Disclosure

- I have no relevant financial relationships with manufacturers of any commercial products and/or providers of commercial services discussed in this presentation.

- This discussion will include the use of medications for off-label indications.

Objectives

- Explain the basics of methadone
- Evaluate barriers to methadone use
- Identify criteria for methadone patient selection
Patient Case

- BS, 71 year old female with lung cancer with metastases to bones
- PPS 40, ambulatory with walker, swallowing normal
- Diagnoses: GERD, hypertension, depression, chronic kidney disease
- Allergies: morphine, penicillin (reactions unknown)
- Medications:
  - Albuterol (Proventil®) 0.083% solution 1 vial per nebulizer q4h prn dyspnea
  - Desmopressin (Decadron®) 4mg PO qam
  - Docusate (Colace®) 100mg PO daily
  - Lisinopril (Prinivil®) 20mg PO daily
  - Lorazepam (Ativan®) 0.5mg PO q6h prn anxiety
  - Oxycodone/APAP (Percocet®) 10/325mg 1 tablet PO q4h prn pain
  - Pantoprazole (Protonix®) 40mg PO daily
- Chief complaint: uncontrolled pain

Methadone Pharmacokinetics

- Synthetic opioid with mixed properties
  - µ (mu) opioid receptor agonist
  - Δ (delta) opioid receptor agonist
  - N-methyl-D-aspartate (NMDA) receptor antagonist
- Lipophilic
- High oral bioavailability
- Long elimination half-life: up to 59 hours (average 20-35 hours)
- Metabolized heptatically
  - N-demethylation via CYP3A4, CYP2B6, CYP2C19
  - No active metabolites
- Excretion: urine
Methadone Pharmacokinetics

- **Onset of analgesic action:**
  - Oral: 0.5-1 hour
  - Parenteral: 10-20 minutes

- **Steady state:**
  - Oral: 5 days (continuous dosing)
  - Parenteral: 1-2 hours

- **Duration of analgesia:**
  - Oral: 4-8 hours (single dosing); increases to 22-48 hours with repeat dosing

Methadone Accumulation Curve

![Plot of Methadone Accumulation](http://www.slideshare.net/jamal53/3978-s1-04-lipman)

Considerations for Methadone Use

- Initiating therapy with a long-acting opioid
- Treatment for neuropathic pain
- Converting from an alternate opioid
  - High doses of previous opioid
  - Intolerable side effects from another opioid
  - Renal insufficiency
  - Inadequate pain control despite escalating doses of previous agent
  - Opioid rotation (opioid-induced neurotoxicity)
- Need for a long-acting liquid or crushable preparation
Methadone and Neuropathic Pain

- Potential benefit for neuropathic pain
- Inhibits reuptake of serotonin and norepinephrine
  - Other opioids do not have this action
- Active N-methyl-D-aspartate (NMDA) receptor antagonist
  - Reduces CNS sensitization to pain/hyperalgesia
  - Reduces CNS amplification of pain sensation
  - Reduces central CNS sensitization to pain
- Other NMDA receptor antagonists:
  - Ketamine (Ketalar®)
  - Dextromethorphan (Delsym®)
  - Memantine (Namenda®)
  - Amantadine (Dext-Amanadine®)

Methadone Side Effects

- Similar to other opioids:
  - Constipation
  - Dry mouth
  - Nausea/vomiting
  - Sedation
  - Diaphoresis
  - Pruritis
  - Urinary retention
  - Delirium
  - Respiratory depression
- However, many patients report side effects are milder with methadone as compared to other opioids

Opioid Induced Neurotoxicity

- Can occur with any opioid if dose is high enough, but most common with morphine and hydromorphone
  - Both have neurotoxic metabolites with no analgesic benefit
  - Risk is higher with renal failure
- Signs:
  - Myoclonus – twitching of large muscle groups
  - Delirium
  - Seizures
  - Hyperalgesia/allodynia
  - Rapidly escalating dose requirement
  - Pain “doesn’t make sense;” not consistent with recent pattern or known disease
Opioid Induced Neurotoxicity

- Early recognition is critical
- NMDA receptor involved in process
  - Methadone is an NMDA antagonist
- Treatment:
  - Rotate to a structurally dissimilar opioid
    - Usually methadone or fentanyl
  - Hydration
    - Dehydration will slow clearance of metabolites
  - Benzodiazepines

Opioid Rotation: Structural Classes

- Phenanthrenes
  - Codeine
  - Hydromorphone (Dilaudid®)
  - Hydrocodone (Norco®)
  - Morphine (Roxanol®, MS Contin®)
  - Oxycodone (Roxicodone®, Oxycontin®)
- Diphenylethane derivatives
  - Methadone (Dolophine®)
- Phenylpiperidine derivatives
  - Meperidine (Demerol®)
  - Fentanyl (Duragesic®)
Methadone Dosage Forms and Administration
- Oral concentrate: 10mg/mL
- Oral solution: 5mg/5mL
- Parenteral solution: 10mg/mL
  - Most clinicians support parenteral : oral ratio of 1 : 2
  - Can be given intermittently or continuous
  - IV administration may be associated with higher risk of QT prolongation
  - SQ administration can cause local irritation
- Oral tablet: 5mg, 10mg, 40mg
  - 40mg tablets are limited to opioid addiction maintenance and hospitals
- Tablets and oral solutions can be given orally, rectally, or sublingually

Methadone Dosing
- Can be challenging when rotating from one opioid to methadone
- There is no literature consensus regarding:
  - Dosage conversion ratio
    - Fixed versus variable
  - When to discontinue the previous opioid
    - Abruptly versus decreasing over 3-5 days
  - How often to administer routine methadone doses
    - Every 6, 8, 12, or 24 hours
  - Breakthrough medication selection
    - Short acting opioid (morphine, hydromorphone) versus methadone

Example Methadone Dosing Method
- Opioid naïve patient:
  - Methadone 2.5mg PO q12h
  - OR
  - Methadone 2.5mg PO q24h
  - In patients who are very frail or sensitive to CNS side effects
Example Methadone Dosing Method

Rotating from another opioid:
- Calculate patient’s total morphine equivalent daily dose (MEDD)
  - Total all opioid doses (routine and breakthrough)
  - Convert to morphine using equianalgesic chart
- Starting methadone dose should be ~20% of the total MEDD (1:5 ratio)
  - Maximum starting dose of 60mg/24 hours (oral)
  - Divide 24 hour methadone dose by 2 for q12h ATC or 3 for q8h ATC dosing
- Consider reducing the starting dose by 30-50% if:
  - Patient has significant hepatic impairment
  - Patient is taking another medication that will increase methadone concentration
  - Patient is over 70 years of age
- Consider tapering previous opioid over 3-5 days if patient is using high dose opioids to prevent opioid withdrawal and psychological failure

Example Methadone Dosing Method

Breakthrough dosing:
- May use another short acting opioid for breakthrough pain if:
  - An opioid is needed for dyspnea
  - Patient is at risk for over-utilizing breakthrough medication
  - Patient prefers
- May use methadone
  - Dose is 30-50% of the 24 hour dose given q4h prn pain

Methadone Monitoring

With initiation or dose increases:
- Monitor patient daily for the first 5-7 days for:
  - Pinpoint pupils, respiratory depression, excessive sedation, and use of breakthrough doses
- The dose should not be increased by more than 25-30%, or increased sooner than every 4-5 days
If Toxicity is Suspected
- Respiratory rate (RR) between 6-9 breaths per minute (not associated with normal dying process):
  - Hold doses until RR returns to baseline or 10-12
  - Reinitiate at 50% of previous methadone dose
- Respiratory rate (RR) less than 6 breaths per minutes (not associated with dying process):
  - Hold dose until RR returns to baseline or 10-12
  - AND
  - Consider giving naloxone 0.1mg subcutaneously every 10-15 minutes
    - May need to repeat due to methadone’s long half-life

Patient Case
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  - Oxycodone/APAP (Percocet®) 10/325mg 1 tablet PO q4h prn pain
  - Pantoprazole (Protonix®) 40mg PO daily
- Chief complaint: uncontrolled pain

Take Note!

Because of methadone’s unique pharmacology, vigilance during initiation and dosage titrations is crucial
What are Potential Barriers to Methadone Use?

- Misconceptions
- The media
- Education
  - Hospice
  - Physicians
  - Patients, families
- Lack of willingness to understand the medication
- Communication

Methadone Misconceptions

- Licensure restrictions for prescribing and dispensing
- Stigma because of its use in drug addiction
- Long half-life is problematic
- Difficult to titrate
- Too many drug interactions
- Unsafe to use
- Patients don’t like it
Education, Understanding, and Communication

- Because misconceptions are common, education and communication are critical.
- Utilize the **BUILD** model to facilitate discussions with patients, families, and other healthcare professionals:
  - **Build** a foundation of trust
  - **Understand** what the patient and caregiver know about the medication
  - **Inform** the patient and caregiver of evidence-based information
  - **Listen** to the patient and caregiver’s goals and expectations
  - **Develop** a plan of care in collaboration with the patient, caregiver, and healthcare team

Education, Understanding, Communication

- **Build**: “I understand how important pain control and quality of life are to you.”
- **Understand**: “What do you know about your options for pain control?”
- **Inform**: “We need to use something that’s safe with your kidney failure and can be crushed. Methadone meets both of these criteria.”
- **Listen**: “What questions do you have about trying methadone?”
- **Develop**: “Ok, I’ll call your doctor and update her about what we’ve discussed.”
Warnings

[U.S. Boxed Warning]:
- May cause serious, life-threatening, or fatal respiratory depression. Monitor closely for respiratory depression, especially during initiation or dose escalation.

[U.S. Boxed Warning]:
- QTc interval prolongation and serious arrhythmias (e.g., torsades de pointes) have occurred during treatment. Most cases involve patients being treated for pain with large, multiple daily doses. Closely monitor patients during initiation and titration for changes in cardiac rhythm.

Respiratory Depression

- Methadone has a long elimination half-life
  - Blood levels gradually rise over the 5 days, leading to accumulation
  - Signs of overdose may not appear for several days

- Methadone’s duration of respiratory depressant effects may be longer than the duration of analgesic effects

- Reversal of overdose may be challenging
  - Methadone lingers in the blood longer than naloxone
    - May need repeat naloxone doses

Methadone and the QTc Interval

- Methadone can increase the QTc interval, potentially leading to torsades de pointes

- Studies in cancer patients:
  - QTc prolongation risk is minimal in patients without baseline QTc prolongation or other risk factors
  - Risk is higher in patients receiving continuous IV infusions

- Assess patients for cardiac risk factors:
  - Patients with predisposing clinical conditions
    - Known cardiac arrhythmias
    - Bradycardia (< 50 beats/minute)
    - Electrolyte disturbance (hypokalemia, hypomagnesemia, hypocalcemia)
    - Congenital QTc interval prolongation
  - Concomitant use of other medications that can prolong the QTc interval
Drugs that Prolong the QTc Interval

- Amiodarone (Cordarone®, Pacerone®)
- Chloroquine (Aralen®)
- Chlorpromazine (Thorazine®)
- Clarithromycin (Biaxin®)
- Disopyramide (Norpace®)
- Domperidone (Inapsine®)
- Erythromycin (Erythrocin®)
- Haloperidol (Haldol®)
- Methadone (Methadose®)
- Pentamidine (Pentam®)
- Pimozide (Orap®)
- Procainamide (Procan®)
- Quinidine (Quinaglute®)
- Sotalol (Betapace®)
- Sparfloxacin (Zagam®)
- Thioridazine (Mellaril®)
- Levofloxacin (Levaquin®)

Highlighted agents have a very low incidence of producing torsades de pointes in and of themselves.

QTc Monitoring Recommendations

- In patients with risk factors for QTc prolongation or history of ventricular arrhythmia: obtain ECG to evaluate QTc interval
  - Baseline
  - 2-4 weeks after therapy initiation or significant dose increases
  - Annually
- Increase ECG monitoring in patients receiving methadone doses > 100mg/day or if unexplained syncope or seizure occurs while taking methadone
- If before or at anytime during therapy:
  - QTc > 450-499 msecs: discuss potential risks and benefits; monitor QTc more frequently
  - QTc > 500 msecs: consider discontinuation or reducing methadone dose or eliminate factors promoting QTc prolongation (ie: potassium-wasting medications)

Impact of CYP450 Metabolism

- Many other medications are metabolized by the same enzymes
  - Some may induce or inhibit methadone’s metabolism
- Patients may experience opioid withdrawal or overmedication when methadone is given concurrently with interacting medications
- When these medications are added or discontinued in a patient that is also taking methadone, the dose of methadone may need adjusted
### Drug Interactions

<table>
<thead>
<tr>
<th>Inducers: reduce methadone levels</th>
<th>Inhibitors: increase methadone levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (Tegretol®)</td>
<td>Cimetidine (Tagamet®)</td>
</tr>
<tr>
<td>Chronic alcohol ingestion</td>
<td>Ciprofloxacin (Cipro®)</td>
</tr>
<tr>
<td>Pentobarbital (Nembutal®)</td>
<td>Clarithromycin (Biaxin®)</td>
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<tr>
<td>Phenobarbital</td>
<td>Doxycycline (Vibramycin®)</td>
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<tr>
<td>Phenytoin (Dilantin®)</td>
<td>Erythromycin (Erythromycin®)</td>
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<td>Flusartine (Prozac®)</td>
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<td>Ritonavir (Norvir®)</td>
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<tr>
<td>Secobarbital (Seconal®)</td>
<td>Grapefruit juice</td>
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<td>Ketoconazole (Nizoral®)</td>
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<td>Sertraline (Zoloft®)</td>
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<td>Verapamil (Isoptin®)</td>
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</tbody>
</table>

### Smoking Tobacco and Methadone

- Smoking reduces methadone levels
  - May require an increased methadone dose for adequate pain control

- If the patient stops smoking, the methadone dose may need reduced to avoid toxicity and adverse effects

### With All These Risks, Why Use Methadone?

- Effective analgesic, especially when other opioids have failed
  - Unique pharmacological properties
- Safe with renal impairment
- Appropriate for patients with swallowing limitations
- When used appropriately, methadone can be safely administered
  - Patient assessment
  - Patient education
  - Appropriate dosing and titration
  - Patient monitoring
- Oral dosage forms are cost effective
Patient Case

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  - Pantoprazole (Protonix®) 40mg PO daily
- Chief complaint: uncontrolled pain

Take Note!

Being aware of methadone’s limitations and cautions is key to safe and successful pain management with methadone
Situation to Consider Methadone

- Initiating therapy with a long-acting opioid
- Converting from an alternate opioid
  - High doses of previous opioid
  - Intolerable side effects from another opioid
  - Renal insufficiency
  - Inadequate pain control despite escalating doses of previous agent
  - Opioid rotation (opioid-induced neurotoxicity)
- Treatment for neuropathic pain
- Need for a long-acting liquid or crushable preparation

Key Assessment Points

- Patient history:
  - Liver dysfunction
  - Current level of sedation
  - Evidence of opioid-induced neurotoxicity
- Pain history:
  - Location
  - Quality
  - Nature
  - Visceral, somatic, or neuropathic
  - Severity of pain
  - Current medications being used (dose, route, frequency)
  - How pain responds to current regimen

Key Assessment Points

- Cognitive dimension:
  - Ideally, patient and/or caregiver should not have cognitive impairment that may limit their ability to rate pain or follow a specific regimen
- Patient’s analgesia perceptions/expectations:
  - Evaluate if the patient:
    - Would prefer to feel sedated with less pain or alert with some pain
    - Associates pain relief with the “feeling” from opioid doses
    - Has the potential for overuse of sedating medications as a method of coping
Key Assessment Points

- Spiritual perspectives:
  - Evaluate if the patient has spiritual concerns that may influence safe use of medications

- Social and family history:
  - Assess for:
    - Ability to follow directions and keep track of methadone doses
    - Current smoking, alcohol use, or prescribed/illicit drug misuse
    - History of drug or alcohol abuse or addiction
    - Family members currently smoking, drinking alcohol, or misusing prescribed/illicit drugs
    - Family members with a history of drug or alcohol abuse or addiction

Key Assessment Points

- Medical/medication history:
  - Evaluate if patient:
    - Has any risk factors for developing arrhythmias
    - Is taking any medications that can prolong the QTc interval or induce torsades de pointes
    - Has any known cardiac arrhythmias, bradycardia, electrolyte disturbances, or congenital QTc prolongation
    - Is taking any medication(s) that can interact with methadone

- Methadone education:
  - Patient/caregiver should be able to:
    - Understand the methadone dosing regimen
    - Communicate pain rating, oversedation, or signs of toxicity
    - Understand that methadone will not typically cause euphoria or sedation if dosed correctly

When to Potentially Avoid Methadone

- Rapid opioid titration is necessary to manage severely uncontrolled pain
- History of cardiac conduction abnormalities or arrhythmia
- Use of other medications that can affect the QTc interval
- Lack of clinician comfort level
- Inability to monitor for safe use
- Patient lives alone
- Abuse, diversion in the home
- Patient is not capable or willing
Patient Monitoring

- With methadone initiation or dose increases, monitor patient daily for 5-7 days for:
  - Pinpoint pupils
  - Respiratory depression
  - Excessive sedation
  - Pain control
    - Frequency of breakthrough dosing

Patient Case

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Patient Case

- What total daily methadone dose would be appropriate?
  - \[ \frac{50mg \text{ oxycodone}}{30mg \text{ oral morphine}} \times \frac{30mg \text{ oral morphine}}{75mg \text{ oral morphine per day}} \times 75mg = 15mg \text{ methadone per day} \]
- How would you dose methadone?
  - 5mg PO q8h versus 7.5mg PO q12h
- What would you use for breakthrough pain?
  - Change oxycodone/APAP to immediate release oxycodone 10mg tablets, take 1-2 tablets PO/SL q1h prn pain/dyspnea
- Do you need to taper oxycodone/APAP?
  - Since total daily dose is low (50mg/day), tapering is likely not necessary
Take Note!

When used appropriately, methadone is an effective and safe analgesic

Key Points

- When used appropriately, methadone is an effective analgesic
- Understand warnings, risk factors, drug interactions, and monitoring parameters
- Conduct a thorough patient assessment prior to starting methadone
- Continually monitor patient response

Questions?

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