

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

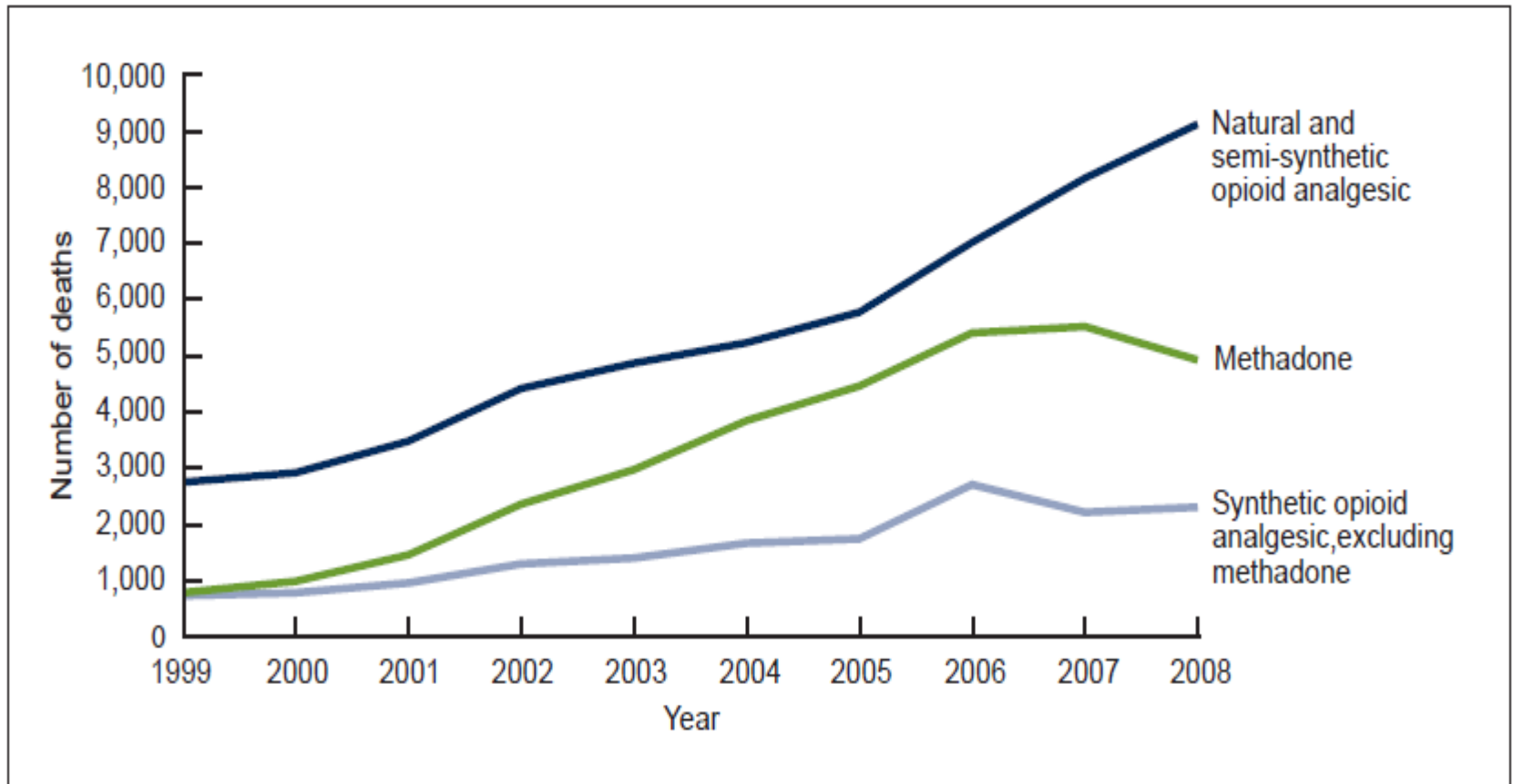
**“Methadone Use for Pain Control May
Result in Death and Life-Threatening
Changes in Breathing and Heart Beat”**

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

Methadone

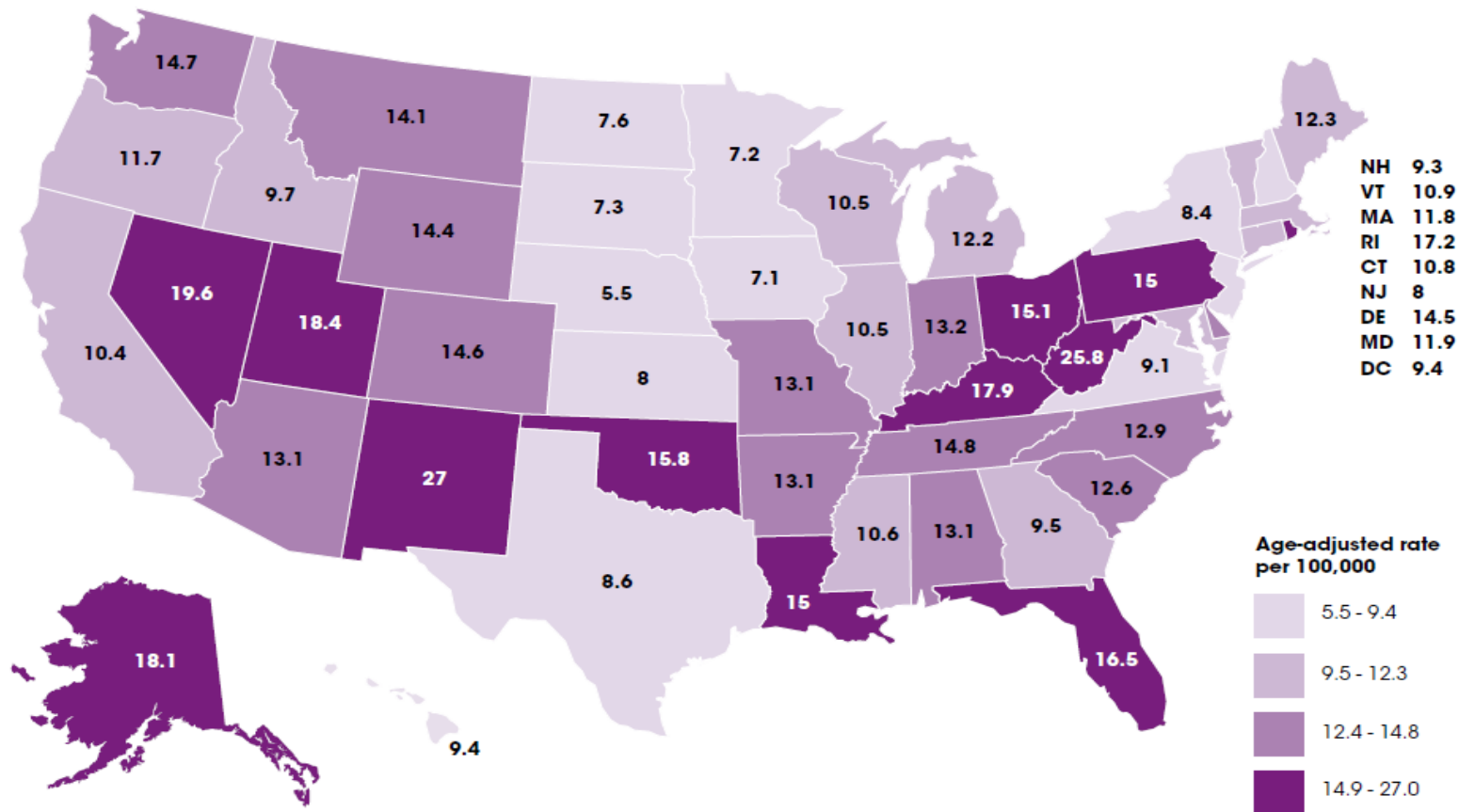
- **Synthetic opioid use for treatment of opioid dependence and treatment of *chronic* pain**
- **Large increase in number of methadone associated deaths**
 - 1999: 800
 - 2007: 5,500
 - 2008: 4,900
- **Part of larger trend regarding prescription opioids**
 - Rate of increase in methadone-associate deaths larger than for any other opioids

Figure 4. Number of drug poisoning deaths involving opioid analgesic by opioid analgesic category: United States, 1999–2008

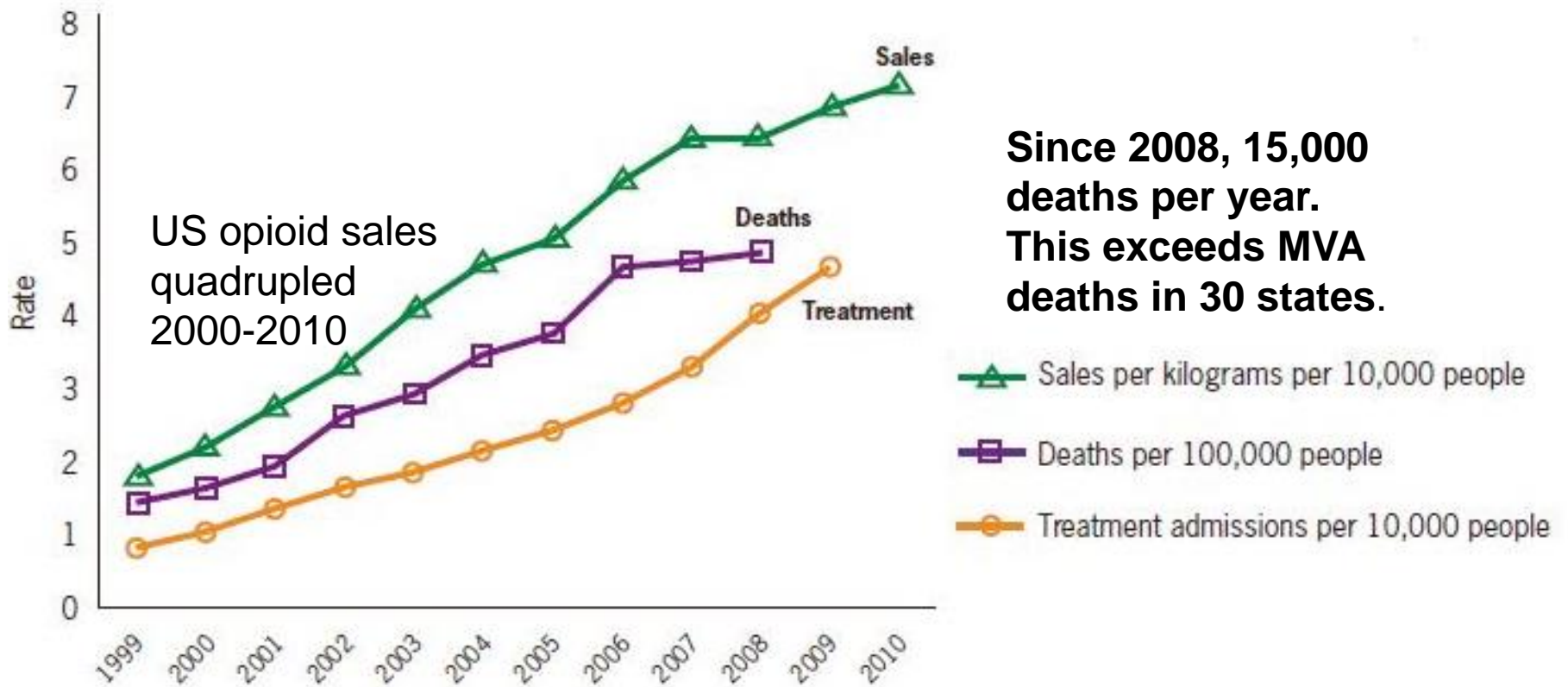


Source: NCHS Data Brief, December 2011

Drug overdose death rates by state, 2008⁴



Rates of prescription painkiller sales, deaths, and substance abuse treatment admissions (1999-2010)



SOURCES: National Vital Statistics System, 1999-2008; Automation of Reports and Consolidated Orders System (ARCOS) of the Drug Enforcement Administration (DEA), 1999-2010; Treatment Episode Data Set, 1999-2009

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**

^aMMWR 2012;61:493-7

^bMorley et al. Palliative Med

2003

Costs of long-acting opioids

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

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)

Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database of Systematic Reviews 2009, Issue 3.

Methadone deaths in patients in opioid treatment programs

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

*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

Research Gaps on Methadone Harms and Comparative Harms: 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

Strength of Recommendation	Quality of Evidence			
<i>Strong</i>	High	Moderate	Low	Very Low
<i>Weak</i>	High	Moderate	Low	Very Low

Patient
assessment
and
selection

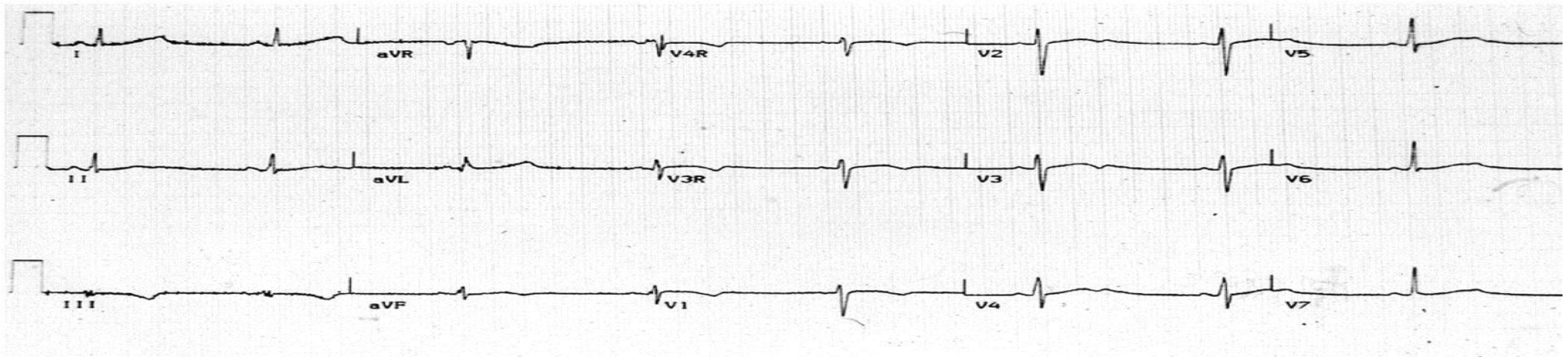
Patient
education and
counseling

Recommendations

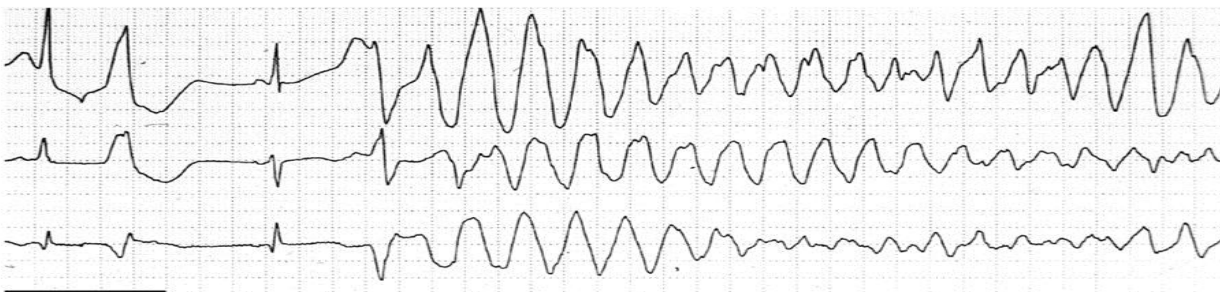
- **Perform an individualized medical and behavioral risk evaluation to assess risks and benefits of methadone (*strong recommendation, low-quality evidence*)**
- **Educate and counsel patients regarding risks and benefits prior to first prescription and periodically while taking methadone (*strong recommendation, low-quality evidence*)**

Prolonged QTc and torsades de pointes

A



B



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

Recommendation

- 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 ≥ 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

Rationale

- 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

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

Chugh SS, et al. Am J Med. 4.12.10 2008;121(1):66-71.

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

Recommendation

- 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 ≥ 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 ≥ 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

Situation	Initial dose
Risk factors for QTc prolongation, prior ECG with QTc >450 ms, or history of syncope	Follow-up ECG 2–4 weeks after initiation of methadone and following significant dose increases
Methadone dose increased	Follow-up ECG when methadone dose reaches 30 to 40 mg/day and again at 100 mg/day
New risk factors for QTc interval prolongation or signs or symptoms of arrhythmia	Follow-up ECG

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

Rationale

- **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**

Morphine to methadone conversion

24 hour total oral morphine	Oral morphine to methadone conversion ratio
<30 mg	2:1
31-99 mg	4:1
100-299 mg	8:1
300-499 mg	12:1
500-999 mg	15:1
>1000 mg	20:1

Managing Cancer Pain in Skeel ed. Handbook of Cancer Chemotherapy. 6th ed., Phil, Lippincott, 2003, p 663

Suggested dosing parameters

Population	Initial dose	Dose titration
Opioid addiction	No more than 30–40 mg/day	No more than 10 mg/day and no more frequently than every 3 to 4 days
Chronic pain, <40–60 mg/day morphine equivalent doses (MED)	2.5 mg tid	No more than 5 mg/day every 5–7 days
Chronic pain, >40–60 mg/day MED	75–90% less than calculated equianalgesic dose and no higher than 30 to 40 mg/day	No more than 10 mg/day every 5–7 days
Children	100 mcg/kg (maximum 5 mg/dose) every 6–8 hours	

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^a
 - Effects on clinical outcomes (e.g., overdose) and optimal strategies for using PDMP not known

^a*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

Rationale

- **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**

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

Recommendation

- **NAS occurs in $\frac{3}{4}$ 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*

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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- **American Pain Society**
- **College on Problems of Drug Dependence**
- **Heart Rhythm Society**

Questions?

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