Methadone for Pain Management: The Clinician’s Role in Reducing the Risk for Overdose

Clinician Outreach and Communication Activity (COCA) Conference Call
August 1, 2012
Objectives

At the conclusion of this session, the participant will be able to accomplish the following:

- Discuss the role of methadone in fatal drug overdoses in the United States
- Compare and contrast methadone prescribing to other opioid analgesics
- State circumstances under which use of methadone might be appropriate
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TODAY’S PRESENTER

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Methadone for Pain Management: The Clinician’s Role in Reducing the Risk for Overdose

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Division of Unintentional Injury Prevention
National Center for Injury Prevention and Control

CDC Clinical Outreach Communications Activity
August 1, 2012
Motor vehicle traffic, poisoning, and drug poisoning death rates of all intents, U.S., 1980-2009

Source: NCHS Data Brief, December, 2011, updated with 2009 mortality data.
Drug overdose deaths of all intents by major drug type, U.S., 1999-2009

Drug overdose deaths of all intents by type of opioid involved, US, 1999-2009

- Methadone
- Hydrocodone, oxycodone, morphine, codeine, hydromorphone, et al.
- Fentanyl, meperidine, propoxyphene, buprenorphine, et al.
Rising rates of methadone use for pain, methadone-related overdose deaths, and methadone prescriptions for pain, United States
## State studies of medical examiner data on methadone overdoses

<table>
<thead>
<tr>
<th>State/Author</th>
<th>Year of Deaths</th>
<th>Number of Deaths</th>
<th>Pct in OTP</th>
<th>Pct with Rx</th>
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</thead>
<tbody>
<tr>
<td>Utah/Sundwall</td>
<td>1999-2003</td>
<td>114</td>
<td>unknown</td>
<td>42%</td>
</tr>
<tr>
<td>Oregon/DOH</td>
<td>2002</td>
<td>103</td>
<td>~25%</td>
<td>33%</td>
</tr>
<tr>
<td>Kentucky/Shields</td>
<td>2000-04</td>
<td>95</td>
<td>10%</td>
<td>48%</td>
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<tr>
<td>Maryland/Anon</td>
<td>2004-05</td>
<td>52</td>
<td>15%</td>
<td>2%</td>
</tr>
<tr>
<td>West Virginia/Paulozzi</td>
<td>2006</td>
<td>87</td>
<td>12%</td>
<td>32%</td>
</tr>
<tr>
<td>North Carolina Medicaid/Whitmire</td>
<td>2007</td>
<td>98</td>
<td>8%</td>
<td>15%</td>
</tr>
</tbody>
</table>
Number of drug-related deaths involving opioids, by type of opioid—Drug Abuse Warning Network Medical Examiner System, 13 states*, 2009

*DE, MA, MD, ME, NH, NM, OK, OR, RI, UT, VA, VT, and WV
MME = morphine milligram equivalent
Rates of drug-related deaths involving opioids, by type of opioid—Drug Abuse Warning Network Medical Examiner System, 13 states*, 2009

*DE, MA, MD, ME, NH, NM, OK, OR, RI, UT, VA, VT, and WV
MME = morphine milligram equivalent
Distribution of methadone prescriptions by prescriber specialty, US, 2009

- Primary care MD: 24
- Mid-level: 6
- Anesthesiology/Pain Med: 18
- Other specialty: 9
- Unspecified: 43

Source: SDI, Vector One: National. Extracted July 2010
Analysis by Laura Governale of FDA presented at the SAMHSA Methadone Mortality Meeting, July 29, 2010

Musculoskeletal disease, 46
Headache, 17
Cancer, 11
All others, 13

Drug abuse/dependence 4%
General symptoms 4%
Trauma 5%

Source: SDI, Physician Drug and Diagnosis audit. Extracted July 2010
Analysis by Laura Governale of FDA presented at the SAMHSA Methadone Mortality Meeting, July 29, 2010
Percentage of opioid distribution accounted for by methadone prescribed for pain by state

United States, 2010
Methadone as a preferred long-acting opioid analgesic on the Medicaid formulary, US, 2012
Role of states in prevention

- Develop and promote the use of safe prescribing guidelines for methadone.
- Use prescription drug monitoring programs to identify patients who are using methadone or other prescription painkillers for nonmedical purposes.
- Continue to support the use of methadone as a treatment for opioid dependence in opioid treatment programs.
Role of health insurers in prevention

- Evaluate methadone’s place on preferred drug lists.
- Consider strategies to ensure that pain treatment with any dose higher than 30 mg of methadone a day (the recommended maximum daily starting dose) is appropriate.
Role of health care providers in prevention

- Follow guidelines for prescribing methadone and other prescription painkillers correctly.
- Educate patients on how to safely use, store, and dispose of methadone.
Thank You

www.cdc.gov/homeandrecreational safety/poisoning

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Methadone for Pain

A Guide for Prescribers

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Disclosures

No conflicts of interest

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- Center for Medicare and Medicaid Innovation: U of New Mexico*, NIH R01, STTR, HRSA. TelePain access for remote interspecialty management of complex disease
- Unrestricted educational grant Endo Pharmaceuticals. University of Washington Pain Champions: Look Over the Expert’s Shoulder/Pain Champions.
Objectives

• Understand indications for use of methadone
• Be knowledgeable about risks of methadone
• Follow safe methadone dosing practice
• Know why and how to apply guidelines for opioid monitoring
Methadone Basic Clinical Pharmacology

• Potent Mu-agonist
• Absorption variability
  – Oral 36-100%
  – Peak plasma 3-4 hrs (up to 1-8 hrs)
• 30-fold inter-patient variability
  – In steady-state concentrations
  – In peak concentrations
• Expect age and illness related increased toxicities
• Frequent drug-to-drug interactions
• Hepatic CYP metabolism
• No active hepatic metabolites
Methadone Special Features

• NMDA antagonist
  – May reduce opioid tolerance
  – Potential non-opioid analgesic effects

• Weak 5-HT/NE Reuptake Inhibitor
  – May also add benefit for neuropathic pain disorders

• Significant accumulation with repeat dosing
  – Initial T½ 13-47 hrs ➔ 48-72 hrs
  – Lipophilic & Protein-bound
  – Inhibits its own CYP metabolism
    
    <20 mg = 3-4 x MS
    30-40 mg = 8 x MS
    40-60 mg = 10 x MS
    >60 mg = 12 x MS
Indications for Methadone Use

✓ For Pain Treatment
  – Effective analgesic
  – Chronic Opioid Therapy
  – Long acting
  – Inexpensive

✓ For Addiction Treatment
  – Requires special DEA licensing and treatment support
  – Once daily liquid dosing eases administration
  – Reduces mortality among heroin users
Clinically Important Comparison: Methadone vs. other Opioids

**Differences:**
- Marked inter-patient pharmacologic variability
- Significant accumulative dosing potency
- Higher OD incidence and mortality
- Indications:
  - When committed to Chronic Opioid Treatment
  - So-called ‘last resort’

**Similarities:**
- Monitoring approach
- Side-effects
  - Sedation
  - Respiratory suppression
  - Anticholinergic
  - Cardiac
- Addiction and diversion risks
Methadone M & M

- Adverse events typically occur early in Rx initiation
  - For Pain treatment and for MMT
- Co-prescription with sedatives adds significant risk
  - Benzodiazepines
  - Carisoprodol
  - Alcohol
- Co-occurring respiratory disorder increases risk
  - Obstructive and Restrictive Lung disease
  - Sleep apnea
- QTc prolongation and arrhythmia risk at higher doses and when used with other drugs that prolong QTc
“Prescribing methadone is complex. Methadone should only be prescribed for patients with moderate to severe pain when their pain is not improved with other non-narcotic pain relievers. Pain relief from methadone lasts about 4 to 8 hours. However, methadone stays in the body much longer, from 8 to 59 hours after it is taken. As a result patients may feel the need for more pain relief before methadone is gone from the body. Methadone may build up in the body to a toxic level if it is taken too often, if the amount taken is too high, or if it is taken with certain other medications or supplements.”

2. Emphasis added
Risks Factors for QTc Prolongation

- Older age; esp. women
- Co-occurring cardiac disease
  - Advanced heart disease
  - Congenital and acquired long-QT syndromes
  - Family history of sudden death
- Low $K^+$, Low $Mg^{++}$

Concomitant use of other QTc prolonging Rx
- $Ca^{++}$ blockers, propafenone, quinidine
- Tricyclics, SNRIs, and SSRIs
- Erythromycin, azithromycin, clarithromycin, quinolones, pentamidine
- Ondansetron, risperidone

>450-499 msecs: Monitor more frequently
≥500 msecs: Consider discontinuation

Methadone Levels and QTc Prolongation

Red dots: prolonged QTc
Yellow dots: borderline QTc intervals
Green dots: normal QTc values

Torsade de Pointes

Methadone dose range 65-1,000 mg
(780-12,000 MED)
Most doses >250 mg (>3000 mg MED)
Review of case series and reports

3Cruciani RA., J Pain Sympt Manage 2008; 36: 545-552
Drug-drug interactions
CYP 3A4 inhibitors (RAISE methadone levels)

Use with caution—moderate risk:

Antibiotics
- Protease inhibitors (ritonavir, nelfinavir, indinavir)
- Macrolides (erythromycin, clarithromycin)
- Azole antifungals (ketoconazole, itraconazole)
- Quinilones (ofloxacin, moxifloxin)
- Others (tetracycline, metronidazole, pentamidine)

Other often used drugs
- Trazodone, haloperidol, respirdone, ondansetron, chlorpromazine, droperidol
Less potent CYP 3A4 inhibitors
Still use caution: may RAISE methadone blood level

Antibiotics
  - saquinavir, fluconazole, clotrimazole

Psychiatric Rx
  - amitriptyline, desipramine, fluoxetine, fluvoxamine, imipramine, sertraline, venlafaxine
  - olanzapine, quetiapine

Foods & beverages
  - grapefruit (especially juice)

Naturopathics
  - St. John’s wort, valerian
CYP 3A4 **Inducers**

*LOWERS* methadone blood levels

May need to *dose increase* to maintain analgesia and/or prevent withdrawal

- Carbamazepine
- Diphenylhydantoin
- Rifampin
Other drugs associated with *Torsade de Pointes*

---Avoid concurrent use with methadone---

- **Cardiac**
  - amiodarone, bepridil, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol,

- **GI motility & antinausea**
  - Chlorpromazine, cisapride, domperidone, droperidol

- **Antibiotics**
  - clarithromycin, erythromycin, sparfloxacin

- **Antipsychotics**
  - Haloperidol, mesoridazine, thioridazine, pimozide
Common Clinical Methadone Concerns

- Anticholinergic
  - Urinary retention
  - Constipation
  - Dry mouth
- Weight gain
- Heavy sweating
- Reduced motor coordination
- Cognitive impairments

- Reduced sex hormone release
- Pregnancy cat. C
  - Withdrawal precipitated miscarriage
  - Neonatal abstinence
  - For opioid addicted pregnant women methadone maintenance is standard of care\(^1\)
  - Volume of distribution increases in 3\(^{rd}\) trimester usually dictating need for a dosage increase\(^1\)

\(^1\)Andrew Saxon, personal communication
Overview of Methadone Dosing

• “Go low and slow”:
  – Start: 2.5 mg/day BID-TID
  – Increase: at 5-10 day intervals

• Use in opioid-naïve patients: probably never
  – Risk of accidental OD when not tolerant
  – When committing to COT
    “when... pain is not improved with other non-narcotic pain relievers”

• Age ± disease related metabolic adjustments: always
• Drug-drug interactions: when appropriate

1FDA Advisory 2006: http://www.fda.gov/CDER/drug/advisory/methadone.htm
Dosing Recommendations
VA/DoD Guidelines Up-Titration

- Dose increments of 2.5 mg q 8 h made every 5-7 d
- Dose increases after 5 to 74 days if no problem with daytime sedation

**NOTE:** Half-life longer than duration of analgesia
Washington State Agency Medical Directors Group: Opioid Dose Calculator

120 mg MED dose threshold for “specialty consultation”

- if high risk and/or adverse effects or lack of functional response

www.agencymeddirectors.wa.gov/guidelines.asp
Conversion Dosing Recommendations
Morphine into Methadone

- 50-67% of calculated equianalgesic dose is conversion dose
- Calculation varies with the total daily dose
- Dose proportion is dependent on MED of previous opioid (PO)

  - Morphine < 200 mg/day:
    Methadone 5 mg q8 hr*
    (*in opioid tolerant patient)
  - Morphine 200-500 mg:
    5-10% of oral MED, given in divided doses q 8 hr
  - MED > 500 mg/day:
    Get expert help

VA/DoD Clinical Practice Guideline for the Management of Chronic Pain 2003 v.1
“Rotation” onto Methadone

• Typically can reduce dose to **10-50% of current MED**
• High but ineffective doses of previous opioids *may overestimate the methadone dose*¹
• Analgesic effects can range 4-13 days to stabilize
  – Repetitive dose equianalgesia at just 10-20%²
  – Reduction in the calculated equianalgesic dose *in all cases*³
• Conversion ratios are *not* bi-directional
• Specific reduction formula based on the MED of the opioid taken at the time of the switch
  – *Methadone potency rises as its dose is increased!!*

¹VA/DoD Clinical Practice Guideline for the Management of Chronic Pain 2003 v.1
Methadone Risk Monitoring

• Similar to Other Long-Acting Opioids
  – Opioids are High Risk Drugs
  – Highest doses given to highest risk patients
    “Principal of adverse selection”

• Chronic Opioid Therapy Risk Assessment Tools- *Use prior to initiation of COT*:
  – ORT, or SOAPP-R or DIRE
  – CAGE-ID or AUDIT

Sullivan MD., Pain 2010: 151; 567–568
### Opioid Risk Tool (ORT)

**Physician Form**

With Item Values to Determine Risk Score

<table>
<thead>
<tr>
<th>Name ____________________________</th>
<th>Date ____________</th>
</tr>
</thead>
</table>

#### 10 Questions to Administer:

- On initial visit for ALL new or inherited COT patients
- _Prior_ to LA Opioid Therapy

### Scoring

- **0-3**: low risk (6%)
- **4-7**: moderate risk (28%)
- **> 8**: high risk (> 90%)

<table>
<thead>
<tr>
<th>Mark each box that applies</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Family history of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>[ ] 1</td>
<td>[ ] 3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>[ ] 2</td>
<td>[ ] 3</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>[ ] 4</td>
<td>[ ] 4</td>
</tr>
<tr>
<td>2. Personal history of substance abuse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>[ ] 3</td>
<td>[ ] 3</td>
</tr>
<tr>
<td>Illegal drugs</td>
<td>[ ] 4</td>
<td>[ ] 4</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>[ ] 5</td>
<td>[ ] 5</td>
</tr>
<tr>
<td>3. Age (mark box if 16-45 years)</td>
<td>[ ] 1</td>
<td>[ ] 1</td>
</tr>
<tr>
<td>4. History of preadolescent sexual abuse</td>
<td>[ ] 3</td>
<td>[ ] 0</td>
</tr>
<tr>
<td>5. Psychological disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, bipolar disorder, schizophrenia</td>
<td>[ ] 2</td>
<td>[ ] 2</td>
</tr>
<tr>
<td>Depression</td>
<td>[ ] 1</td>
<td>[ ] 1</td>
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<table>
<thead>
<tr>
<th>Low (0-3) Moderate (4-7) High (≥8)</th>
<th>Scoring totals</th>
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</table>

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## Adherence Monitoring

*Urine toxicology based on risk assessment score*

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>UDT Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk by ORT</td>
<td>Periodic (e.g. up to 1/year)</td>
</tr>
<tr>
<td>Moderate Risk by ORT</td>
<td>Regular (e.g. up to 2/year)</td>
</tr>
<tr>
<td>High Risk by ORT or opioid doses $&gt;120$ mg MED/d</td>
<td>Frequent (e.g. up to 3-4/year)</td>
</tr>
<tr>
<td>Aberrant Behavior (lost prescriptions, multiple requests for early refills, opioids from multiple providers, unauthorized dose escalation, apparent intoxication, etc.)</td>
<td>At time of visit (Address aberrant behaviors in person, not by telephone)</td>
</tr>
</tbody>
</table>

Methadone Urine Monitoring

• Point of Care
  • *Generally* reliable
  • Detection for 3-14 days
  • Expect 20+% false results

False positives:
  Chlorpromazine
  Clomipramine
  Diphenhydramine
  Doxylamine
  Quetiapine
  Thioridazine
  Verapamil

• Confirmation testing by LC or GC/MS
  • When results are unexpected *AND* patient does not admit to use of drugs identified on initial testing
  • Can request reflex confirmation when false positives and negative results are expected
  • Adulterants can interfere with confirmation assay

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1 Christo PJ., Manchikanti L., Ruan X. Pain Physician 2011; 14:123-143
2 Herring C., Muzyk AJ., Johnston C. J Pharm Pract 2011 24: 102
Adherence Monitoring
Currently Available Solutions

Prescription Monitoring
State level programs capturing all scheduled medication prescribing, even cash purchased

Emergency Department Information Exchange(s)
Save $70-100,000/year in reduced admissions, labs, excessive exposures to CT imaging in emergency rooms by utilizing this system

Monitoring Co-occurring Conditions

• Sleep apnea
  – *STOP-BANG* screening tool¹

• Depression, Anxiety, PTSD
  – PHQ-9, GAD-7, PCL-C²

• Drug-drug interactions/poly-pharmacy
  – Rx Reconciliation and/or shared EMR system

• Cardiac
  – Advanced heart disease or h/o sudden death
  – “..To ECG or Not to ECG... That Is Still the Question”³

²UW Pain Toolkit http://depts.washington.edu/anesth/education/pain/index.shtml
³Cruciani RA., J Pain Sympt Manage 2008; 36: 545-552
Guidelines for Tapering Methadone

• Decrease 20-50% until 30 mg; then by 5 mg/day q 3-5 d until 10 mg/d; then by 2.5 mg/d every 3-5 d\(^1\)
• Decrease 10% weekly, use clonidine for symptom management\(^2, 3\)
• Taper 10% weekly until 30% of initial total MED, then resume by 10% less of new dose weekly\(^4\)
• Taper 10% of daily dose/day to 30% of daily dose every 1-2 wks, once 1/3 of original dose is reached, slow taper to ½ of previous rate\(^5\)

\(^1\)VA/DoD 2010
\(^2\)WA AMDG Guidelines 2007
\(^3\)Utah State Guidelines 2008
\(^4\)WA State HCA NRP Program 2011
\(^5\)Canadian Guidelines 2010
Tapering Methadone
Some Clinical Caveats

• If “Addiction” (aka “Substance use disorder”)
  – >90% relapse onto opioids, prescribed or otherwise

• Following prolonged epoch of high dose use
  – Many patients “de-stabilize” and demonstrate behaviors meeting DSM criteria for SUD
    (aka “Complex persistent opioid dependency”)
  – Often requires protracted taper schedule with frequent plateaus based on clinical response
  – Best outcomes require significant behavioral health support
Prescribing Methadone
Conclusions

• Effective analgesic
• Inexpensive
• Analgesic interval shorter than half-life
• Enormous inter-patient variability
• Accumulative potency/complex dosing
• Complicated DDI and metabolic interactions
• When used carefully---both effective and safe
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Atlanta, Georgia
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