



THE UNIVERSITY OF KANSAS HEALTH SYSTEM

# Methadone for Pain Management

**Melanie Simpson, PhD, RN-BC, OCN, CHPN, CPE**

Pain Management Resource Team Coordinator

The University of Kansas Health System

President, American Society for Pain Management Nursing



**METHADONE IS ONE OF THE  
MOST CLINICALLY STUDIED  
DRUGS IN THE WORLD,  
YET REMAINS ONE OF THE  
MOST MISUNDERSTOOD.**

METHADONE!  
YOU DON'T LOOK LIKE  
YOU'RE ON METHADONE!



# Methadone – Unique characteristics

- Synthetic mu opioid
- Developed more than 60 years ago
- Lack of known active metabolites
  - No dose adjustments in renal insufficiency
- Is metabolized by CYP3A4 and CYP2B6

# Methadone – Unique characteristics

- Long & unpredictable half-life (12-120 hours)
- Initially short analgesic action (3-6 hours)
- Duration of action extends to 8-12 hours with repeated dosing
- Because of its long half-life, it may take 5-7 days to reach steady state

# Methadone – Unique characteristics

- 3-5 half-life elimination periods to obtain steady state – do not increase dose rapidly to avoid accumulation and overdose
- High lipid solubility – excellent absorption and bioavailability (~80%) PO, PR
- Action as a noncompetitive N-methyl-D-aspartic acid (NMDA) receptor antagonist –blocks hypersensitivity to mechanical stimuli in neuropathic pain and may potentate the analgesic activity of opioids

# Methadone – Unique characteristics

- Metabolized by cytochrome P450 enzymes
  - Some meds that **decrease** Methadone levels
    - Rifampin, Phenytoin, Carbamazepine, and many antiretrovirals
  - Some meds that **increase** Methadone levels
    - Amitriptyline, Ciprofloxacin, Diazepam, Fluconazole, Fluoxetine, Erythromycin, Metronidazole, Spironolactone, (grapefruit juice)

# Precautions

- Clinical evidence for QTc prolongation and in high doses can cause torsades de pointes
  - PO – limited to case studies
  - IV – direct correlation (Preserved with Chlorobutanol)
    - Electrocardiograms
    - Monitor serum electrolytes (especially potassium)

## Methadone Accounted for 23% of Opioid OD Deaths in 2014

CDC report: Higher use of the prescription drug found among Medicaid population

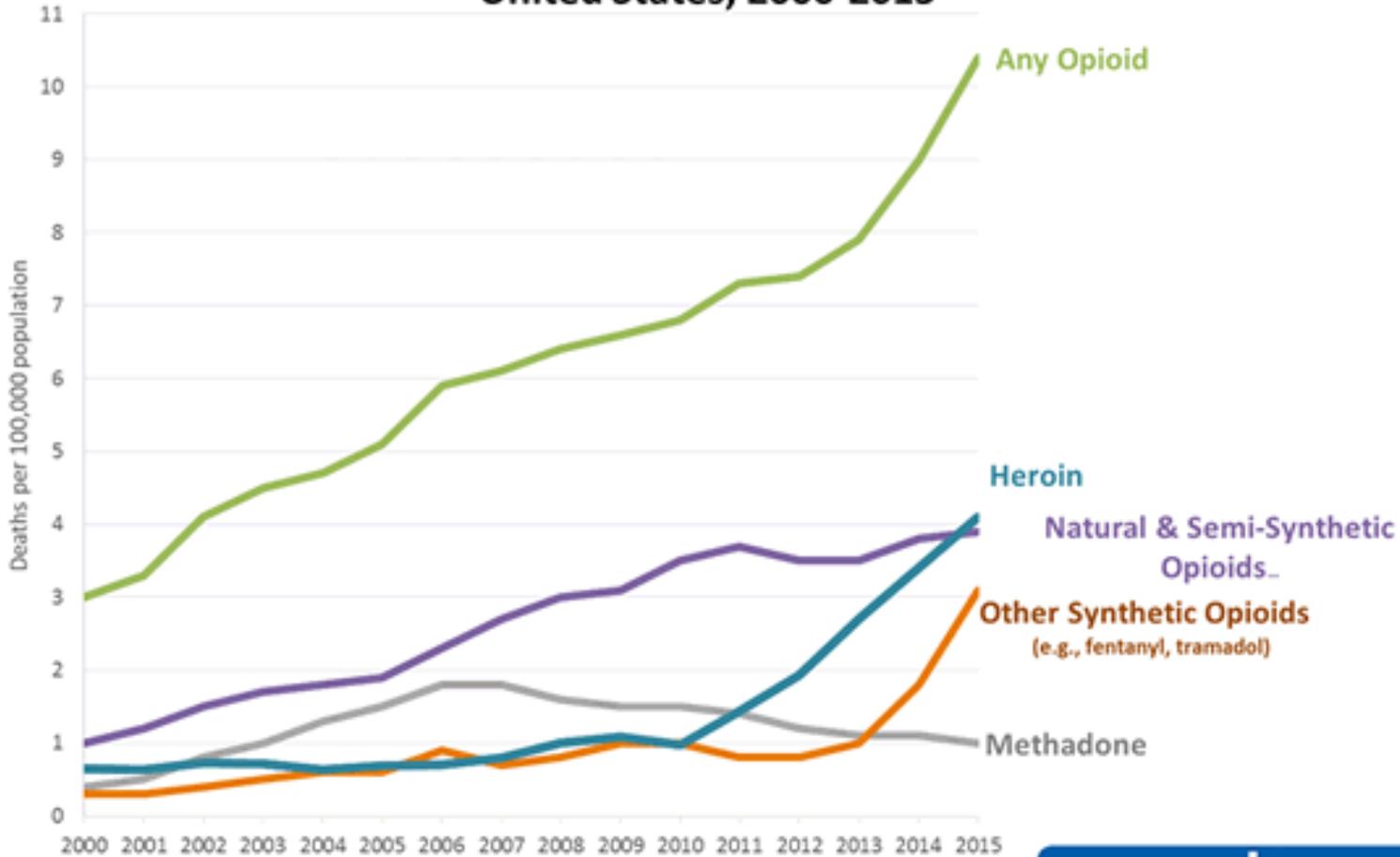
•by Molly Walker, Staff Writer, MedPage Today March 30, 2017

Methadone-related overdoses accounted for nearly one in four deaths related to prescription opioids in 2014, despite a recent decline in drug overdose deaths involving methadone, said researchers from the Centers for Disease Control and Prevention.

Overall, the rate of methadone-overdose deaths increased 600% from 1999 to 2006 (from 0.3 persons per 100,000 to 1.8 per 100,000) before declining to 1.1 per 100,000 in 2014, reported Mark Faul, PhD, and colleagues.

While the drug accounted for only 1% of all opioid prescriptions, methadone-related deaths were responsible for 22.9% of opioid-related deaths in 2014, the authors wrote in the [\*Morbidity and Mortality Weekly Report\*](#),

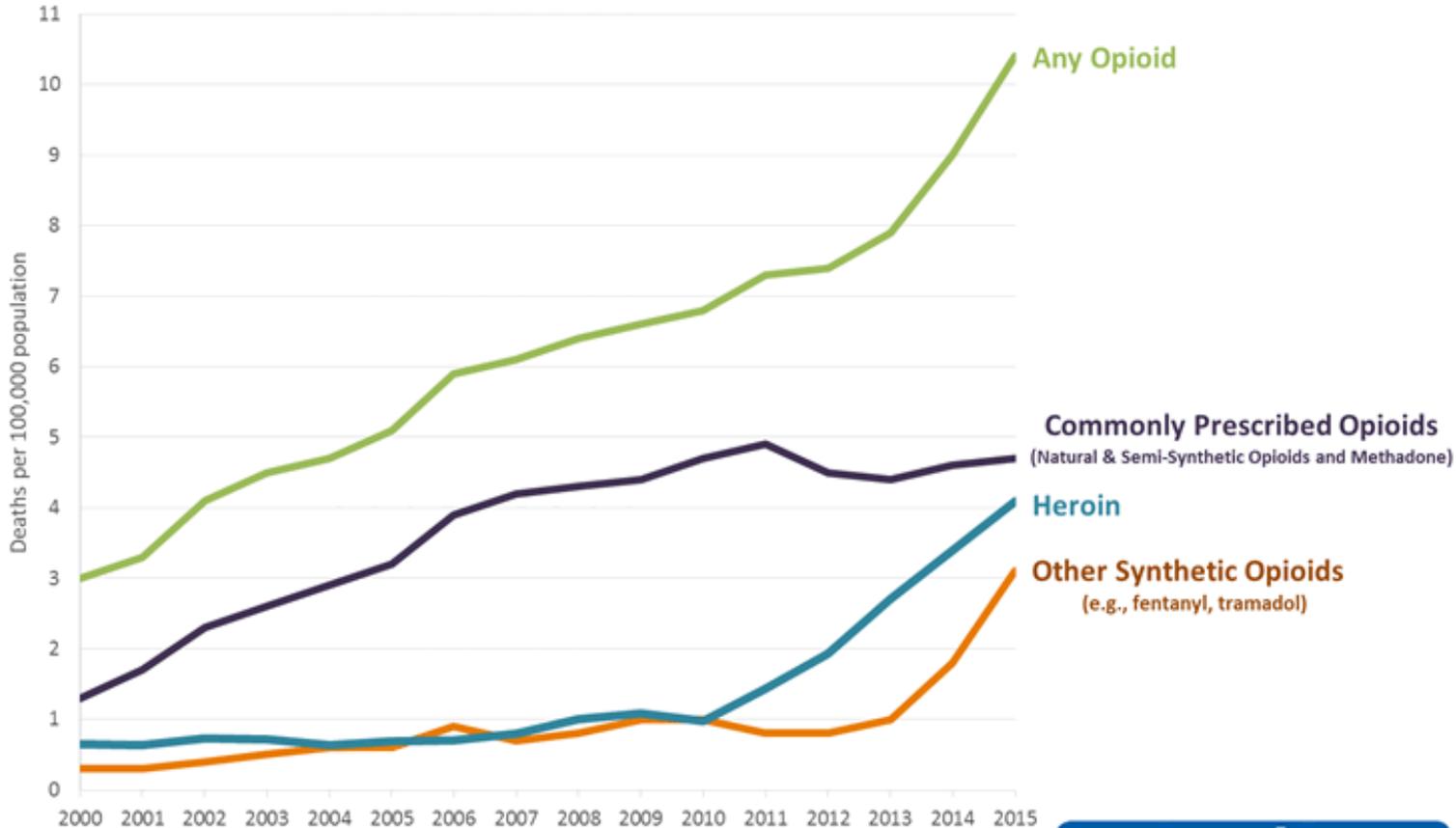
## Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2015



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.



## Overdose Deaths Involving Opioids, United States, 2000-2015



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

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## Guidelines for Methadone Use for Analgesia

1. Assess appropriateness of patient for methadone, including both medical and behavioral risks.
2. Educate patient on risks and side effects of methadone for analgesia using informed consent.
3. Perform baseline ECG if not done in past 3 months for any patient with risk factors for QTc prolongation, prior QTc > 450ms, or a history of ventricular arrhythmia.
  - QTc Interval > 500 ms: avoid use of methadone
  - QTc interval  $\geq$  450 ms but < 500 ms consider alternate opioid or correct reversible causes of QTc prolongation

4. Identify prior opioid intake and select starting dose of methadone, stopping other opioids, if present.
  - Opioid-naïve: 2.5 mg po q8h
  - Opioid-tolerant on lower doses of oral morphine equivalent (ie,40-60 mg): 2.5 mg po q8h
  - Opioid-tolerant on higher doses of oral morphine equivalent: Calculate equianalgesic dose and reduce by 75-90%, never to exceeding 30-40 mg daily
5. Titrate to effect no more frequently than every 5-7 days with conservative dose increases.

## 6. Monitor for adverse effects judiciously.

- Assess for constipation, nausea, sedation, respiratory depression, pruritus, endocrinologic effects, and others frequently with anticipation of reaching the max effect 5-7 days following dosage change.
- Practice appropriate risk-mitigation strategies.
- Perform follow-up ECGs 2-4 weeks following initiation, when daily methadone doses surpass 30 mg, and again if they surpass 100 mg.
- Follow-up ECG should be considered in any instance in which new QTc interval prolongation risk factors are present or the patient presents with signs or symptoms suggesting arrhythmia.

APS 2016, Adapted from Chou, R. et al. (2014). 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. *Journal of Pain*, 15(4), p. 321-337.



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# Dosing Guidelines and Equianalgesia

# Methadone Equianalgesia

- Very controversial
- Many, many different methods

# Ripamonti Method

- Determine 24-hour oral morphine equivalent dose
- For 24-hour morphine dose of:
  - 0-90 mg                      Use 4:1 morphine:methadone
  - 90-300 mg                    Use 8:1 morphine:methadone
  - 300+ mg                      Use 12:1 morphine:methadone
- Generally use another opioid for breakthrough pain

# Morley and Makin Method

- Day 1
  - Stop morphine
  - Commence fixed-dose of methadone q 3h prn
  - Methadone dose = 1/10 of daily morphine (max 30 mg/day)
- Day 6
  - Calculate average daily methadone dose for days 4 and 5
  - Administer as BID dosing with breakthrough dose q 3h prn
  - Increase dose as needed q 4-6 days by 30-50%

# Ayonrinde Method

- For 24-hour morphine dose of:
  - <100mg                      Use 3:1 morphine:methadone
  - 101-300 mg                 Use 5:1 morphine:methadone
  - 301-600 mg                 Use 10:1 morphine:methadone
  - 601-800 mg                 Use 12:1 morphine:methadone
  - 801-1000 mg                Use 15:1 morphine:methadone
  - >1000 mg                    Use 20:1 morphine:methadone

# MD Anderson Method

- Determine 24-hour oral morphine equivalent daily dose (MEDD)
- For 24-hour morphine dose of:
  - <30 mg            Use 2:1 morphine:methadone
  - 30-99 mg            Use 4:1 morphine:methadone
  - 100-299 mg            Use 8:1 morphine:methadone
  - 300-499 mg            Use 12:1 morphine:methadone
  - 500-999 mg            Use 15:1 morphine:methadone
  - >1000 mg            Use 20:1 morphine:methadone

# Edmonton Method

- 10:1 at any dose morphine:methadone

Cleary, J. F. and Foley, D. (2002). Methadone: The ideal long-acting opioid? *AAHPM*, Winter

# The University of Kansas Health System Method

- For 24-hour morphine dose of:
  - <90 mg      Use 4:1 morphine:methadone
  - 90-300 mg    Use 8:1 morphine:methadone
  - 300-600 mg   Use 12:1 morphine:methadone
  - 600-1000 mg   Use 15:1 morphine:methadone
  - >1000 mg     Use 20:1 morphine:methadone

# Dosing Methadone

- Divide the starting dose of methadone by 3 to determine the q 8 hours dose
- Stop the current opioid and begin methadone
- Use patient's current breakthrough med as needed, and record doses and times
- If pain persists, titrate methadone q 5-7 days by converting all of breakthrough and add to methadone dose

## Case study - MW

- MW has sickle cell disease, his doses of Morphine SR (MS Contin) have risen steadily for the last couple of years.
- There is some concern about his opioid use so he does not receive rescue meds
- He is now on 200 mg of Morphine SR q 12 h for a total of 400 mg morphine in 24 h
- He no longer has a payor source so he must be switched to methadone for cost issues.

# 400mg

- 300-600 mg
  - Use 12:1 morphine:methadone
  - $400 \div 12 = 33.3$
  - $33.3 \div 3 = 11.1$
  - Start patient on Methadone 10 mg po q 8 h
- Rescue dose
  - 10-20% of 400 mg = 40-80 mg po morphine
  - Morphine IR (MSIR) 30 mg – 2 tabs (60 mg) po q 2 h prn

- MW has been doing well on methadone for > a month
- He was just admitted for sickle cell crisis. The resident writes to continue home meds:
  - Methadone 10 mg TID
  - MSIR 30 mg – one po q 4 h prn
- And add Morphine 2-4 mg IV q 4 h prn
- How many things can you find wrong with these orders?

## Case study - TS

- TS has terrible diabetic neuropathy. She is on Oxycodone SR (OxyContin) 40mg po q 12 h.
- She is not comfortable and doesn't like the way the oxycodone makes her feel
- She is taking 80 mg oxycodone in 24 h

# 80 mg

- <90 mg
  - Use 4:1 morphine:methadone
  - $80 \div 4 = 20$
  - $20 \div 3 = 6.6$
  - Methadone 5 mg po q 8 h

# Discussion

# References

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