
Managing the Mysteries of Methadone

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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.
 - All medication treatments and doses discussed are only applicable to adult patients.
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Objectives

- Discuss the characteristics and appropriateness of methadone use for pain management.
 - Develop a plan for methadone initiation and monitoring in hospice patients.
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Methadone Pharmacology

Methadone Mechanism of Action

- Synthetic opioid with mixed properties
- Binds to opiate receptors:
 - μ (mu) opioid receptor agonist
 - Δ (delta) opioid receptor agonist
 - κ (kappa) opioid receptor agonist
- Alters perception of and response to pain
 - N-methyl-D-aspartate (NMDA) receptor antagonist
 - Inhibits norepinephrine and serotonin reuptake

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Methadone Pharmacokinetics

- Absorption
 - Bioavailability ~80%
- Distribution
 - Lipophilic
 - Protein binding 85-90%
- Metabolism
 - N-demethylation via CYP450 system
 - CYP3A4, CYP2B6, CYP2C19, CYP2D6
 - No active metabolites
- Excretion
 - Elimination half-life: up to 59 hours (average 20-35 hours)
 - Feces, <10% urine

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Methadone Pharmacokinetics

- Steady state:
 - Oral: 5 days (continuous dosing)
 - Parenteral: 1-2 hours
- Onset of analgesic action:
 - Oral: 30-60 minutes
 - Parenteral: 10-20 minutes
- Duration of analgesia:
 - Single dosing: 4-8 hours
 - Repeated dosing: 22-48 hours

Methadone Accumulation Curve

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

INDUCERS ↓ methadone levels	INHIBITORS ↑ methadone levels
Carbamazepine (Tegreto®) Chronic alcohol ingestion Pentobarbital (Nembutal®) Phenobarbital Phenytoin (Dilantin®) Risperidone (Risperdal®) Rifampin (Rifadin®) Ritonavir (Norvir®) Secobarbital (Seconal®) Spironolactone (Aldactone®) Tobacco	Cimetidine (Tagamet®) Ciprofloxacin (Cipro®) Clarithromycin (Biaxin®) Doxycycline (Vibramycin®) Erythromycin (Erytab®) Fluconazole (Diflucan®) Fluoxetine (Prozac®) Fluvoxamine (Luvox®) Grapefruit juice Ketoconazole (Nizoral®) Paroxetine (Paxil®) Sertraline (Zoloft®) Verapamil (Isoptin®)

- Methadone Adverse Effects
- Similar to other opioids:
 - Constipation
 - Dry mouth
 - Nausea/vomiting
 - Sedation
 - Diaphoresis
 - Pruritus
 - Urinary retention
 - Delirium
 - Respiratory depression
 - Many patients report side effects are milder with methadone as compared to other opioids

- 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.
- *List is not all inclusive

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

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Methadone and the QTc Interval

- Methadone may prolong the QTc interval, potentially leading to torsades de pointes
- Increased risk of QTc prolongation:
 - High doses (e.g., >100 mg/day)
 - Continuous IV infusions
 - Cardiac risk factors or predisposing clinical conditions
- Studies in cancer patients:
 - QTc prolongation risk is minimal in patients without baseline QTc prolongation or other risk factors

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Methadone and the QTc Interval

- Assess patients for cardiac risk factors or 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

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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

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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 msec: discuss potential risks and benefits; monitor QTc more frequently
 - QTc > 500 msec: consider discontinuation or reducing methadone dose or eliminate factors promoting QTc prolongation (ie: potassium-wasting medications)

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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

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Poll Question

Which of the following situations would we consider using methadone for pain?

- A. A 65 year old patient with lung cancer who is using PRN morphine doses about every 4 hours for pain relief
- B. A 78 year old patient with breast cancer with arm pain that is "burning and tingling"
- C. An 85 year old patient taking OxyContin who can no longer swallow medications whole
- D. A 59 year old patient with end-stage heart failure and stage 4 chronic kidney disease

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Considerations for Methadone Use

Situations to Consider Methadone

- 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

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Methadone and 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
- Other NMDA receptor antagonists:
 - Ketamine
 - Dextromethorphan
 - Memantine
 - Amantadine

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Opioid Rotation: Structural Classes

Phenanthrenes	<ul style="list-style-type: none"> ✘ Codeine (Tylenol® #3, #4) • Morphine (MS Contin®, Roxanol®) • Hydrocodone (Vicodin®, Lortab®, Norco®, Zohydro ER®) • Hydromorphone (Dilaudid®, Exalgo®) • Oxycodone (OxyContin®, Percocet®) • Oxymorphone (Opana®) • Buprenorphine (Butrans®, partial agonist)
Diphenylheptanes	<ul style="list-style-type: none"> • Methadone (Dolophine®)
Phenylpiperidines	<ul style="list-style-type: none"> • Fentanyl (Duragesic®) ✘ Meperidine (Demerol®)
Miscellaneous	<ul style="list-style-type: none"> • Tapentadol (Nucynta®) • Tramadol (Ultram®)


✘ = Not recommended for pain

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Opioid Induced Neurotoxicity




Hyperalgesia, allodynia, agitation/delirium



Misinterpretation as pain





Opioid dose increase

- Hallucinations
- Myoclonus
- Hyperalgesia
- Allodynia
- Seizures
- Rapidly escalating dose requirements

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Opioid-Induced Neurotoxicity

- Can occur with any opioid if the dose is high enough
- Incidence varies by opioid
 - Morphine > Hydromorphone > Oxycodone > Fentanyl > Methadone
- Risk factors:
 - Renal impairment
 - Rapid dose escalation
 - Dehydration
 - Underlying delirium
 - Advanced age
 - Psychoactive medications



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Opioid Induced Neurotoxicity

- Early recognition is critical
- NMDA receptor involved in process
 - Methadone is an NMDA antagonist
- Treatment:
 - Opioid dose reduction
 - Rotate to a structurally dissimilar opioid (with a lower risk of neurotoxicity)
 - Hydration to facilitate clearance of metabolites
 - Benzodiazepines

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Methadone: Who is a good candidate?

<p style="text-align: center;"> Consider methadone</p> <ul style="list-style-type: none"> • Neuropathic pain • Need a crushable/liquid long-acting opioid • Neurotoxicity from other opioids • Renal insufficiency • Allergies to multiple opioids • Intolerable side effects from other opioids • Cost of opioid therapy is a barrier to effective pain control 	<p style="text-align: center;"> Possibly avoid methadone</p> <ul style="list-style-type: none"> • Known cardiac arrhythmia/bradycardia • Electrolyte imbalances (<i>hypokalemia</i>) • Acute pain crisis • Rapid titration of analgesia is necessary • Unable to monitor use • Unreliable caregiving situation • Patient taking multiple interacting medications • Prognosis limited to < 1 week
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Consult a skilled clinician prior to initiating methadone

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Poll Question

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- B. A 78 year old patient with breast cancer with arm pain that is "burning and tingling"
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- D. A 59 year old patient with end-stage heart failure and stage 4 chronic kidney disease

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Methadone Dosing

Methadone Dosage Forms and Administration

- Oral tablet: 5 mg, 10 mg, 40 mg
 - 40 mg tablets are limited to opioid addiction maintenance and hospitals
- Oral concentrate: 10 mg/mL
- Oral solution: 5 mg/5 mL
- Parenteral solution: 10 mg/mL
 - Most clinicians support parenteral : oral ratio of 1 : 2
 - Intermittent or continuous administration
 - IV administration may be associated with higher risk of QTc prolongation
 - SC administration can cause local irritation
- Tablets and oral solutions can be given orally, rectally, or sublingually

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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

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Methadone Dosing Example: Opioid Naïve Patient

- 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

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Patient Case

- 71 year old female with lung cancer with bone metastases
- PPS 40%, ambulatory with walker, swallowing normal
- Diagnoses: hypertension, depression, chronic kidney disease
- Allergies: morphine, penicillin (reactions unknown)
- Medications:
 - Dexamethasone (Decadron®) 4 mg PO qam
 - Docusate (Colace®) 100 mg PO daily
 - Lisinopril (Prinivil®) 20 mg PO daily
 - Lorazepam (Ativan®) 0.5 mg PO q6h PRN anxiety
 - Oxycodone/APAP (Percocet®) 10/325 mg 1 tablet PO q4h PRN pain
- Chief complaint: uncontrolled pain
 - Oxycodone/APAP 10/325 mg is effective but does not last
 - Taking about 5 doses of oxycodone/APAP 10/325 mg per day

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Methadone Dosing Example: Opioid Rotation

1. Calculate patient's total daily oral morphine equivalent (OME)
 - Total all opioid doses (routine and breakthrough) over a 24 hour period
 - Convert to morphine using equianalgesic chart
2. Calculate oral methadone 24 hour dose equivalent based on OME
 - Starting methadone dose should be ~20% of the total OME (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

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Methadone Dosing Example: Opioid Rotation

3. Assess patient factors necessitating a calculated dose reduction by 30-50%
 - Incomplete cross-tolerance
 - Addition of co-analgesics
 - Neurotoxicity present
 - Significant hepatic impairment
 - Medications that may increase methadone concentration
4. Consider tapering previous opioid over 3-5 days if patient is using high dose opioids to prevent opioid withdrawal and psychological failure

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Patient Case – Methadone Dosing

1. Calculate patient's total daily oral morphine equivalent (OME)
 - Total all opioid doses (routine and breakthrough) over a 24 hour period
 - Oxycodone/APAP 10/325 mg x 5 doses/day = 50 mg/day of oxycodone
 - Convert to morphine using equianalgesic chart
 - $\frac{50 \text{ mg oxycodone}}{x \text{ mg oral morphine}} = \frac{20 \text{ mg oxycodone}}{30 \text{ mg oral morphine}}$
$$x = 75 \text{ mg OME per day}$$
2. Calculate oral methadone 24 hour dose equivalent based on OME
 - Starting methadone dose should be ~20% of the total OME (1:5 ratio)
 - 75 mg OME x 20% = 15 mg oral methadone per day
 - Divide 24 hour methadone dose by 2 for q12h ATC or 3 for q8h ATC dosing
 - Methadone 7.5 mg PO Q12h -OR- methadone 5 mg PO Q8h

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Patient Case – Methadone Dosing

3. Assess patient factors necessitating a calculated dose reduction by 30-50%
 - Incomplete cross-tolerance
 - Addition of co-analgesics
 - Neurotoxicity present
 - Significant hepatic impairment
 - Medications that may increase methadone concentration
4. Consider tapering previous opioid over 3-5 days if patient is using high dose opioids to prevent opioid withdrawal and psychological failure
 - Do you need to taper oxycodone/APAP?
 - Since total daily dose is low (50mg/day), tapering is likely not necessary

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Methadone Dosing Example: Breakthrough Dosing

- 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 preference
 - May use methadone
 - Dose is about 10-15% of the 24 hour dose given q4h PRN pain

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Patient Case – Breakthrough Pain Medication

- What are the options for breakthrough pain?
 - Continue oxycodone/APAP PRN as ordered
 - Change oxycodone/APAP to immediate release oxycodone 10mg tablets (1-2 tablets PO/SL q1h PRN)
 - Change oxycodone/APAP to methadone 2 mg PO/SL Q4h PRN

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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
- Methadone dose should not be increased by more than 25-30%, or increased sooner than every 4-5 days

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If Toxicity is Suspected

Respiratory Rate 6-9 breaths/minute*	Respiratory Rate < 6 breaths/minute*
↓	↓
Hold doses until RR returns to baseline or 10-12	Hold dose until RR returns to baseline or 10-12
↓	↓
Reinstate at 50% of previous methadone dose	Consider giving naloxone 0.1mg subcutaneously every 10-15 minutes (may need to repeat due to methadone's long half-life)

*not associated with the dying process

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Take Note!

Because of methadone's unique pharmacology, vigilance during initiation and dosage titrations is crucial

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Barriers to Methadone Use

What are Potential Barriers to Methadone Use?

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

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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

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The Media



<http://www.methadonesupport.org/ISSUES.html>

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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

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Education, Understanding, and 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."

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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

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Questions

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