ECG prior to initiation of methadone in patients with risk factors for QTc prolongation, history of QTc prolongation, or history of prior ventricular arrhythmia (ECG within 3 months is sufficient) (strong recommendation, low-quality evidence)

- Consider obtaining a baseline ECG in patients not known to be at higher risk of QTc prolongation (ECG within 12 months is sufficient) (weak recommendation, low-quality evidence)
Baseline ECG (continued)

Recommendation

• Recommend against use of methadone in patients with a baseline QTc interval >500 ms (*strong recommendation, low-quality evidence*)

• Recommend that clinicians consider alternative to methadone for QTc interval \( \geq 450 \) ms but \(< 500 \) ms; evaluate and correct reversible causes of QTc prolongation (*weak recommendation, moderate-quality evidence*)

• Consider buprenorphine for patients treated for opioid addiction who have risk factors or known QTc interval prolongation (*weak recommendation, moderate-quality evidence*)
Baseline ECG

- Torsades de pointes usually preceded by QTc prolongation
- ECG is the only way to detect QTc prolongation and to identify persons who might benefit from steps to mitigate risks
- Risk of torsades increases with greater prolongation of QTc interval
  - Risk primarily in persons with QTc >500 ms, but starts to increase around QTc >450 ms
- Methadone appears to increase risk of prolonged QTc through inhibitory effects on the hERG cardiac channel
- Case reports of sudden deaths in patients prescribed methadone

Rationale
Risk factors for QTc interval prolongation

- High proportion (but not all) cases of methadone-associated torsades had identifiable risk factors for QTc prolongation
- Electrolyte abnormalities such as hypokalemia or hypomagnesemia
- Impaired liver function
- Structural heart disease (e.g., congenital heart defects or history of endocarditis or heart failure)
  - One case-control study found higher proportion of cases involving methadone had no structural heart abnormalities (77%; 17/22) compared to cases not involving methadone (40%; 42/106, p=0.003).
- Genetic predisposition such as congenital prolonged QT syndrome or familial history of prolonged QT syndrome
- Use of drugs with QTc-prolonging properties
  - Antiretroviral drugs, macrolide antibiotics, quetiapine, tricyclic antidepressants, cocaine

QTc interval and cardiac risks

• Normal QTc interval 10-20 ms longer in women than in men (clinical significance unclear)
• In general populations of U.S. adults, <5% of men and women have QTc interval of >450 ms
• In patients with long QT syndrome, QTc interval >500 ms associated with OR for syncope or sudden death of 4.2 (95% CI 1.1 to 16)
• Each 10-ms increase in QTc interval associated with 5-7% exponential increase in risk of torsades
  • QTc of 540 ms associated with 63-97% greater risk than QTc of 440 ms
• Little data on normal QTc intervals in children
Cardiac risks of methadone in perspective

- Estimated risk of torsades 0.001% for cisapride, 8% for quinidine
  - Manufacturer voluntarily discontinued marketing in U.S. in 2000 based on 341 cases of cardiac arrhythmias (including 80 deaths) from 1993 to 1999
  - 85% of cisapride-associated arrhythmias occurred with known risk factors
  - ECG monitoring recommended for a number of drugs associated with prolonged QTc interval, though evidence showing effectiveness of monitoring lacking
Follow-up ECG

- Perform follow-up ECGs based on baseline ECG findings, methadone dose changes, and other risk factors for QTc interval prolongation (*strong recommendation, low-quality evidence*)

- Switch patients with QTc interval $\geq 500$ ms to an alternative opioid or immediately reduce the methadone dose; evaluate and correct causes of QTc interval prolongation, and repeat ECG (*strong recommendation, low-quality evidence*)

- Consider switching patients with QTc interval $\geq 450$ ms but $<500$ ms to an alternative opioid or reduce opioid dose; discuss risks if methadone continued (*strong recommendation, low-quality evidence*)
Follow-up ECG

Rationale

• Patients with risk factors for or prior QTc interval prolongation may be at greater risk for QTc interval prolongation on methadone

• Higher doses of methadone associated with increased risk of QTc interval prolongation
  • High proportion of reported cases of torsades de pointes occurred in patients prescribed >200 mg/day
# Suggested parameters for follow-up ECG

<table>
<thead>
<tr>
<th>Situation</th>
<th>Initial dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors for QTc prolongation, prior ECG with QTc &gt;450 ms, or history of syncope</td>
<td>Follow-up ECG 2–4 weeks after initiation of methadone and following significant dose increases</td>
</tr>
<tr>
<td>Methadone dose increased</td>
<td>Follow-up ECG when methadone dose reaches 30 to 40 mg/day and again at 100 mg/day</td>
</tr>
<tr>
<td>New risk factors for QTc interval prolongation or signs or symptoms of arrhythmia</td>
<td>Follow-up ECG</td>
</tr>
</tbody>
</table>
One Substance Abuse Center
ECG Experience

• Implementation challenges
  • Staff education
  • Patient education
  • PCP/provider education

• Funding barriers
  • Equipment
  • Unreimbursed physician and staff time

• Are treatment outcomes different?
• Will we improve overall patient safety?
Initiation of methadone

Recommendation

• Initiate methadone at low doses, individualized based on the indication for treatment and prior opioid exposure status, titrate doses slowly, and monitor patients for sedation (strong recommendation, moderate-quality evidence)
Initiation of methadone

• Half-life usually assumed to be about 1 day, rarely outside range of 15 to 60 h (up to 120 h)
  • For 60 h half-life, 12 days on stable dose to reach steady state
  • Half-life unknown in individual patients

• Consider patient factors (opioid tolerance) when initiating doses

• Caution when switching from another opioid to methadone

Rationale
# Morphine to methadone conversion

<table>
<thead>
<tr>
<th>24 hour total oral morphine</th>
<th>Oral morphine to methadone conversion ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg</td>
<td>2:1</td>
</tr>
<tr>
<td>31-99 mg</td>
<td>4:1</td>
</tr>
<tr>
<td>100-299 mg</td>
<td>8:1</td>
</tr>
<tr>
<td>300-499 mg</td>
<td>12:1</td>
</tr>
<tr>
<td>500-999 mg</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000 mg</td>
<td>20:1</td>
</tr>
</tbody>
</table>

## Suggested dosing parameters

<table>
<thead>
<tr>
<th>Population</th>
<th>Initial dose</th>
<th>Dose titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid addiction</td>
<td>No more than 30–40 mg/day</td>
<td>No more than 10 mg/day and no more frequently than every 3 to 4 days</td>
</tr>
<tr>
<td>Chronic pain, &lt;40–60 mg/day MED</td>
<td>2.5 mg tid</td>
<td>No more than 5 mg/day every 5–7 days</td>
</tr>
<tr>
<td>Chronic pain, &gt;40–60 mg/day MED</td>
<td>75–90% less than calculated equianalgesic dose and no higher than 30 to 40 mg/day</td>
<td>No more than 10 mg/day every 5–7 days</td>
</tr>
<tr>
<td>Children</td>
<td>100 mcg/kg (maximum 5 mg/dose) every 6–8 hours</td>
<td></td>
</tr>
</tbody>
</table>
Monitoring for and management of adverse events

Urine drug testing

Recommendation

• Monitor patients receiving methadone for common opioid adverse effects and toxicities (strong recommendation, moderate-quality evidence)

• Obtain urine drug screens prior to initiation of methadone and at regular intervals (strong recommendation, low-quality evidence)
Monitoring for and management of adverse events

Rationale

• Opioid AE’s include constipation, nausea, sedation, respiratory depression, pruritus, endocrinologic effects, and others
• Proactive interventions for opioid-induced constipation
• Counsel on sedation after dose initiation and increases
• Follow-up important; mortality higher in period after methadone initiation
  • Can probably be done via phone or via email
Prescription drug monitoring programs

- Available now in many states
- PDMPs vary in who can access, information not available across states
- Studies show that use of PDMPs can identify cases of diversion and doctor shopping
  - Recent study found decreased inappropriate drug prescribing with use of a centralized prescribing system in Canada
  - Effects on clinical outcomes (e.g., overdose) and optimal strategies for using PDMP not known

\[^a\text{Dormuth et al. CMAJ 2012}\]
Medication interactions

Recommendation

- Use methadone with care in patients using concomitant medications with potentially additive side effects or pharmacokinetic or pharmacodynamic interactions with methadone (strong recommendation, low-quality evidence)
Medication interactions

- Some drugs alter methadone absorption, metabolism, and/or excretion
  - Methadone primarily metabolized in the liver and GI tract by cytochrome P450 enzymes
  - CYP inhibitors increase methadone levels
  - CYP inducers decrease methadone levels
- Some drugs have additive or synergistic sedative or respiratory suppressant effects
  - High proportion of overdoses occurred in patients with benzodiazepines in system at time of death
- Some drugs also associated with QTc prolongation

Rationale
Methadone use in pregnancy

**Recommendation**

- Monitor neonates born to mothers receiving methadone for neonatal abstinence syndrome (NAS) and treat for NAS when present (*strong recommendation, moderate-quality evidence*)
Methadone use in pregnancy

- NAS occurs in ¾ or more of infants exposed to methadone prenatally
- Risk of NAS may be higher with methadone than with buprenorphine
- Opioid agonist treatment with methadone standard of care for opioid addiction during pregnancy
- Methadone more frequently being used for chronic pain in women of childbearing age
  - In 2007, 23% of Medicaid patients were prescribed an opioid during pregnancy*

Recommendation

Chronic Pain Case

• 45 yo man with history of multiple sclerosis maintained on methadone 30mg every 8 hours who presented with AMS in the setting of hypokalemia (K 1.4) and a QTc of 694ms. His QTc corrects to 500ms with potassium replacement.

• Should he continue on methadone for pain treatment?
Opioid Use Disorder Case

• 23 yo man with a history of IV heroin use is successfully treated in the hospital for endocarditis. He presents to an opioid treatment center for methadone maintenance therapy. His baseline QTc is 480ms. His electrolytes and liver function are normal.

• What do you recommend?
Key research gaps

- Comparative risks of methadone vs. other opioids
- Risk factors for methadone-related deaths
- Effectiveness of ECG monitoring for reducing harms associated with methadone use
- Effectiveness of other risk mitigation strategies
- Optimal dosing strategies
- Methods for safely managing pregnant women with chronic pain
- Methadone use in children
Conclusions

- Large increase in number of methadone associated deaths in parallel with increased prescribing
- Methadone associated with unique properties that increase risks
  - Long and variable half-life
  - Prolonging effects on QTc interval
  - Interactions with multiple medications
  - Variability in equianalgesic dose ratios at different doses
- Actions can be taken to promote safer use of methadone
  - Education and counseling
  - Use of ECG monitoring
  - Use of alternative opioids in patients at higher risk of complications
  - Cautious dose initiation and titration
  - Diligent monitoring and follow-up
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Questions?

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