



# Responsible Prescribing of Methadone for Pain Management: Safety First

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# Planning Committee, Disclosures

- Vitaly Gordin, MD  
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  - No relevant financial relationships
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- Angela Casey  
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# Target Audience

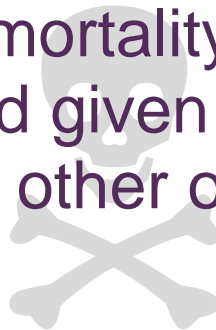
- The overarching goal of PCSS-O is to offer evidence-based trainings on the safe & effective prescribing of opioid medications in the treatment of pain &/or opioid addiction
- Our focus is to reach providers &/or providers-in-training from diverse healthcare professions including physicians, nurses, 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

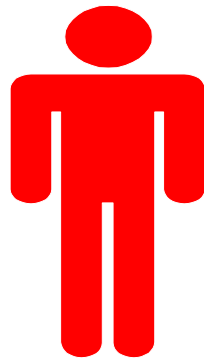
- Developed in 1937 as a synthetic opioid analgesic
  - Introduced into the United States in 1947
- Can be effective for otherwise refractory chronic pain
  - However, clinical management can be challenging
- Methadone appears in mortality reports with greater frequency than expected given the smaller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

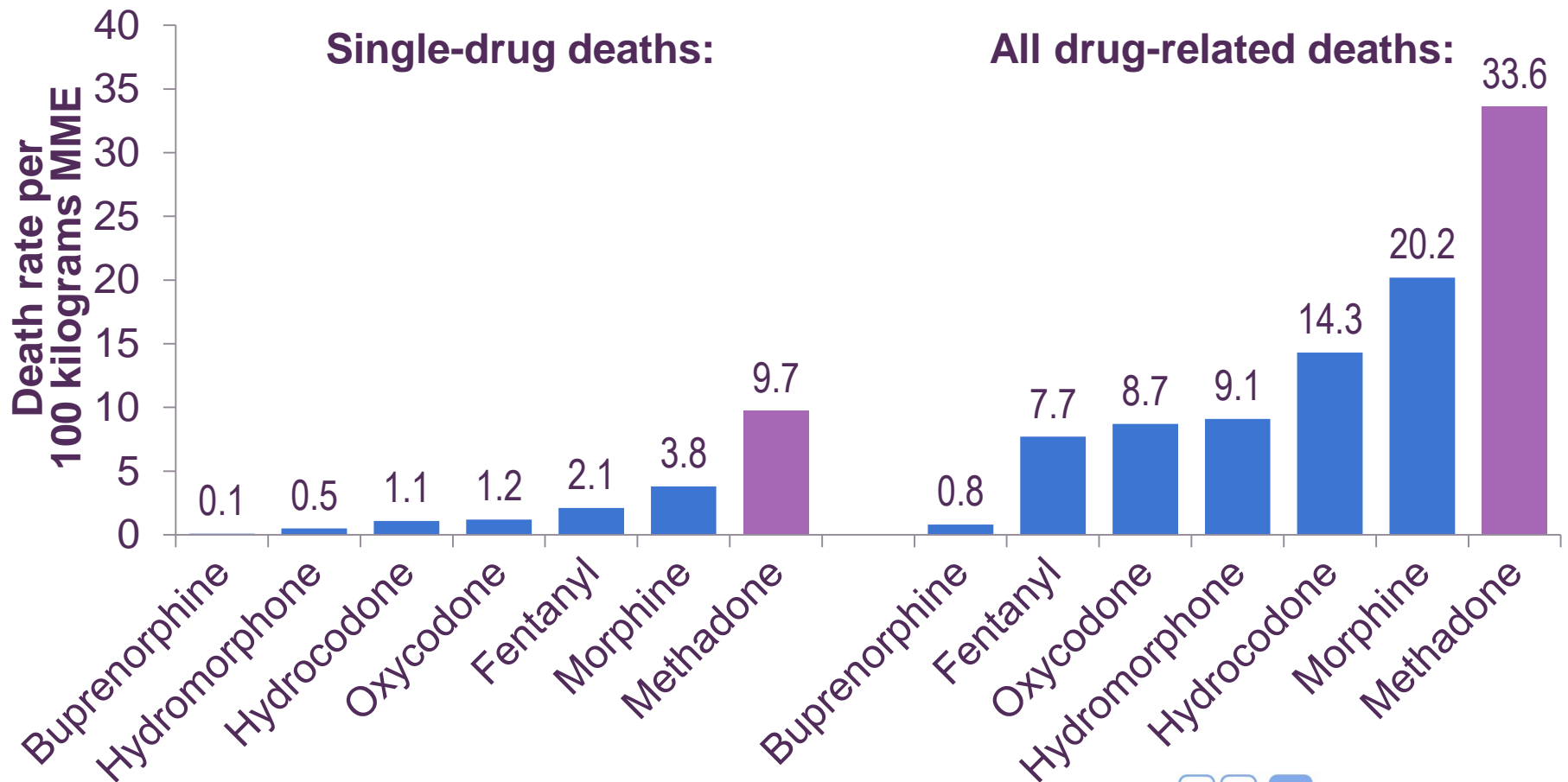


- Only 2% of opioid analgesic prescriptions were for methadone



# Death Rate from Prescription Opioids

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



# 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



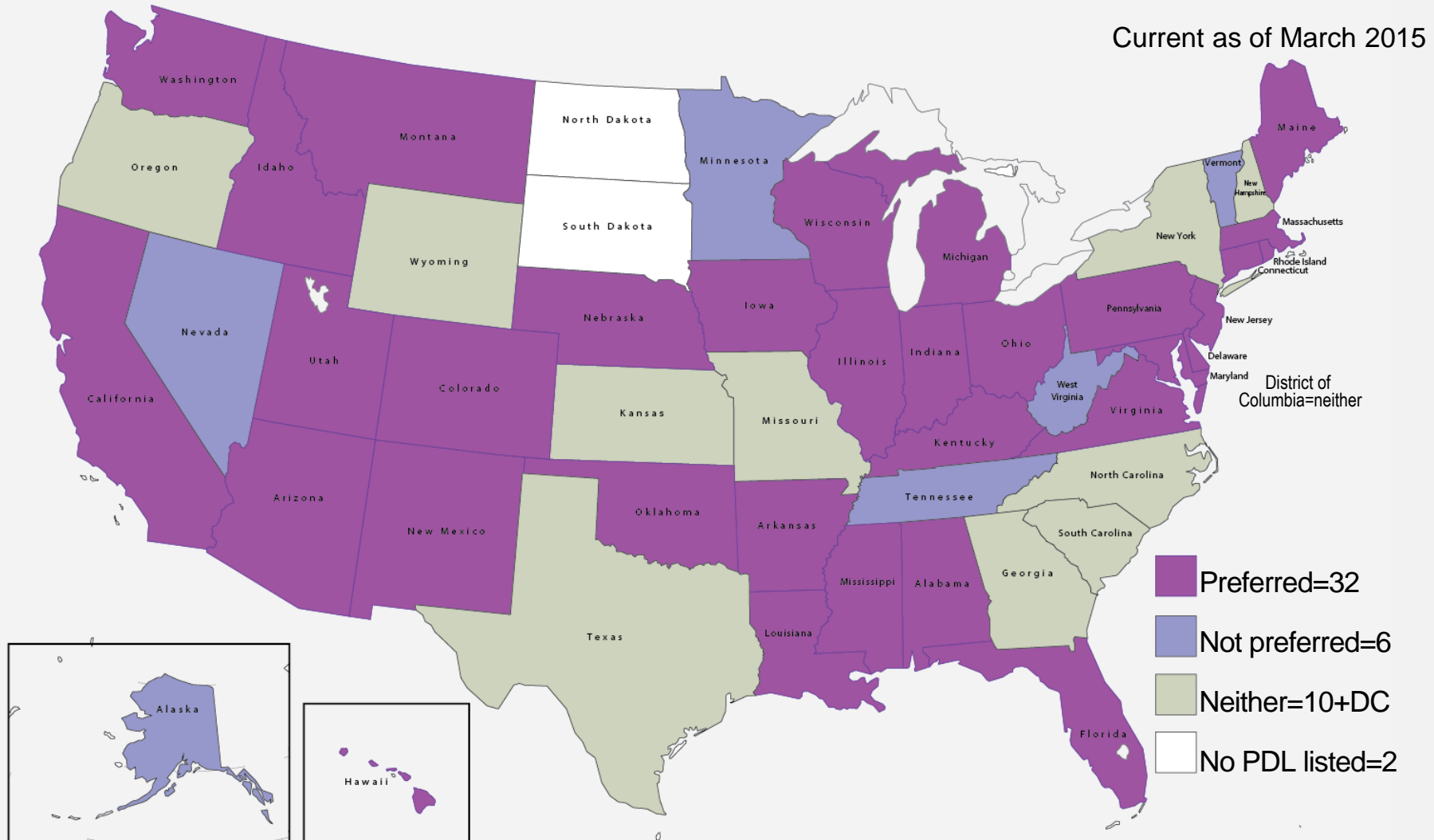
ER/LA=extended-release, long-acting

# 2012 Methadone Cost Vs Other LA Opioids

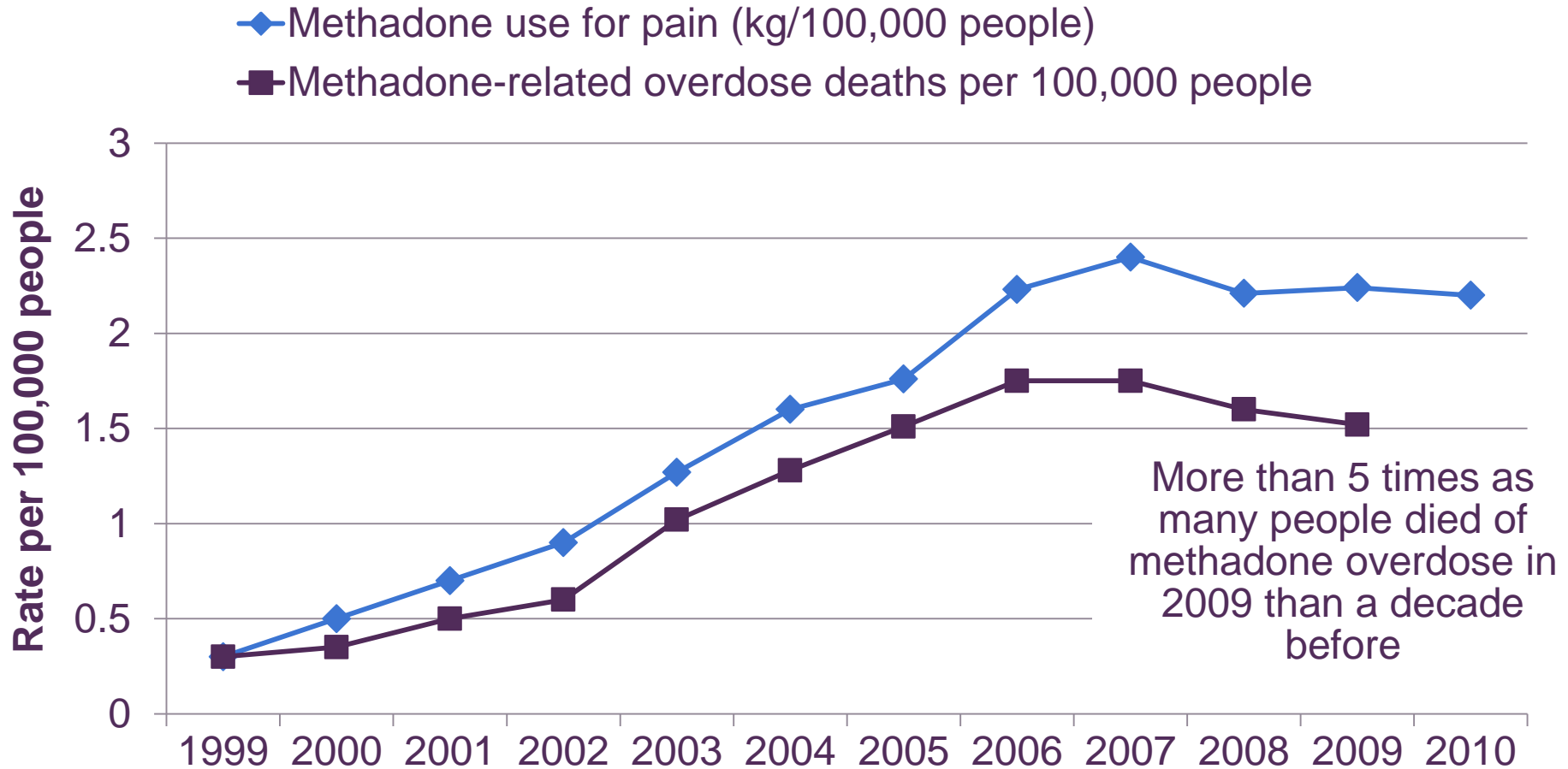
Generic name & strength	Brand name	Frequency of use	Total dose/day	Average cost/month
Buprenorphine patch 5 mcg/h	Butrans	q72h	120 mcg	\$189
Buprenorphine patch 10 mcg/h	Butrans	q72h	240 mcg	\$276
Buprenorphine patch 20 mcg/h	Butrans	q72h	480 mcg	\$495
Fentanyl patch 25 mcg/h	Duragesic	q72h	600 mcg	\$303
Fentanyl patch 25 mcg/h	Generic	q72h	600 mcg	\$126
Fentanyl patch 25 mcg/h	Duragesic	q72h	1200 mcg	\$666
Fentanyl patch 25 mcg/h	Generic	q72h	1200 mcg	\$205
Hydromorphone SR 8 mg	Exalgo	q24h	8 mg	\$349
Hydromorphone SR 12 mg	Exalgo	q24h	12 mg	\$520
Hydromorphone SR 16 mg	Exalgo	q24h	16 mg	\$520
Methadone 5 mg	Generic	q8h	15 mg	\$17
Methadone 10 mg	Generic	q8h	30 mg	\$20
Morphine ER 15 mg	Generic	q12h	30 mg	\$48
Morphine ER 30 mg	Avinza	q24h	30 mg	\$177
Morphine ER 30 mg	Kadian	q24h	30 mg	\$247
Morphine ER 30 mg	MS-Contin	q12h	60 mg	\$270
Morphine ER 30 mg	Generic	q12h	60 mg	\$72
Morphine ER 60 mg	Avinza	q24h	60 mg	\$313
Morphine ER 60 mg	Generic	q12h	120 mg	\$101
Morphine ER 90 mg	Avinza	q24h	90 mg	\$456
Morphine ER 100 mg	Kadian	q24h	100 mg	\$692
Oxymorphone SR 10 mg	Opana ER	q12h	20 mg	\$290
Oxymorphone SR 15 mg	Opana ER	q12h	30 mg	\$343
Oxymorphone SR 15 mg	Generic	q12h	30 mg	\$319
Oxymorphone SR 20 mg	Opana ER	q12h	40 mg	\$509
Oxymorphone SR 40 mg	Opana ER	q12h	80 mg	\$955
Oxycodone SR 10 mg	OxyContin	q12h	20 mg	\$164
Oxycodone SR 20 mg	OxyContin	q12h	40 mg	\$306
Oxycodone SR 40 mg	OxyContin	q12h	80 mg	\$529
Oxycodone SR 80 mg	OxyContin	q12h	160 mg	\$1,031

A Position Statement from the American Academy of Pain Medicine. *The Evidence Against Methadone as a "Preferred" Analgesic.* 2014.

# Methadone Status in State Medicaid Preferred Drug Lists

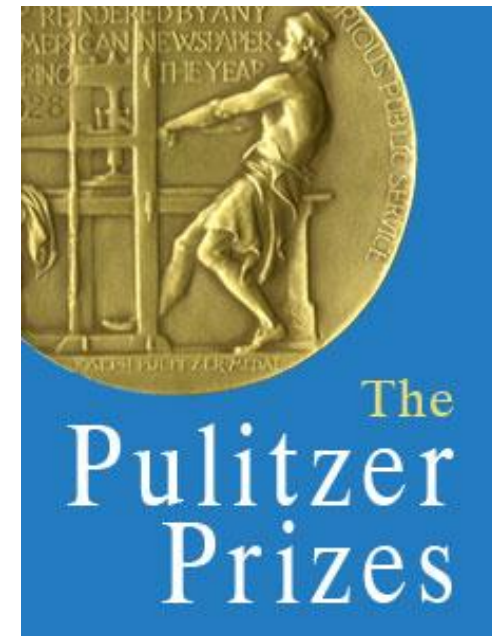


# Growth of Methadone Use for Pain & Methadone Overdose Deaths



# 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



**The Seattle Times**

The logo for The Seattle Times, featuring the text "The Seattle Times" in a serif font above a stylized eagle with its wings spread.

Berens MJ, Armstrong K. State pushes prescription painkiller methadone, saving millions but costing lives. *Seattle Times*. 12/10/2011.  
Berens MJ, Armstrong K. 'Preferred' pain drug now called last resort. *Seattle Times*. 1/27/2012  
A Position Statement from the American Academy of Pain Medicine. *The Evidence Against Methadone as a "Preferred" Analgesic*. 2014.

# Position of AAPM



- 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

AE=adverse effect

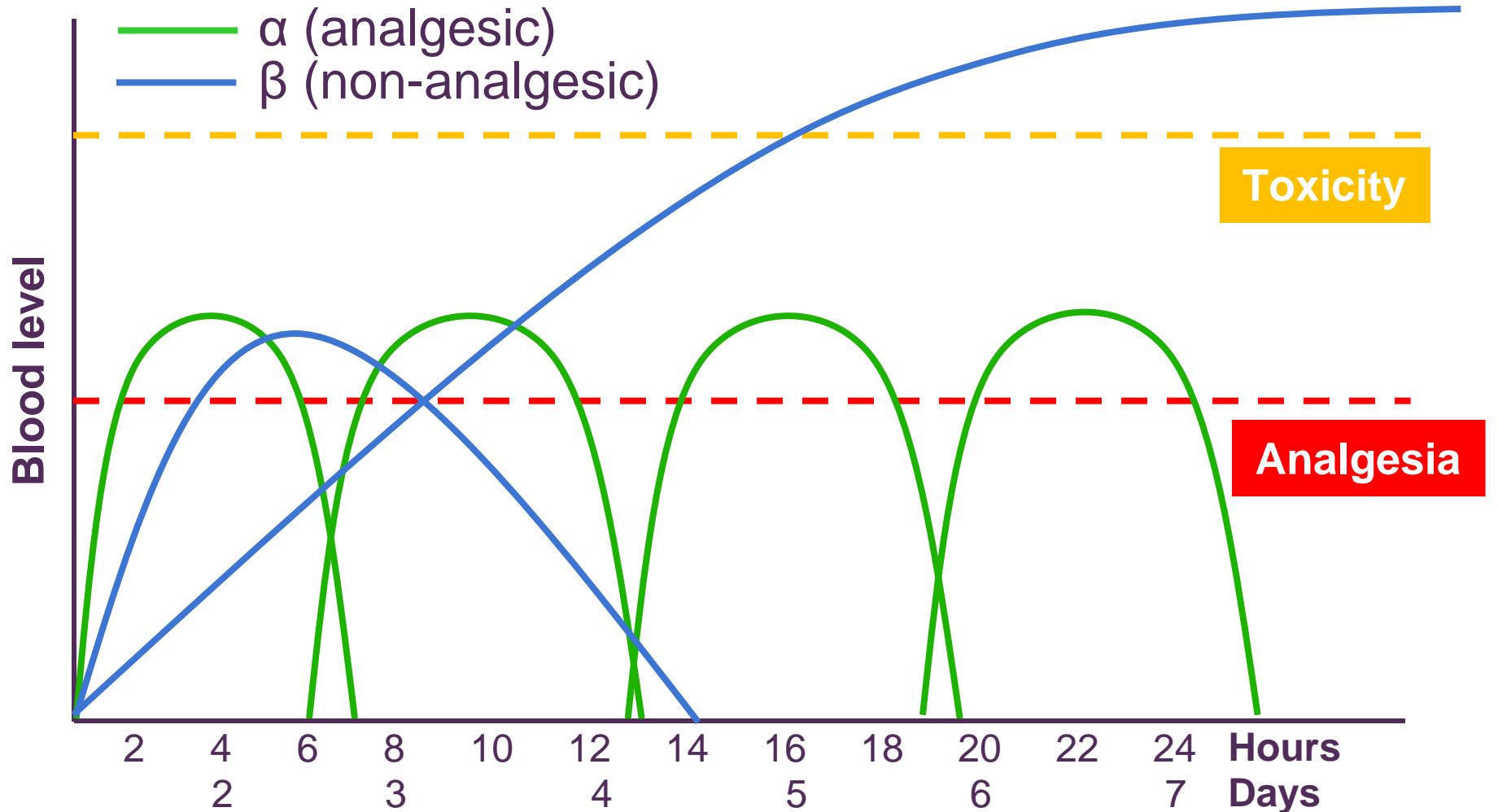
# Providers Who Prescribe Methadone for Pain Should Demonstrate Proficiency

- 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



Webster LR. Unintentional overdose deaths: reversing the trend. Presented at: The American Academy of Pain Medicine's 28th Annual Meeting; February 22-26, 2012; Palm Springs, CA.

# 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



# Examples of Drug Interactions With Methadone

Interaction effect	Drug	Effect
Inhibitors	Ketoconazole	Inhibit methadone metabolism (increase methadone levels)
	Fluconazole	
	Itraconazole	
	Voriconazole	
	Ciprofloxacin	
	Biaxin	
Inducers	Fluvoxamine	Increase methadone metabolism (decrease methadone levels)
	Rifampin	
	Phenytoin	
	Carbamazepine	
	Ritonavir-boosted therapy	
	Nevirapine	
Synergism	Efavirenz	Additive sedative or respiratory depressant effects
	St. John's wort	
	Benzodiazepines	
	Barbiturates	
	Tricyclic antidepressants	
	Ethanol	
	Antihistamines	

Bart G, Walsh SL. Methadone Pharmacodynamics and Pharmacokinetics. In: Cruciani RA, Knotkova, eds. *Handbook of Methadone Prescribing and Buprenorphine Therapy*. New York, NY: Springer; 2013:59-72. McCance-Katz EF, et al. *Am J Addict*. 2010;19:4-16. Chou R, et al. *J Pain*. 2014;15:321-37.

# 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

Webster LR. Methadone Side Effects: Constipation, Respiratory Depression, Sedation, Sleep-Disordered Breathing, and the Endocrine System. In: Cruciani RA, Knotkova, eds. *Handbook of Methadone Prescribing and Buprenorphine Therapy*. New York, NY: Springer; 2013:59-72. Zanger UM, Klein K. *Front Genet*. 2013;4:1-12. Levrano O, et al. *Addict Biol*. 2013;18:709-16. Eap CB, et al. *Clin Pharmacol Ther*. 2007;81:719-28. Dennis BB, et al. *PLoS One*. 2014; 9:e86114.

# 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  $\geq$ 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



Total daily MED	Starting methadone dose	
	Healthy adults age <70 years	Adults with chronic illness or age >70 years
Opioid naïve	5 mg TID	2.5 mg TID
60-100 mg	5 mg TID	5 mg TID
>100 mg	5 mg TID	5 mg TID

- 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

MED=morphine equivalent dose

Webster LR. Methadone Side Effects: Constipation, Respiratory Depression, Sedation, Sleep-Disordered Breathing, and the Endocrine System. In: Cruciani RA, Knotkova, eds. *Handbook of Methadone Prescribing and Buprenorphine Therapy*. New York, NY: Springer; 2013:59-72. Webster LR. *Pain Med*. 2013;14:959-61.



# 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 preceded 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



# A Methadone-Related Death

- 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 4<sup>th</sup> 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

Office of the Chief Medical Examiner State of USA 1313 Mockingbird Ln. (555) 867-5309							
TOXICOLOGY REPORT				Date of Report: 9/15/2008			
LAB NUMBER: 007		DECEASED: Peter Smith		ME CASE NUMBER: 007-01			
SPECIMENS SUBMITTED BY: Dr Sue Jones							
Sample Type	Amount	Received	Received by	Sample type	Amount	Received	Received by
Blood, Cardiac	75 mL	8/30/08	JPJ	Brain	105 g	8/30/08	JPJ
Gastric Contents	97mL	8/30/08	JPJ	Liver	89 g	8/30/08	JPJ
DNA Label		8/30/08	JPJ	DNA Label		8/30/08	JPJ
Evidence		8/30/08	JPJ	Vitreous	3.5mL	8/30/08	JPJ
ANALYTICAL FINDINGS							
SCREEN	Blood, Cardiac	Analyte		Results	Method		
Alcohol				None Detected	Micro Diffusion		
Acidic/Neutral Drugs		Caffeine and/or Caffeine metabolite(s) Methadone Nordiazepam		Detected Detected Detected	GC/MS GC/MS GC/MS		
Basic Drugs		Caffeine Diazepam Methadone Nordiazepam		Detected <0.3 mg/L Detected Detected	GC/MS GC/MS GC/MS GC/MS		
Opiates				None Detected	RIA		
QUANT	Blood, Cardiac	Analyte		Results	Method		
Methadone or Propoxyphene		Methadone		0.65mg/L	HPLC		

*MBolite*

Meta Bolite, PhD  
Director of Toxicology

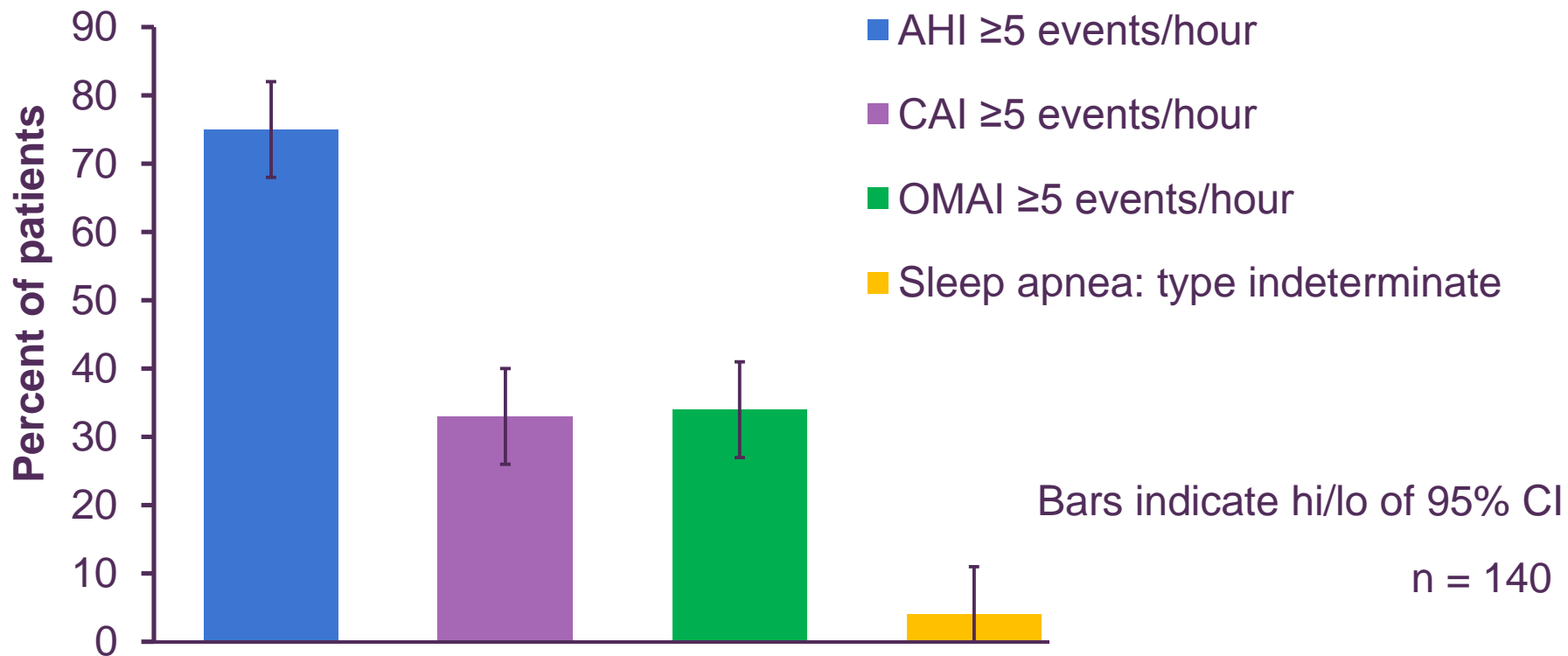
# Sleep-Disordered Breathing

- 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

Webster LR. Methadone Side Effects: Constipation, Respiratory Depression, Sedation, Sleep-Disordered Breathing, and the Endocrine System. In: Cruciani RA, Knotkova, eds. *Handbook of Methadone Prescribing and Buprenorphine Therapy*. New York, NY: Springer; 2013:59-72.

Webster LR, et al. *Pain Med*. 2008;9:425-32. Wang D, et al. *Chest*. 2005;128:1348-56.

# Sleep Disorders & Opioids: Events per Hour



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

<b>Level 3</b> (highest risk)	<ul style="list-style-type: none"><li>• Taking around-the-clock opioids with CAI <math>\geq 5</math> events/hour</li><li>• Taking around-the-clock opioids with AHI <math>\geq 30</math> events/hour</li></ul>
<b>Level 2</b> (moderate risk)	<ul style="list-style-type: none"><li>• Taking around-the-clock opioids with AHI <math>\geq 5</math> events/hour</li></ul>
<b>Level 1</b> (lowest risk)	<ul style="list-style-type: none"><li>• Patients with AHI <math>&lt; 5</math> events/hour</li></ul>

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

# Eight Opioid Prescribing Principles for Providers<sup>®</sup>

*Help Minimize Harm When Prescribing Opioids and Other Psychotherapeutics*

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

# 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

AE=adverse effect

# 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

# References

- A Position Statement from the American Academy of Pain Medicine. *The Evidence Against Methadone as a “Preferred” Analgesic*. 2014.
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# 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](https://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](mailto: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.pcass-o.org](http://www.pcass-o.org)

For questions email: [pcass-o@aaap.org](mailto:pcass-o@aaap.org)



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