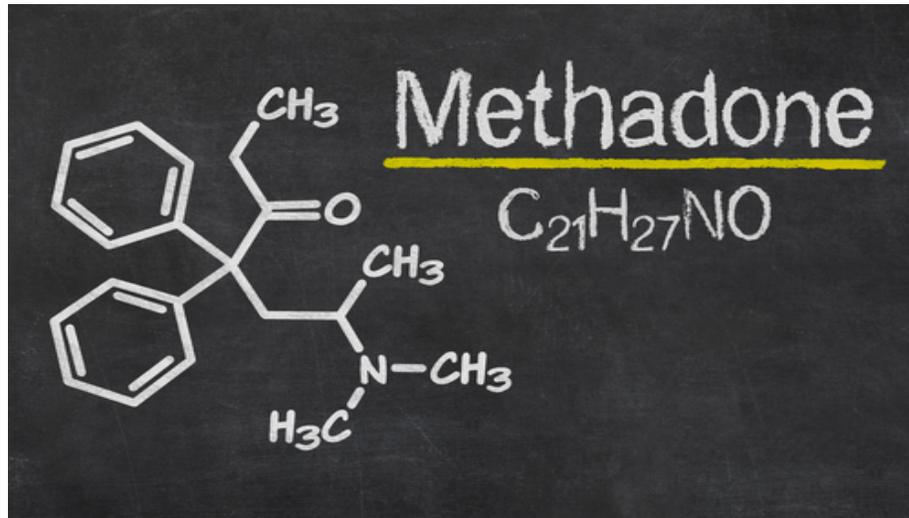


# Pain Management: The Use of Methadone in Hospice and Palliative Care



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# Successful Completion Criteria

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# Objectives

- ▶ Explore the use of methadone for pain management in the hospice and palliative care setting
- ▶ Assess the benefits, risks, and myths surrounding methadone
- ▶ Understand when methadone may be an appropriate choice for your hospice patient
- ▶ Review appropriate dosing of methadone
- ▶ Examine case studies involving pain management of hospice patients using methadone

# What is Methadone?

- ▶ A synthetic opioid analgesic
- ▶ Belongs to the phenylheptylamine class of opioids
- ▶ Is a mu opioid agonist (also binds to kappa and delta opioid receptors)
- ▶ Acts as an antagonist at NMDA receptors
- ▶ Prevents re-uptake of monoamines, including serotonin and norepinephrine
- ▶ Exists in two different isomers: *l*-methadone and *d*-methadone
  - ❖ *L*-methadone is 50 times more potent as an analgesic than *d*-methadone
  - ❖ Methadone formulation that is used clinically contains both *l*- and *d*- forms

# History of Methadone

- ▶ Developed in the late 1940s by German scientists
- ▶ Introduced in the US in 1947
- ▶ Historically, it has been used in the treatment of patients with narcotic addiction and heroin maintenance since the 1960s.

# Advantages of Methadone

- ▶ Excellent for nociceptive and neuropathic pain (burning, tingling, shooting pain)
- ▶ Multiple routes of administration (PO, SL, buccal, PR, IV, IM, sub cut, via PEG tube)
- ▶ Tablets are crushable and is available in a liquid concentrate
- ▶ Synthetic opioid, so lower risk of true allergic reaction
- ▶ No active metabolites
- ▶ Can be started in opioid-naive patients
- ▶ *Very low cost*
  - ▶ Morphine ER 15mg tablet AWP \$1.87 per tablet
  - ▶ Oxycodone ER 10mg tablet AWP \$3.02 per tablet
  - ▶ Fentanyl 12mcg patch AWP \$20.30 per patch
  - ▶ Methadone 5mg tablet AWP \$0.27 per tablet

# Disadvantages of Methadone

- ▶ Long and variable half-life due to unusual pharmacokinetics
  - Risk of cumulative toxicity
  - Requires specific dosing protocols and gradual titration
- ▶ Takes longer to reach steady-state
  - May not be suitable in patient who is actively dying
- ▶ Numerous drug interactions
- ▶ Stigma and fear due to methadone's association with opioid addicts

# Myths Surrounding Methadone

- ▶ Only for opioid addicts
- ▶ Available only through a clinic
- ▶ Physicians need a “special license” to prescribe it

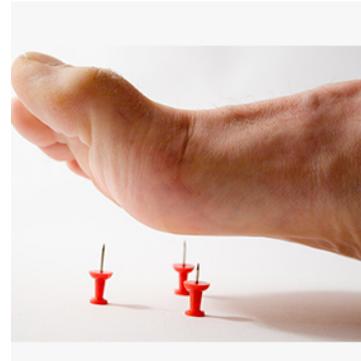


# Prescribing Methadone

- ▶ A prescriber may prescribe methadone for analgesic purposes (“for pain”)
- ▶ Methadone is also used for the maintenance or detoxification of opioid addicted individuals, in which case the practitioner is required to be registered with the DEA as a Narcotic Treatment Program (NTP).

# Methadone for Pain

- ▶ Treats nociceptive pain
  - ❖ Somatic and visceral pain
- ▶ Treats neuropathic pain
  - ❖ Due its actions as an NMDA antagonist



# Choosing the Right Hospice Patient for Methadone

- ▶ Neuropathic pain
- ▶ Uncontrolled pain on other opioids
- ▶ Opioid induced adverse effects, including signs of possible opioid toxicity (hyperalgesia, myoclonus, delirium)
- ▶ True morphine allergy
- ▶ Renal impairment
- ▶ Need for long-acting opioid that can be crushed
- ▶ Opioid naïve patient can use methadone

# Who May Not Be Suitable for Methadone?

- ▶ Patient who is actively dying (less than a week's prognosis)
- ▶ Patient who lives alone, or has a poor caregiving situation
- ▶ Patient with poor cognitive functioning, unreliable, non-compliant
- ▶ Patient with significant cardiac history, including arrhythmias, bradycardia, TdP
- ▶ Patient with other risk factors for QT prolongation (electrolyte imbalances, increased age, etc.)
- ▶ Multiple interacting medications

# Is Methadone an Appropriate Choice For This Patient?

Patient is currently on fentanyl 100mcg patch q72h and his pain is uncontrolled.

- ▶ How is the patient describing his pain?
- ▶ Does he have a significant cardiac history?
- ▶ Is he taking any interacting medications?
- ▶ Consider cost of fentanyl vs. methadone

# Patient is currently on fentanyl 100mcg patch q72h and his pain is uncontrolled.

- ▶ Patient describes his pain as burning pain down his left leg
- ▶ His past medical history includes asthma and seasonal allergies - no cardiac history
- ▶ His medication list includes
  - ▶ Albuterol 0.083% inhale one vial via nebulizer q4h prn SOB
  - ▶ Lorazepam 0.5mg 1 tab po q4h prn anxiety
  - ▶ Fentanyl 100mcg patch q72h
  - ▶ Morphine 20mg/ml 20mg po/sl q2h prn break through pain
- ▶ Is this patient appropriate for methadone? Yes, methadone can be an option for him.

# Is Methadone an Appropriate Choice For This Patient?

Patient is on morphine ER 75mg po q8h, but can no longer swallow it, and is actively dying.

- ▶ What is the patient's prognosis?
- ▶ Consider other routes of administration

Patient is on morphine ER 75mg po q8h, but can no longer swallow it, and is actively dying.

- ▶ Prognosis estimated to be hours-days
- ▶ Consider time it takes for methadone to reach steady state
- ▶ Consider patient's current state of pain
- ▶ Is this patient appropriate for methadone? No, he is actively dying, and since methadone can take several days to reach steady-state, methadone is not a suitable option for him.

# Is Methadone an Appropriate Choice For This Patient?

Patient is elderly and opioid naïve, and reports burning and shooting pain in his legs.

- ▶ How is the patient describing his pain?
- ▶ Does he have a cardiac history?
- ▶ How old is he?
- ▶ Is he on any interacting medications?

# Patient is elderly and opioid naïve, and reports burning and shooting pain in his legs.

- ▶ Describing pain as “burning and shooting” ; neuropathic pain
- ▶ Consider patient’s age: he is 88 years old
- ▶ He has not taken any opioids; no cardiac history; not on any interacting medications
- ▶ Is this patient appropriate for methadone? Yes methadone may be an option for him, and because he is elderly and opioid naïve, he should be dosed conservatively.

# Is Methadone an Appropriate Choice For This Patient?

Female patient is 81yo and currently taking prn morphine IR for her pain. She has a significant cardiac history, has a pacemaker, and takes amiodarone for atrial fibrillation

- ▶ How is the patient describing her pain?
- ▶ Consider her cardiac history, and other risk factors.
- ▶ Consider interacting medications.

Female patient is 81yo and currently taking prn morphine IR for her pain. She has a significant cardiac history, has a pacemaker, and takes amiodarone for atrial fibrillation.

- ▶ Patient describes pain as aching and constant pain
- ▶ Risk factors for QT prolongation:
  - ▶ Female, elderly
  - ▶ Significant cardiac history
  - ▶ Drug interaction with methadone and amiodarone
- ▶ Is this patient appropriate for methadone? It would be prudent to avoid methadone in this patient due to her pre-existing risk factors.

# Pharmacokinetics of Methadone - Absorption

- ▶ When taken orally, methadone is detectable in the plasma ~30min after administration
- ▶ Variable bioavailability - can range from 40-100%
- ▶ Peak effects with continuous dosing are seen in 3-5 days
- ▶ Duration of analgesia is 4-8 hours with single doses; increases to 22-48 hours with repeated doses

# Absorption From Other Routes of Administration

## Sublingual:

- Literature suggests that SL absorption may be better than PO
- Tablets may be crushed and given SL
- Methadone oral concentrate may be given SL

## Parenteral:

- Methadone may be given IM, IV, or sub cut
- Onset of action is 10-20 minutes; peak effects are seen within 1-2 hours
- Unpredictable absorption from IM and sub cut routes

## Rectal:

- Whole tablet or oral solution may be given PR

# Pharmacokinetics of Methadone - Distribution

- ▶ Highly lipid soluble
- ▶ Widely distributed, particularly to liver, kidney, lungs, intestines, muscles, brain
- ▶ 60-90% bound to plasma proteins, mostly to alpha-1 acid glycoprotein
- ▶ Builds up in tissues after repeated doses

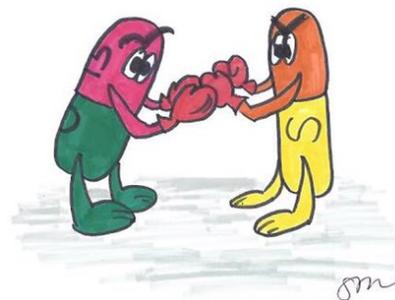
# Pharmacokinetics of Methadone - Metabolism

- ▶ Is metabolized in the liver by cytochrome P450 enzymes, to inactive metabolites
- ▶ Primarily metabolized by CYP3A4 and CYP2B6
- ▶ This can lead to significant drug-drug interactions
- ▶ Use extreme caution in severe liver disease

# Pharmacokinetics of Methadone - Elimination

- ▶ Excreted in the urine and feces
- ▶ Half-life elimination can vary widely (8-59 hours in adults)
- ▶ Excretion is increased when urine pH <6

# Drug Interactions With Methadone



- ▶ Opioids
  - Increased sedation, CNS depression, and respiratory depression
- ▶ Benzodiazepines, anti-psychotics, alcohol
  - Increased CNS depression
- ▶ Anti-depressants
  - SSRIs - increase risk of serotonin syndrome

# Drug Interactions With Methadone

- ▶ Medications that prolong QT interval:
  - Anti-arrhythmics: amiodarone
  - Anti-psychotics: quetiapine, haloperidol
  - Anti-depressants: citalopram, fluoxetine
  - Antibiotics: ciprofloxacin, levofloxacin, azithromycin
  - Others: fluconazole, ondansetron, donepezil

# Drug Interactions With Methadone

- ▶ CYP enzyme inhibitors/inducers
  - Enzyme inhibitors
    - Slowed metabolism of methadone
    - Increased serum level of methadone
    - Can occur quickly
    - Consider 25% reduction in methadone dose
    - Examples:
      - ▶ Fluconazole, ketoconazole, clotrimazole
      - ▶ Amiodarone
      - ▶ Diltiazem
      - ▶ Fluoxetine, sertraline
      - ▶ HIV protease inhibitors
      - ▶ Grapefruit juice

# Drug Interactions With Methadone

- Enzyme inducers
  - Increased metabolism of methadone
  - Decreased serum level of methadone
  - Can take up to two weeks to become significant
  - Encourage use of break-through short-acting opioid
  - Examples:
    - ▶ Carbamazepine
    - ▶ Phenytoin
    - ▶ Primidone
    - ▶ Phenobarbital
    - ▶ Dexamethasone

# Case Study-Reviewing Drug Interactions With Methadone

Mrs. L is a 60 year old female with breast cancer, whose pain is currently well controlled on methadone 5mg po q12h. She develops oral thrush, and despite a round of nystatin oral suspension, her symptoms still persist. The MD ordered fluconazole 100mg po qday for 7 days. What is the drug interaction in this case?

# Case Study - Discussion

- ▶ Fluconazole is a CYP 3A4 enzyme inhibitor
- ▶ Methadone is a CYP 3A4 substrate
- ▶ Fluconazole will inhibit the metabolism of methadone, thereby increasing serum levels of methadone
- ▶ Fluconazole can also prolong the QT interval; additive effects with methadone
- ▶ May consider dose reduction in methadone
- ▶ Monitor closely for evidence of increased methadone serum levels, including respiratory depression, over-sedation, and QT prolongation

# Adverse Effects of Methadone

- ▶ Sedation
- ▶ Constipation
- ▶ Nausea/vomiting
- ▶ Itching
- ▶ Respiratory depression
- ▶ QT prolongation

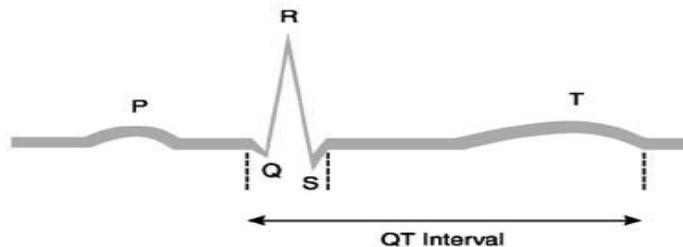


# Management Strategies For Methadone's Adverse Effects

- ▶ Constipation
  - Senna, senna-docusate
  - Bisacodyl
- ▶ Nausea/vomiting
  - Haloperidol, promethazine, prochlorperazine
- ▶ Itching
  - Anti-histamines, such as diphenhydramine

# Adverse Effects - QT Prolongation

- ▶ QT interval prolongation can occur during methadone treatment
- ▶ As QT interval increases, so does the risk of life-threatening arrhythmias, including ventricular tachycardia and Torsades de Pointes (TdP)



# Evidence of QT Prolongation

- ▶ Studies suggest that many incidences of QT prolongation occurred in the setting of additional risk factors and involved relatively high doses of methadone exceeding 100mg/day
- ▶ Patients who experienced TdP were at increased risk for recurrent arrhythmia if methadone therapy was continued
- ▶ Higher risk with intravenous methadone than the oral preparation

# Risk Factors for QT Prolongation

- ▶ Electrolyte imbalances (hypokalemia or hypomagnesemia) caused by laxatives, vomiting or diarrhea, diuretics
- ▶ Age
- ▶ Female sex
- ▶ Advanced heart disease, history of arrhythmias, bradycardia
- ▶ Congenital and acquired long-QT syndromes
- ▶ Family history of sudden death
- ▶ Anorexia
- ▶ QT prolonging medications (amiodarone, citalopram, fluoxetine, ciprofloxacin, quetiapine, haloperidol, ondansetron)

# Considerations When Prescribing Methadone Concerning QT Prolongation

- ▶ Patients should be informed of arrhythmia risk
- ▶ Clinicians should ask patients about any history of structural heart disease, arrhythmia or syncope
- ▶ Reduce modifiable risk factors, such as dehydration due to n/v/d, drug interactions with QT prolonging medications, and CYP enzyme inhibitors
- ▶ Monitor closely for any non-specific signs and symptoms of QT prolongation, such as syncope, seizures, or palpitations

# Methadone Overdose

- ▶ Excessive drowsiness
- ▶ Slow/shallow/difficult/stopped breathing
- ▶ Slurred speech
- ▶ Limp muscles
- ▶ Cold, clammy skin
- ▶ Small pinpoint pupils

# Dosing Methadone

- ▶ Several methods exist to convert an opioid regimen to methadone
- ▶ Oral morphine is the standard opioid that is used when converting to methadone
- ▶ Conversion to methadone is not linear

# Dosing Methadone - Overview

- ▶ Initially, methadone duration of analgesia ranges from 4-6 hours; however, with repeated dosing, duration of analgesia can extend to 8-12 hours
- ▶ Methadone accumulates in the tissues; takes several days for plasma levels to stabilize; thus, as a general rule, dose titration should not be more frequent than every 5-7 days
- ▶ Methadone checks: patients should be re-assessed daily for 5-7 days when methadone is initiated and when the dose is increased

# What is a Methadone Check?

- ▶ Recommendation to closely monitor the patient for 5-7 days after starting methadone and after dose increases
  - ▶ Overall pain control
  - ▶ Level of sedation/lethargy
  - ▶ Number of doses of prn break-through opioid required
  - ▶ General well-being of the patient

# Dosing Strategies - Opioid Naïve Patients

- ▶ May be started on methadone 2.5-5mg po q8-12h for pain
- ▶ As a general rule, start low and go slow

# “Non-Linear” Conversion to Methadone

24 Hour Oral Morphine Equivalent	Morphine : Methadone (per 24 h)
<30 mg/ 24 h	2 : 1
30 – 99 mg/24 h	4 : 1
100-299 mg/24 h	8 : 1
300-499 mg/24 h	10 : 1
500-999 mg/24 h	15 : 1
>1000 mg/24 h	20 : 1

# Points to Consider

- ▶ The conversion ratio increases as the total morphine dose increases
  - The oral morphine to oral methadone conversion ratio can be very high, and the methadone dose unexpectedly low, for patients that previously received very high doses of morphine
- ▶ The use of high but ineffective doses of previous opioid may result in overestimation of the equivalent dose of methadone
- ▶ The calculated dose should be further decreased for incomplete cross-tolerance
- ▶ Methadone dose conversions are not bi-directional; they cannot be used in reverse to convert methadone back to morphine

# Making the Switch to Methadone

- ▶ Two general approaches:
  - Rapid conversion method
    - stop previous opioid and begin methadone
  - Step-wise conversion
    - Taper down on previous opioid and taper up on methadone
    - Used when patient is on greater than 300mg of oral morphine equivalents per day

# Break-Through Pain

- ▶ A short-acting opioid preparation (e.g. immediate-release morphine, acetaminophen with hydrocodone, oxycodone with or without acetaminophen) should be added to the methadone regimen
- ▶ Typically 10-15% of total daily dose of oral morphine equivalents dosed q2h prn break through pain
- ▶ Avoid prn methadone for break-through pain due to drug accumulation

# Converting Between Different Routes of Administration of Methadone

- ▶ Converting from PO to SL to PR administration of methadone is 1:1:1
- ▶ Methadone PO:IV → 2:1 conversion

# Converting FROM Methadone TO Morphine

- ▶ Not a lot of data to support this
- ▶ Many clinicians use a 1:3 ratio (methadone: morphine ratio)
- ▶ Monitor closely for opioid withdrawal symptoms, pain control, level of sedation

# Case Study - Dosing Methadone

BL is a 68 year old male with metastatic end-stage lung cancer. His current pain regimen includes morphine ER 60mg po q12h and Morphine sulfate 20mg/ml 10mg po q2h prn break-through pain (he takes 4 x 10mg doses of morphine for BTP per day). He complains of shooting pain down his right leg, and reports that his current regimen is not helping him. What can we do to help BL's pain? He is not on any interacting medications, he does not have a cardiac history, and is allergic to penicillin (hives).

# Case Study - Discussion

- ▶ Questions to ask:
  - ▶ Cardiac history? Prognosis?
  - ▶ How does the patient rate and describe his pain?
  - ▶ Is he over-sedated?
- ▶ Calculate the total oral morphine equivalents he is taking per day and use the methadone equianalgesic dosing table to calculate your daily methadone dose
- ▶ Methadone 7.5mg po q12h -OR- methadone 5mg po q8h
- ▶ Morphine sulfate 20mg/ml 15-20mg po/sl q2h prn breakthrough pain
- ▶ Daily methadone checks x 5-7 days

# Questions?

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