Responsible Prescribing of Methadone for Pain Management: Safety First

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Salt Lake City, UT

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Dr Webster: Disclosures

12-Month disclosures of financial relationships with commercial interests:

<table>
<thead>
<tr>
<th>Honorarium: Consultant</th>
<th>Honorarium: Advisory Board</th>
<th>Travel Expenses</th>
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<td>Kaleo</td>
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This presentation does not contain off-label or investigational use of drugs or products.
Planning Committee, Disclosures

- Vitaly Gordin, MD
  Director of Pain Division
  Penn State Hershey Medical Center
  Hershey, PA
  - No relevant financial relationships

- Jennifer Westlund, MSW
  Director of Education
  American Academy of Pain Medicine
  - No relevant financial relationships

- Angela Casey
  VP, Medical Director
  PharmaCom Group
  - No relevant financial relationships
Target Audience

• The overarching goal of PCSS-O is to offer evidence-based trainings on the safe & effective prescribing of opioid medications in the treatment of pain &/or opioid addiction.

• Our focus is to reach providers &/or providers-in-training from diverse healthcare professions including physicians, nurses, dentists, physician assistants, pharmacists, & program administrators.
Educational Objectives

• At the conclusion of this activity participants should be able to:
  1. Understand the unique pharmacologic properties of methadone
  2. Utilize recommended practices when prescribing methadone
  3. Implement a plan to improve patient safety through assessment, patient education, management, & monitoring practices
Methadone Background

- Developed in 1937 as a synthetic opioid analgesic
  - Introduced into the United States in 1947
- Can be effective for otherwise refractory chronic pain
  - However, clinical management can be challenging
- Methadone appears in mortality reports with greater frequency than expected given the smaller number of prescriptions written vs. other opioids

Methadone-Associated Deaths

- 5,000 people die every year of overdose related to methadone
- Methadone contributed to nearly 1 in 3 prescription opioid deaths in 2009
- Only 2% of opioid analgesic prescriptions were for methadone

Death Rate from Prescription Opioids

Drug Abuse Warning Network Medical Examiner System, 13 States, 2009

Single-drug deaths:

- Buprenorphine: 0.1
- Hydromorphone: 0.5
- Hydrocodone: 1.1
- Oxycodone: 1.2
- Fentanyl: 2.1
- Morphine: 3.8
- Methadone: 9.7

All drug-related deaths:

- Buprenorphine: 0.8
- Fentanyl: 7.7
- Oxycodone: 8.7
- Hydrocodone: 9.1
- Morphine: 14.3
- Methadone: 20.2
- MME: 33.6

MME=morphine milligram equivalent

Methadone ≠ Drug of First Choice

- Methadone should not be considered as a drug of first choice for chronic pain.
- It should only be prescribed by providers experienced in its use.
- Methadone belongs in the armamentarium of pain medications, but specific medical education is necessary to prescribe it safely.

Methadone Cost

- Methadone is less expensive than other ER/LA opioids prescribed for pain
- Contributes to its frequent appearance on formularies as a drug of first choice
  - Payer policies promoting methadone as a preferred treatment for chronic pain contribute to methadone mortality


ER/LA=extended-release, long-acting
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<th>Frequency of use</th>
<th>Total dose/day</th>
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Growth of Methadone Use for Pain & Methadone Overdose Deaths

- Methadone use for pain (kg/100,000 people)
- Methadone-related overdose deaths per 100,000 people

More than 5 times as many people died of methadone overdose in 2009 than a decade before.

Growth of Methadone-Related Deaths

- A 2012 Pulitzer Prize-winning investigation by the Seattle Times
  - Washington State experience after listing methadone as a preferred drug in 2001
  - By 2006, methadone-associated deaths had doubled
    - Concentrated in lower income areas
  - Medicaid recipients made up only 8% of the state’s adult population
    - Accounted for 48% of 2,173 methadone deaths since 2003

AAPM is opposed to methadone use as a preferred treatment option for chronic pain

- Calls for prescriber education on safe practices
- Methadone’s unique pharmacologic properties make it risky to prescribe by clinicians without special training
  - Does not mean that other opioids are without risks
  - All opioids demand caution & training in their use

AAPM goal is not to remove methadone from the armamentarium of pain medications

- Prescribers who select methadone for chronic pain should complete specific education

Primary Problems Identified in Methadone Prescribing

- Initiating methadone at too high a dose
- Inflexibly applying published equianalgesic conversion tables when converting to methadone
- Underestimating the risk of respiratory depression in patients with prior opioid use
- Titrating too rapidly

Primary Problems Identified in Methadone Prescribing

- Failing to identify & monitor patients at risk for misuse/abuse
- Risk of QTc interval prolongation
- Possible risks with sleep apnea
- Failure to use caution with co-prescribing benzodiazepines, tricyclic antidepressants, & other sedatives
- Knowledge deficits of common drug-drug interactions

Patient Non-Adherence to Medication Regimen

- Attempts to achieve greater pain relief, self-medicate a comorbid mental health disorder, or a substance use disorder
  - Escalating doses without prescriber knowledge
  - Taking extra doses
  - Taking methadone with alcohol, benzodiazepines, or other CNS depressants without prescriber knowledge
- Fail to take all medication as prescribed
  - Leading prescriber to overestimate the degree of opioid tolerance present

Providers Who Prescribe Methadone for Pain Should Demonstrate Proficiency

- Be familiar with methadone’s unique pharmacology
  - Long elimination half-life compared to analgesia
- Use methadone only:
  - When pain is severe enough to warrant it
  - When alternative treatment opioids are inadequate
  - After conducting a risk-benefit analysis
- Assess patients for risk of substance abuse & mental-health comorbidities that could increase risk of non-adherence
- Initiate, titrate, rotate methadone conservatively, even in opioid-tolerant patients, & closely monitor patient response
- Monitor patients for adherence, analgesic response, effect on daily activities, & AEs

Providers WhoPrescribe Methadone for Pain Should Demonstrate Proficiency

• Monitor for potential
  ▪ Cardiac toxicities
  ▪ Drug interactions
• Watch for & address aberrant drug-related behaviors & psychosocial issues that could compromise therapy
• Counsel patients to adhere strictly to directions
• Prepare a strategy to taper & discontinue methadone if needed
• Consider co-prescribing naloxone to reduce overdose deaths

Unique Pharmacologic Properties of Methadone

- Methadone’s analgesia lasts for 4-8 hours
- Methadone’s half-life estimated at 8-59 hours
  - Up to 130 hours due to variations in individual metabolism
  - By comparison, half-lives of morphine, fentanyl, hydromorphone, & oxycodone range from 2-3.5 hours
- Steady-state levels require 5 half-lives
  - Correct individual doses are difficult to calculate *a priori*

Simulated Methadone Dosing

α (analgesic)  β (non-analgesic)

Toxicity

Analgesia

Methadone Metabolism

- Metabolized in the liver predominately by CYP450 enzymes
  - Mainly CYP3A4 and CYP2B6
  - Also CYP1A2, CYP2C19, and CYP2D6
- Inducers & inhibitors of these enzymes have potential to affect methadone levels


CYP450 = cytochrome P450
## Examples of Drug Interactions With Methadone

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<tr>
<th>Interaction effect</th>
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<th>Effect</th>
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<tr>
<td></td>
<td>Ketoconazole</td>
<td>Inhibit methadone metabolism (increase methadone levels)</td>
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<tr>
<td></td>
<td>Fluconazole</td>
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<td></td>
<td>Itraconazole</td>
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<td>Ciprofloxacin</td>
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<td>Biaxin</td>
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<td>Fluvoxamine</td>
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<td><strong>Inducers</strong></td>
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<td>Rifampin</td>
<td>Increase methadone metabolism (decrease methadone levels)</td>
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<td>Phenytoin</td>
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<td>Carbamazepine</td>
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<td>Ritonavir-boosted therapy</td>
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<td>Nevirapine</td>
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<td></td>
<td>Efavirenz</td>
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<tr>
<td></td>
<td>St. John’s wort</td>
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<td>Tricyclic antidepressants</td>
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<td>Ethanol</td>
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</tr>
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<td></td>
<td>Antihistamines</td>
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Pharmacogenetics

- Individual genetics that determine CYP450 enzyme activity affect methadone metabolism
  - For example, a CYP2B6 gene variant is linked to slow methadone metabolism
    - Methadone plasma levels are increased
    - Potentially higher risk of methadone-associated deaths
    - Methadone dose requirement* may be reduced in carriers of this genotype

*Studied for treatment of opioid addiction


Baseline Electrocardiograms

- Obtain ECG prior to initiating methadone in patients with:
  - Risk factors for QTc interval prolongation
    - Electrolyte abnormalities
    - Impaired liver function
    - Structural heart disease
    - Genetic predisposition
    - Use of drugs with QTc-prolonging properties
  - Any prior ECG with a QTc >450 ms
  - History suggestive of prior ventricular arrhythmia

- Consider ECG prior to initiating methadone in patients not known to be at higher risk for QTc interval prolongation
  - QTc interval prolongation without arrhythmia is asymptomatic

- Perform ECG at higher methadone doses

Risk of Torsades de Pointes

- Risk increases with greater prolongation of QTc interval
  - Primarily occurs with QTc intervals >500 ms
  - Risk increases starting around QTc intervals of 450 ms
- Recommendations for methadone use
  - **Baseline QTc interval >500 ms:** do not use methadone
  - **Baseline QTc interval ≥450 ms but <500 ms:** consider alternate opioids
    - Evaluate for & correct reversible causes of QTc interval prolongation before initiating methadone
  - **Baseline QTc interval <450 ms:** may start methadone with routine follow-up & monitoring

Initiating Methadone: Start at a Very Low Dose

- Safest to treat all patients as opioid naïve, regardless of prior opioid dose
  - Starting dose may not control all pain
    - Provide short-acting opioid until methadone titration complete
- Titrate slowly
  - Increase total daily dose by no more than 25%-50%, no more frequently than every 7 days

<table>
<thead>
<tr>
<th>Total daily MED</th>
<th>Healthy adults age &lt;70 years</th>
<th>Adults with chronic illness or age &gt;70 years</th>
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<tr>
<td>Opioid naïve</td>
<td>5 mg TID</td>
<td>2.5 mg TID</td>
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<td>60-100 mg</td>
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<tr>
<td>&gt;100 mg</td>
<td>5 mg TID</td>
<td>5 mg TID</td>
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MED=morphine equivalent dose

Legal Review of Opioid Deaths: Methadone

- Starting doses 20 mg-140 mg/day
  - Most <30 mg/day
- ~90% opioid tolerant
- ~80% died within 4 days of first methadone
- Snoring common
- Occasional upper respiratory infection/flu onset preceding death

Malpractice Case Study

- 48-year-old woman with rheumatoid arthritis & chronic low back pain
- PCP prescribed
  - IR oxycodone to treat around-the-clock pain
  - Methadone as needed for breakthrough pain
- Pain relief was inconsistent, various medications were tried
- Prior to her death:
  - 4 hydrocodone/acetaminophen 10 mg up to 4 times a day
  - Fearing acetaminophen poisoning, PCP switched to methadone 20 mg TID or as needed up to 60 mg/day

Respiratory Depression

- Because of variations in individual patient metabolism, including speed of distribution & vulnerability to respiratory depressant effects, methadone calls for:
  - An individualized approach to prescribing
  - Close monitoring
  - Consider co-prescribing naloxone to reduce overdose deaths
    - Develop an opioid emergency plan with family members/caregivers

Sedation

• Common with any opioids
• Methadone-specific pharmacologic properties require special caution
• Pay particular attention to signs of sedation as a possible warning sign of respiratory depression
  ▪ Patients initiated on methadone may experience high level of sedation, but not achieve sufficient analgesia
• Reduce methadone dose if sedation occurs

Case: A Methadone-Related Death

- Peter: a 44-yr-old slender male
- First visit w/ Dr Jones
- Chronic daily neck pain (intensity 7/10), s/p 2 cervical fusions
- Tried:
  - Physical therapy
  - TENS
  - Multiple meds

TENS=transcutaneous electrical nerve stimulation
Dr Jones sees him monthly, & prescribes:
- amitriptyline 100 mg QHS
- gabapentin 600 mg TID
- celecoxib 200 mg QD
- cyclobenzaprine 10 mg TID
- diazepam 5 mg TID
- hydrocodone/APAP 5 mg/325 mg PRN

Still no improvement

On 4th visit, Dr Jones
- Starts methadone at 10 mg BID #60
- Refers to see a pain specialist in 1 month
A Methadone-Related Death

- Next day
  - Peter’s pain was better
  - His wife noticed he was sleepy
- Next 2 days
  - Progressively more sleepy
  - Fell asleep watching TV
  - Snored loudly at night
- Morning of day 4
  - Wife awoke to find Peter dead
A Methadone-Related Death: Medical Examiner Findings

- Toxic methadone levels in Peter’s blood
- Count revealed 4 pills unaccounted for
- Key points
  - Starting dose too high
  - Peter should have been counseled: Not to take extra methadone
  - To report sedation
  - Concomitant CNS depressants increase respiratory depression risk
  - Ask about signs of sleep apnea

CNS=central nervous system

<table>
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<tr>
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<th>Sample Type</th>
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**ANALYTICAL FINDINGS**

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**Office of the Chief Medical Examiner State of USA**
1313 Mockingbird Ln. (555) 867-5309

**TOXICOLOGY REPORT**
LAB NUMBER: 007  DECEASED: Peter Smith  ME CASE NUMBER: 007-01

Dr. Sue Jones

MBolte, PhD
Director of Toxicology
Sleep-Disordered Breathing

- Respiratory depression is a risk, particularly during sleep.
- One study found a positive correlation between methadone dose & central sleep apnea in chronic pain patients.
  - 75% of patients on chronic opioid therapy had sleep disordered breathing.
- In another study, 30% of patients treated for addiction on clinically stable doses of methadone had central sleep apnea.

Sleep Disorders & Opioids: Events per Hour

Bars indicate hi/lo of 95% CI

n = 140

AHI=apnea-hypopnea index
CAI=central apnea index
OMAI=obstructive & mixed apnea Index

Sleep-Disordered Breathing is a Risk for Patients on Methadone

- Prior to initiating methadone for pain:
  - Question patients about history, signs, & symptoms of sleep apnea
  - Conduct a sleep study in any patient with signs of sleep-disordered breathing
  - Consider a sleep study for all patients to be treated with moderate-to-high methadone doses
    - Conservative “safety first” approach is to perform sleep study for patients currently taking or whose daily dose is expected to exceed >50 mg methadone/day or >150 mg MED/day
- Two main types of sleep study are polysomnography performed in a sleep laboratory or a home sleep study

MED=morphine equivalent dose

Patient Risk Stratification After Initial Sleep Study

| Level 3 (highest risk) | • Taking around-the-clock opioids with CAI ≥5 events/hour  
• Taking around-the-clock opioids with AHI ≥30 events/hour |
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<tbody>
<tr>
<td>Level 2 (moderate risk)</td>
<td>• Taking around-the-clock opioids with AHI ≥5 events/hour</td>
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<tr>
<td>Level 1 (lowest risk)</td>
<td>• Patients with AHI &lt;5 events/hour</td>
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CAI=central apnea index; AHI=apnea-hypopnea index

- Consult with a sleep specialist for assistance in choosing the appropriate therapy
- If sleep apnea does not respond, it may be necessary to reduce the methadone dose

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<tr>
<td>1.</td>
<td>Assess patients for risk of abuse before starting opioid therapy and manage accordingly</td>
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<td>2.</td>
<td>Watch for and treat comorbid mental disease if present</td>
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<td>3.</td>
<td>Conventional conversion tables can cause harm and should be used cautiously when rotating (switching) from one opioid to another</td>
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<td>4.</td>
<td>Avoid combining benzodiazepines with opioids, especially during sleep hours</td>
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<td>5.</td>
<td>Start methadone at a very low dose and titrate slowly regardless of whether your patient is opioid tolerant or not</td>
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<td>6.</td>
<td>Assess for sleep apnea in patients on high daily doses of methadone or other opioids and in patients with a predisposition</td>
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<td>7.</td>
<td>Tell patients on long-term opioid therapy to reduce opioid dose during upper respiratory infections or asthmatic episodes</td>
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<td>8.</td>
<td>Avoid using long-acting opioid formulations for acute, post-operative, or trauma-related pain</td>
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Patient Education

• Common opioid-related risks, benefits, & AEs
• Methadone-specific risks that may be associated with overdose
  - Long & variable half-life
  - Potential for drug-drug interactions
  - Potential association between methadone & QTc interval prolongation

Patient Education

• Methods to mitigate risks
  ▪ Take methadone exactly as prescribed
    − Never take an extra dose without checking with the prescriber
  ▪ Adhere with recommended follow-up & monitoring
  ▪ Disclose methadone use to other providers
    − Avoid drug-drug interactions
  ▪ Withhold additional methadone doses & contact prescriber if signs of respiratory depression or somnolence occur
    − Teach family members to recognize & respond to signs of opioid overdose
  ▪ Never share methadone
  ▪ Store methadone in a safe place


Questions & Answers

Please type your question in the text chat box
PCSS-O Colleague Support Program

- PCSS-O Colleague Support Program is designed to offer general information to health professionals seeking guidance in their clinical practice in prescribing opioid medications.
- PCSS-O Mentors comprise a national network of trained providers with expertise in addiction medicine/psychiatry and pain management.
- Our mentoring approach allows every mentor/mentee relationship to be unique and catered to the specific needs of both parties.
- The mentoring program is available at no cost to providers.

For more information on requesting or becoming a mentor visit: pcss-o.org/ask-colleague

- Listserv: A resource that provides an “Expert of the Month” who will answer questions about educational content that has been presented through PCSS-O project. To join email: pcss-o@aaap.org.
PCSS-O is a collaborative effort led by American Academy of Addiction Psychiatry (AAAP) in partnership with: Addiction Technology Transfer Center (ATTC), American Academy of Neurology (AAN), American Academy of Pain Medicine (AAPM), American Academy of Pediatrics (AAP), American College of Physicians (ACP), American Dental Association (ADA), American Medical Association (AMA), American Osteopathic Academy of Addiction Medicine (AOAAM), American Psychiatric Association (APA), American Society for Pain Management Nursing (ASPMN), International Nurses Society on Addictions (IntNSA), and Southeast Consortium for Substance Abuse Training (SECSAT).

For more information visit: [www.pcss-o.org](http://www.pcss-o.org)
For questions email: [pcss-o@aaap.org](mailto:pcss-o@aaap.org)

Twitter: [@PCSSProjects](https://twitter.com/PCSSProjects)

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