Learning Objectives

- Articulate the potential advantages & disadvantages of methadone
- Name the most serious & potentially fatal side effects of methadone
- Detect several potential drug interactions involving methadone
- Identify patients for whom methadone may be an appropriate opioid
- Describe two different processes of switching from other opioids to methadone
- Recommend a methadone starting dose & titration schedule for patients who are opioid naïve & for patients who are switched from other opioids to methadone
First Objective

Articulate the potential advantages & disadvantages of methadone
Advantages of Methadone

- Methadone is chemically dissimilar from other opioids
- Methadone is a lipophilic drug
- Methadone has excellent absorption
Advantages of Methadone

- Methadone does not have active metabolites & does not undergo significant renal elimination
- Methadone is available in a variety of dosage formulations
- Methadone is easily manufactured & inexpensive
Disadvantages of Methadone

- Methadone has a long and unpredictable half-life
- Methadone administered SC is associated with local toxicity
- Using methadone as a first-line opioid has not been well studied
Disadvantages of Methadone

- Switching from other opioids to methadone is a complex process
- Switching from methadone to other opioids has not been well studied
- Methadone is associated with serious side effects & many potential drug interactions
Second Objective

Name the most serious and potentially fatal side effects of methadone
Side Effects of Methadone

- **Common**
  - Constipation
    - Reportedly less than most other opioids
  - Dry mouth
  - Nausea/vomiting
  - Somnolence
  - Sedation
    - Reportedly less than most other opioids, but sedation may be more problematic with methadone because of its long and unpredictable half-life, which can lead to accumulation
  - Sweating
Side Effects of Methadone

- Serious
  - Cardiac arrhythmias
    - QT interval prolongation
    - Torsades de Pointes (TdP)
  - Respiratory depression
    - Death
Third Objective

Detect several potential drug interactions involving methadone
Drug Interactions with Methadone

- Metabolism-related
  - Drug Inhibition
  - Drug Induction
- Action-related
  - Cardiac Effects
  - CNS Effects
  - Respiratory Effects

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Drug Interactions with Methadone

- Action-related (respiratory effects)
  - Concomitant administration with drugs that cause respiratory depression
    - Exemplar drugs that cause respiratory depression:
      - Benzodiazepines (e.g. Diazepam [Valium®])
      - Opioids (e.g. Oxycodone [OxyContin®])
  
- Use of methadone in patients with conditions accompanied by hypoxia, hypercapnia, or decreased respiratory reserve
  - COPD, cor pulmonale, severe obesity
Drug Interactions with Methadone

- **Action-related (cardiac effects)**
  - Concomitant administration with drugs that prolong the QT interval or induce TdP
    - Exemplar drugs that prolong the QT interval:
      - Antiarrhythmics (e.g. Amiodarone [Cordarone®])
      - Antibiotics (e.g. Erythromycin [Ery-Tab®])
      - Antipsychotics (e.g. Chlorpromazine [Thorazine®])

- Use of methadone in patients with predisposing cardiac risk factors / at risk for development of prolonged QT interval
  - Cardiac hypertrophy, concomitant diuretic use, hypokalemia, hypomagnesemia
Drug Interactions with Methadone

- Action-related (CNS effects)
  - Concomitant administration with drugs that cause CNS depression
    - Exemplar drugs that cause CNS depression:
      - Benzodiazepines (e.g. Diazepam [Valium®])
      - Tricyclic antidepressants (e.g. Amitriptyline [Elavil®])
      - Neuroleptics (e.g. Chlorpromazine [Thorazine®])
Drug Interactions with Methadone

- Metabolism-related
  - Inhibition of CYP450 enzymes
    - Giving methadone concurrently with a drug that inhibits methadone’s metabolism may result in toxicity
    - Discontinuing a drug that inhibits methadone’s metabolism may result in opioid withdrawal
    - Exemplar drugs that may inhibit methadone’s metabolism:
      - Delavirdine (Rescriptor®) – CYP2B6 inhibitor
      - Sertraline (Zoloft®) – CYP2B6 substrate (moderate affinity)
      - Paroxetine (Paxil®) – CYP2D6 substrate (strong affinity & suicide inhibitor)
Drug Interactions with Methadone

- Metabolism-related
  - Induction of CYP450 enzymes
    - Giving methadone concurrently with a drug that induces methadone’s metabolism may result in opioid withdrawal
    - Discontinuing a drug that induces methadone’s metabolism may result in toxicity
    - Exemplar drugs that may induce methadone’s metabolism:
      - Nelfinavir (Viracept®)
      - Phenytoin (Dilantin®)
      - Ritonavir (Norvir®)

CYP2B6 inducers
Fourth Objective

Identify patients for whom methadone may be an appropriate opioid for pain management
Patient Selection

- Methadone may be appropriate for patients:
  - With a true allergy to morphine
  - With significant renal impairment
  - With neuropathic pain
  - With refractory pain
  - With intolerable opioid-related side effects
  - Who require ATC pain control with a non-oral formulation of an opioid
Patient Selection

- Methadone may not be appropriate for patients:
  - With a very short life expectancy (< 1 week)
  - Prescribed multiple interacting drugs
  - With a significant cardiac history
  - With conditions accompanied by decreased respiratory reserve, hypercapnia, or hypoxia
  - With significant hepatic impairment
  - With a history of or at risk for drug non-adherence
Fifth Objective

Describe two different processes of switching from other opioids to methadone for pain management
Process of Switching to Methadone

- Steps for determining an initial dose
  - Calculate the patient’s oral morphine equivalent (OME) daily dose (mg/day)
  - Determine the equianalgesic dose ratio for switching to oral methadone
    - Refer to tables in handout
  - Calculate the initial oral methadone daily dose (mg/day) by dividing the OME daily dose by the equianalgesic dose ratio
Process of Switching to Methadone

- **Steps for determining an initial dose**
  - Determine the oral methadone dose (mg/dose)
    - Divide the calculated methadone daily dose by 2 or 3 to obtain a 12-hour or 8-hour dosing interval, respectively
  - Double check the initial oral methadone daily dose (mg/day)
    - Methadone daily dose (mg/day) = 5.3956 + (0.09401[OME] – 0.0000435[OME]^2)

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Process of Switching to Methadone

- “Stop and Go” process
  - Follow the steps for determining an initial dose
  - Stop the previous opioid(s) and start methadone using the calculated oral methadone dose (mg/dose)
  - Prescribe a short-acting opioid for breakthrough pain
Process of Switching to Methadone

- “Reduce and Replace” process
  - Follow the steps for determining an initial dose
  - Day 1
    - Continue the other opioid but reduce the dose by 30%, and
    - Prescribe 30% of the calculated oral methadone dose, and
    - Prescribe a short-acting opioid for breakthrough pain
Process of Switching to Methadone

“Reduce and Replace” process

Day 2

- Continue the other opioid but further reduce the dose by 30%, and
- Either leave the methadone dose as is or prescribe another 30% of the calculated oral methadone dose, depending on the patient’s pain control

Day 3

- Stop the other opioid, and
- Either leave the methadone dose as is or prescribe another (or the last) 30% of the calculated oral methadone dose, depending on the patient’s pain control
Sixth Objective

Recommend a methadone starting dose and titration schedule
Opioid-Naïve Patients

- Methadone starting dose
  - "Start Low and Go Slow"
    - Typically start at 2.5mg orally every 8 hours
    - Start at 2.5mg orally every 12 hours in the frail, elderly

- Titrating methadone
  - Titrate no more frequently than every 5-7 days
  - Increase the dose by 25-50%
Opioid-Tolerant Patients

- Methadone starting dose
  - Follow the steps for determining an initial dose described previously
  - Use either the “Stop and Go” or “Reduce and Replace” process

- Titrating methadone
  - Titrate no more frequently than every 5-7 days
  - Increase the dose by 25-50%
Opioid-Tolerant Patients

- Case examples
  - Case 1
    - Using the “Stop and Go” process
  - Case 2
    - Using the “Reduce and Replace” process
Case 1

- 65 year-old female with widely metastatic renal cell carcinoma that has replaced the bony architecture of her humerus
- Co-morbid conditions
  - HTN
  - Obesity
- Pain assessment
  - Mid-upper left arm pain that radiates up her neck, into head, down back and left arm
  - “Numbness and shooting”
  - >10/10
  - Constant
Case 1

- **Physical examination**
  - Obese, pale Caucasian woman lying in bed
  - Yelling out in apparent pain
  - Flaccid, extremely tender and edematous left arm
  - Anasarca
  - Persistent generalized myoclonus

- **Other considerations**
  - She lives in remote area (40 miles from your office)

- **Drugs**
  - Morphine 30 mg/hr continuous infusion + 15 mg q 15 minutes IV push PRN
    - Using maximum dose
  - Dexamethasone (Decadron®) 4 mg po bid
Case 1

- **Current Regimen**
  - Morphine 30 mg/hr infusion + 15 mg q 15 min IV push PRN
  - Using 4 PRN doses/hour (60mg/hr PRN)

- **Calculate the total daily OME dose**
  - Total daily OME dose = 2160 mg IV morphine/day = 6480 OME/day (i.e., 2160 x 3:1 [oral:IV morphine])

- **Determine the conversion ratio**
  - > 1000 mg/day = 20:1 ratio
Case 1

- Calculate the equivalent oral methadone dose
  - 6480 mg/day ÷ 20 = methadone 324 mg/day

- Use the “Stop and Go” process to determine the methadone regimen
  - Calculated methadone regimen
    - Methadone 100 mg po q 8 hour + methadone 30 mg q 3 hour PRN
  - Reduce the calculated methadone dose by ~ 50% due to opioid-induced neurotoxicity (methadone 162 mg/day)
  - Actual methadone regimen
    - Methadone 50 mg po q 8 hour + 15 mg q 3 hour PRN
Case 2

- 56 year-old male with advanced AIDS
- Co-morbid conditions
  - CAD s/p PTCA with multiple stents
  - Generalized anxiety disorder
  - Newly diagnosed cerebral toxoplasmosis
- Pain assessment
  - “Burning” in his feet bilaterally
    - Radiates up his calves
    - 8/10, constant but worsens with weight bearing
- Other assessment
  - Frequent periods of nausea and vomiting
  - Anorexia and extreme cachexia
Case 2

- Prior opioid history
  - Oxycodone/APAP (Percocet®) (“pour and pop”)
    - Chewing > 20 Percocet tablets/day
      - “Minimal to no relief”
  - At visit to pain specialist, converted to:
    - Morphine long-acting (MS Contin®) 100 mg po q 8 hour + morphine short-acting (Roxanol®) 30 mg po q 1 hour PRN
  - Improved pain control with 24-hour intake of 500 mg/day for 2 days, then seemingly unresponsive to morphine
Case 2

Other drugs
- Alprazolam (Xanax®)
- Digoxin (Lanoxin®)
- Enalapril (Vasotec®)
- Amitriptyline (Elavil®)
- Fluconazole (Diflucan®)
- Haloperidol (Haldol®)
- Furosemide (Lasix®)
- Senna/docusate sodium (Senna-S®)
- Sulfamethoxazole/trimethoprim (Bactrim®)
- Atazanavir (Reyataz®)
- Emtricitabine/tenofovir disoproxil fumarate (Truvada®)
Case 2

- **Current Regimen**
  - MS Contin® 100 mg po q 8 hour + Roxanol® 30 mg q 1 hour PRN
  - Using 12 PRN doses/day

- **Calculate the total daily OME dose**
  - Total daily OME dose = 660 mg/day

- **Determine the conversion ratio**
  - 500-999 mg/day = 15:1 ratio
Case 2

- Calculate the equivalent oral methadone dose
  - $660 \text{ mg/day} \div 15 = \text{ methadone 44 mg/day}$

- Use the “Reduce and Replace” process to determine the methadone regimen
  - Day 1: MS Contin 60 mg po q 8 hour + methadone 5 mg po q 8 hour + Roxanol PRN
  - Day 2: MS Contin 30 mg po q 8 hour + methadone 10 mg po q 8 hour + Roxanol PRN
  - Day 3: Stop MS Contin, methadone 15 mg po q 8 hour + Roxanol PRN
Take Away Points

- Methadone is an extremely useful drug for managing pain, yet it can be challenging to use methadone safely.

- Using methadone safely requires knowledge of its:
  - Unique pharmacodynamic and pharmacokinetic properties,
  - Potential for side effects & drug interactions, and
  - Complex dosing.
BASIC TRAINING