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EDUCATIONAL RESOURCES

HOSPICE

METHADONE BASICS FOR HOSPICE PROVIDERS

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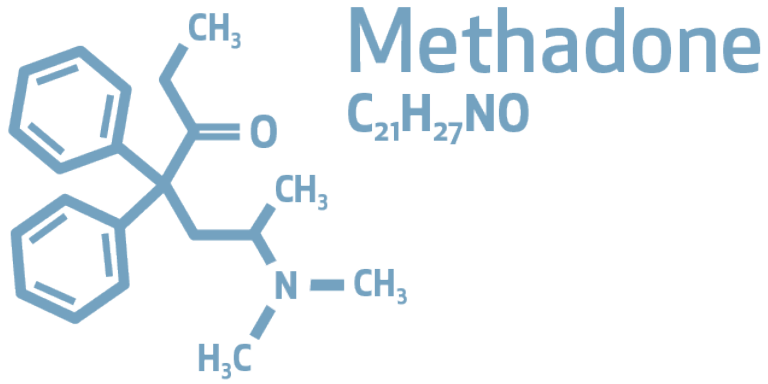
AvaCare Inc.

OBJECTIVES

- Discuss the history of methadone
- Review types of pain and basic pain assessment
- Discuss the risks and benefits
- Describe the appropriate use of methadone in the hospice population
- Review dosing and monitoring strategies

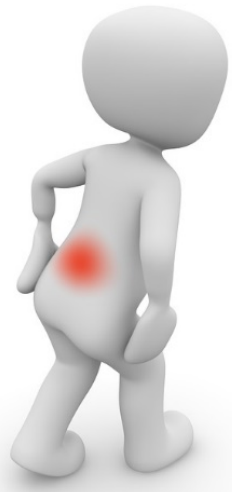


HISTORY

- Developed by German scientists in the 1930s
  - Used in Europe in WWII
- Marketed by Eli Lilly in the U.S. as Dolophine
  - Claims methadone is a "safe" alternative to morphine due to reduction in sedation or nausea
- 1990s: growing evidence for neuropathic pain control
  - Resurgence of use for chronic and malignant pain
- 2006: FDA Public Health Advisory

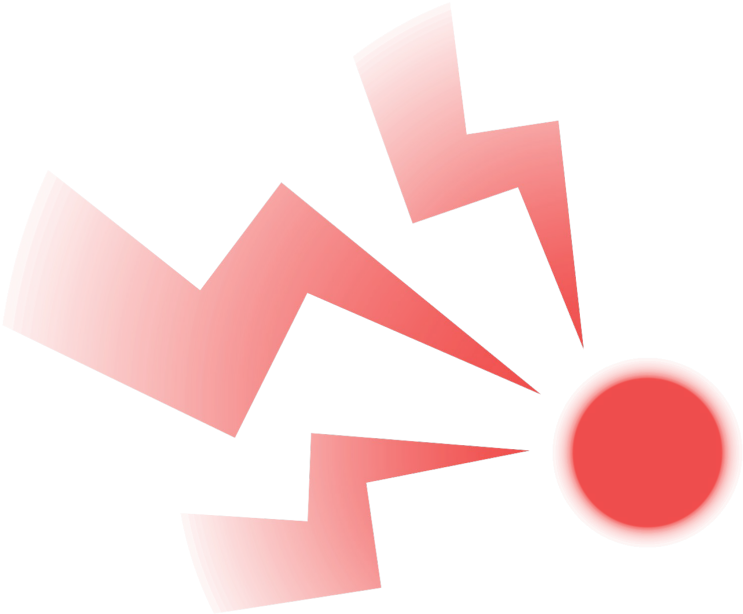
TYPES OF PAIN

- Acute
  - Duration = brief
    - Hours, days, weeks, or a few months
  - Tissue damage, inflammation, brief disease process, procedural
- Chronic
  - Duration = extended period
    - Months, years, lifetime
  - Chronic malignant pain
  - Chronic nonmalignant pain



TYPES OF PAIN

- Nociceptive pain
  - Visceral
  - Somatic
- Neuropathic pain
- Mixed, unspecified pain
- Pain resulting from psychological disorders

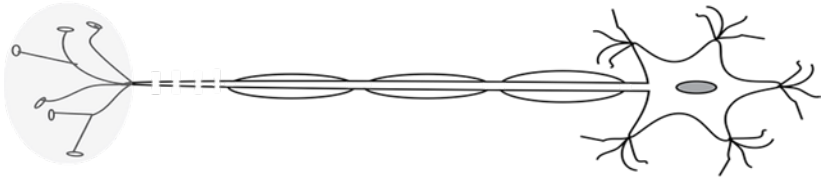


PAIN SCREENING & ASSESSMENT

- NQF #1634 Pain Screening
  - Measure Description: Percentage of patient stays during which the patient was screened for pain during the initial nursing assessment.
- NQF #1637 Pain Assessment
  - Measure Description: Percentage of patient stays during which the patient screened positive for pain and received a comprehensive assessment of pain within 1 day of the screening.
    - Location, severity, character, duration, frequency, what relieves or worsens that pain, and the effect on function or quality of life

METHADONE AND NEUROPATHIC PAIN

- Most effective opioid for neuropathic pain
- Active N-methyl-D-aspartate (NMDA) receptor antagonist
  - Reduces CNS sensitization to pain/hyperalgesia
  - Reduces CNS amplification of pain sensation
- Few other known NMDA receptor antagonists:
  - Dextromethorphan
  - Ketamine
  - Memantine



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PHARMACOKINETICS

ABSORPTION

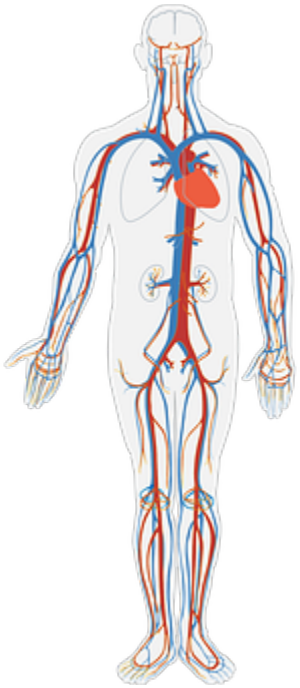
- Variety of routes for administration
  - Oral, Rectal, Intravenous (IV), Subcutaneous (SQ), Epidural
    - Oral tablets (5mg, 10mg, 40mg), liquid (10 mg/5 mL), liquid intensol (10 mg/mL)
  - Intramuscular (IM): Should generally be avoided in pain management
  - Intrathecal: Not FDA approved
- Basic, Lipophilic
- Peaks 2-4 hours after oral dosing
- Oral, rectal and IV routes of administration yield a mean bioavailability of 70-80%

DOSING PEARL: IV ROUTE

- Danger: QT prolongation and lack of data
- Given IV or Subcutaneous via PCA, continuous or intermittent bolus infusion
  - Subcutaneous infusions may result in localized reactions; rotate site
- Total Daily Dose (TDD) parenteral methadone dose is 50% of the oral TDD
- PCA is the preferred method
  - Calculate basal rate
    - Not to be increased for AT LEAST 12 hours
  - Continuous basal rate or intermittent doses Q6-8H

DISTRIBUTION

- Lipophilic = fat soluble
  - Distributed throughout the body and slowly released back into the plasma
- Extremely long half-life
- Protein binding
  - Free/unbound drug results in pharmacologic effect
  - Results in a wide variance of response among patients



METABOLISM

- Primarily metabolized in the liver
  - CYP3A4, 2B6, 2C8, 2C9, 2C19, 2D6
  - Auto-Inducer
- CYP3A4 and/or 2B6 INHIBITORS: methadone toxicity
  - Examples: Verapamil, Fluconazole, Paroxetine, Doxycycline, Clarithromycin
- CYP3A4 and/or 2B6 INDUCERS
  - Examples: Carbamazepine, Phenytoin, Phenobarbital

ELIMINATION

- Inactive metabolites eliminated in urine and feces
  - Useful medication in renal disease
- Average elimination half-life of 20-35 hours
  - Result = potential toxicity
- Four to ten days to reach steady state
  - Steady state = the rate of the drug in equals the rate of the drug out.
  - Do I only have to worry about reaching steady state once?

HEPATIC & RENAL CONSIDERATIONS

- Safe in renal failure → No active metabolites
  - Dose should still be reduced in severe renal impairment
- Does undergo hepatic metabolism → should be avoided in severe liver disease

Estimated Renal Function	Preferred Opioids
CrCl > 40 mL/min	Morphine Oxycodone Hydromorphone Methadone
CrCl = 30-40 mL/min	Oxycodone Hydromorphone Methadone
CrCl < 30 mL/min	Oxycodone Methadone

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QT PROLONGATION

QT PROLONGATION & METHADONE

QT Prolongation

↓

Torsades de Pointes (TdP)

↓

Ventricular tachycardia

QT PROLONGATION & METHADONE

- Risk Factors
  - Female
  - Impaired liver function
  - Heart disease: arrhythmias, CAD, history of MI, CHF
  - QT prolonging medications
    - Examples: amiodarone, quetiapine, haloperidol, chlorpromazine, citalopram, paroxetine, fluoxetine, sotalol, trazodone, ranolazine, and ondansetron
  - Electrolyte imbalances
    - Examples: hypokalemia, hypomagnesemia
    - May be caused by diuretics, laxatives, vomiting and diarrhea
  - Methadone doses >200 mg per day

QT PROLONGATION: CLINICAL CONSIDERATIONS

- Avoid in multiple risk factors
- Reduce controllable risk factors
  - Example: dehydration, nausea/vomiting/diarrhea, medications
- Arrhythmia alone is not a contraindication
- Risk vs benefit discussion with patient and caregivers
- Monitor for new or increased tachycardia, syncope, palpitations, diaphoresis
- Consider baseline and periodic EKG in patients with longer prognoses

QT PROLONGATION: MONITORING

- EKG Monitoring Guidelines
  - Center for Substance Abuse Treatment Expert Panel
    - *Ann Intern Med*. 2009;150:387-395.
  - U.S. Consensus Guideline
    - *Palliat Support Care*. 2008; 6(2): 165-176.
  - American Pain Society (APS)
    - *J Pain*. 2014; 15(4):321-337.
- General Guidelines
- Not written specifically for hospice patients
- New Hospice and Palliative Care Consensus White Paper
  - *J Pain Symptom Manage*. 2019;57(3):635-645.

SUMMARY: RISKS VS BENEFITS

RISKS

- QT Prolongation
- Time to steady-state
- Clinician discomfort
- Patient discomfort
- Respiratory depression
- Drug-drug interactions

BENEFITS

- Neuropathic Pain
- Long half-life
- Multiple formulations
- Bioavailability
- Morphine allergy
- ESRD
- Cost

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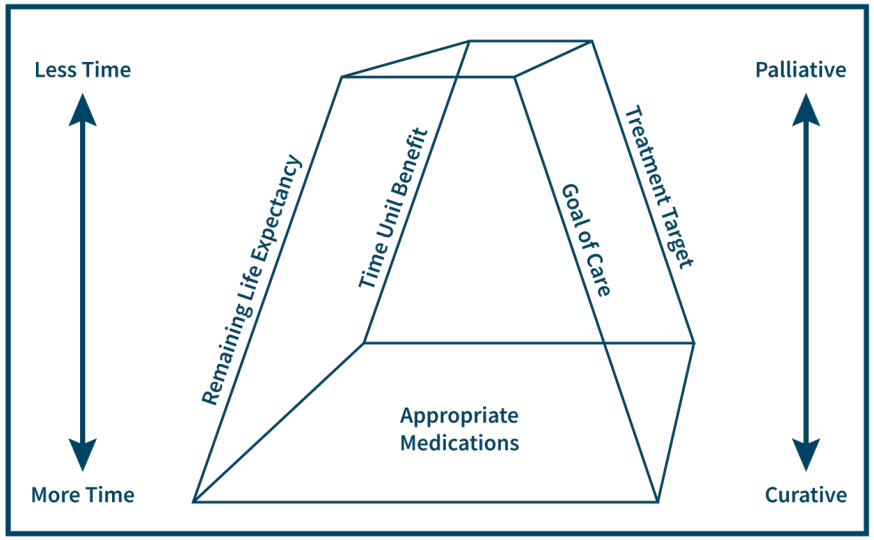
HOSPICE CONSIDERATIONS

REMS

- Monitoring includes therapeutic response, adverse reactions, environment oversight, and REMS
- Risk Evaluation and Mitigation Strategy (REMS)
  - Patient, family, and caregiver education
  - Locked medication storage boxes
  - Designated caregivers to assist with administration
  - Alternate routes of administration
  - Limited prescription quantities
  - Adjusted basal regimens when appropriate
  - Alternate suggestions: treatment agreements and urine drug testing (UDT)

METHADONE IN HOSPICE

- Medication appropriateness refers to whether a medication is <u>useful</u> in an individual clinical situation based on both the attributes of the medication and its recipient.
- Important factors to consider:
  - Remaining life expectancy of patient
  - Time until therapeutic benefit of medication
  - Goals of care
  - Treatment target



Clin. Pharmacol Ther. 2009;85(1):103-7.

IS MY PATIENT A METHADONE CANDIDATE?

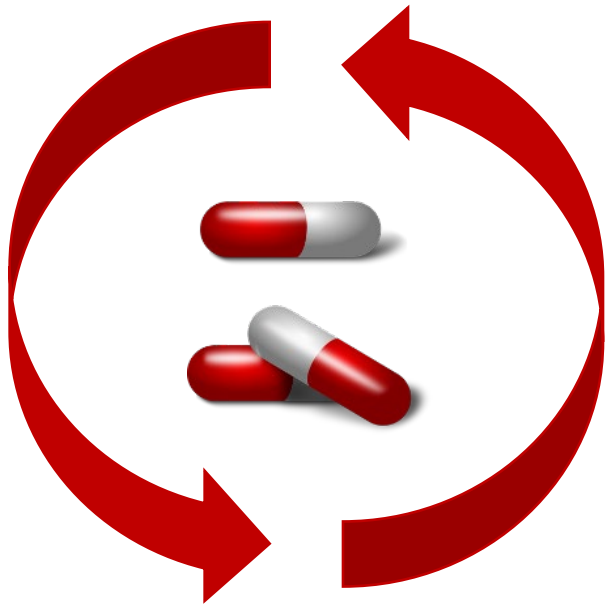
- Patient A is a 53-year-old male with esophageal cancer recently admitted to the hospital after a pain crisis.
- Home Regimen:
  - Morphine ER 200 mg po q8h
  - Morphine IR 60 mg po q2h PRN breakthrough pain
- Dysphagia secondary to disease progression
- Hospital Regimen:
  - Hydromorphone 1.2 mg/hour continuous subcutaneous infusion with 0.5 mg bolus q20 minutes PRN breakthrough pain

IS MY PATIENT A METHADONE CANDIDATE?

- Patient B is a 52-year-old female on hospice for 10 days with a primary diagnosis of metastatic melanoma.
  - Palpable tumors
  - Significant pain with minimal movement
- History of substance use disorder and diversion
- Home Medications:
  - Hydroxyzine HCl, Hydrocodone/Acetaminophen, Lyrica, MiraLax OTC, Oxycodone ER, Promethazine, Senna-S
  - Analgesics:
    - Oxycodone ER 160 mg po q6h
    - Hydrocodone/Acetaminophen 10/325 mg 2 tabs po q4h PRN
    - Pregabalin 200 mg po bid

METHADONE IN HOSPICE

- Opioid Rotation
  - Switching to a different opioid due to inadequate analgesic response or intolerable adverse effects
- Incomplete cross tolerance
  - Improved pain control
  - Decreased intensity of adverse effects
- Failure to respond to one opioid does not represent a class response



METHADONE IN HOSPICE: CONSIDERATIONS

- Patients with rapidly escalating opioid requirements (greater than 200 mg of morphine equivalents a day)
  - Full conversion
  - Adjunct dosing
- Patients with dose-limiting adverse effects from other opioids
  - Nausea, constipation, hallucinations, myoclonus
- Dysphagia
- Patients or caregivers with a history of substance use disorders

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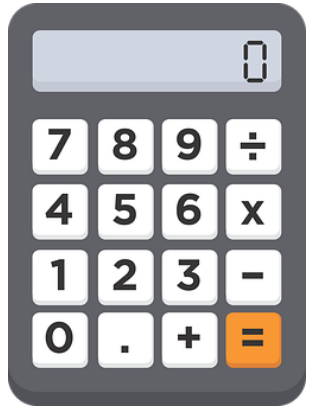
DOSING

METHADONE DOSING

1. Calculate total daily opioid dose in oral morphine equivalents (OME)
2. Use oral morphine: oral methadone ratio
3. Establish methadone dose schedule
   (total daily methadone dose divided into 2-3 doses per day)
4. Use a traditional opioid for breakthrough pain
   (10-15% of basal opioid requirement)
5. Monitor pain and adverse effects
   - Increase methadone total daily dose no more frequently than every 5 days
   - Patients with higher OME requirements may require a cross-taper (rule of thirds)

METHADONE DOSING: CONVERSION RATIO

- Methadone is dosed using a non-linear conversion
  - The higher the dose of oral morphine equivalents, the less methadone per oral morphine equivalents required.
- Methadone (NMDA blockade) reverses tolerance — increases sensitivity to opioids
- Increased opioid sensitivity results in a lower methadone requirement



METHADONE DOSING: CONVERSION RATIO

OPIOID NAÏVE		
Consider 2 to 7.5 mg oral methadone per day, in divided doses		
OPIOID TOLERANT		
ORAL MORPHINE EQUIVALENTS (OME) PER DAY	**PATIENT AGE**	**OME: ORAL METHADONE RATIO**
<60 mg		Use opioid naïve dosing
60-199 mg	<65 years-old	10:1
60-199 mg	>65 years-old	20:1
>200 mg		20:1

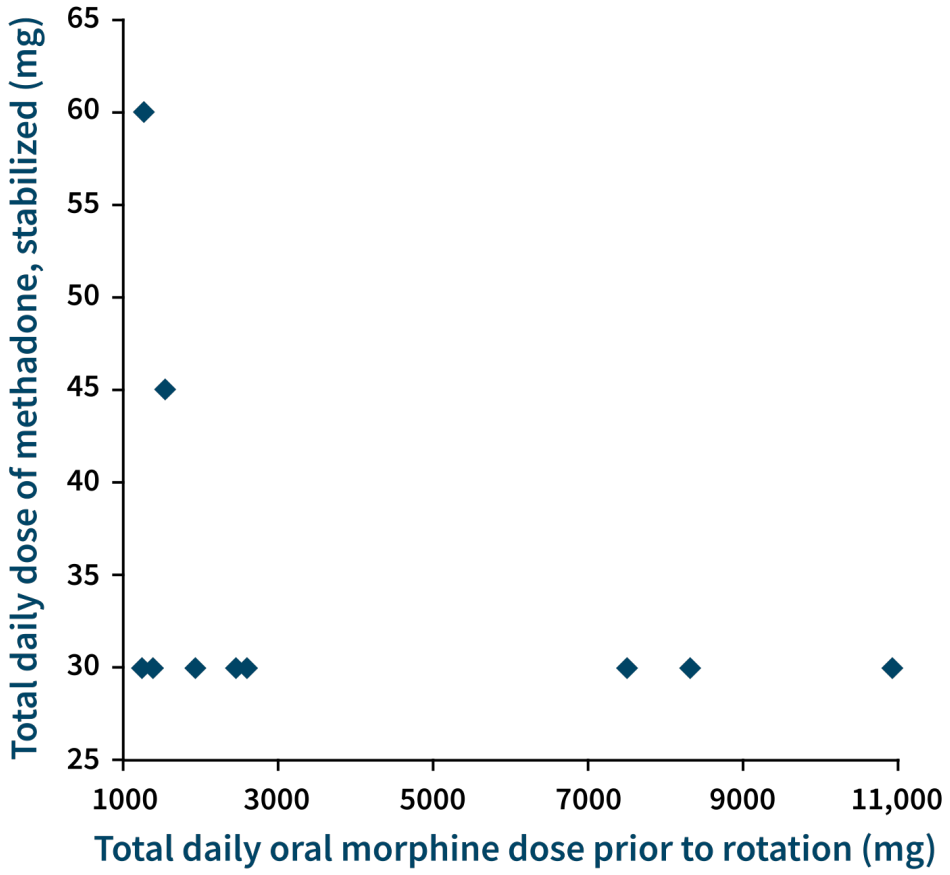
J Pain Symptom Manage. 2019;57(3):635-645.

METHADONE DOSING: CONVERSION RATIO

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

Story P, et al. AAHPM Dosing Conversion Guidelines; 2017.

METHADONE DOSING DATA



JPM.2013;16(8): 947-950.

METHADONE DOSING DATA

APPENDIX TABLE A1. END OF LIFE/PALLIATIVE EDUCATION RESOURCE CENTER AND FRIEDMAN MORPHINE-TO-METHADONE CONVERSION RATIOS

MEDD (mg)	*Morphine:Methadone (EPERC)*	*Morphine:Methadone (Friedman)*
<100	3:1	and <65 years old, 10:1
101–300	5:1	
301–600	10:1	
601–800	12:1	
801–1000	15:1	
>1001	20:1	and/or >65 years old, 20:1
>2000	40:1 and confirm with Pain or Palliative PharmD	40:1 and confirm with Pain or Palliative PharmD

EPERC, end of life/palliative education resource center; MEDD, morphine equivalent daily dose.

JPM.2017;20(12):1385-1388.

METHADONE DOSING DATA

AAHPM Methadone Dose Conversion Guidelines	
Steps:	**Notes:**
Step 1: Calculate total daily morphine dose	Convert all current opioid therapy to PO Morphine
Step 2: Convert to Methadone	PO Morphine: PO Methadone ration; Non-linear
Step: 3: Account for incomplete cross-tolerance	50% dose reduction; opioid rotation
Step 4: Determine dosing schedule	Divided doses; typically TID (q8h)
Step 5: Choose a PRN medication	Traditional opioid; short half-life
Step 6: Determine PRN dose	10-15% of the total opioid dose
Step 7: Make adjustments to regimen	No more frequently than steady-state achieved

AAHPM Dosing Conversion Guidelines; 2017.

BREAKTHROUGH PAIN

- Especially important during initial titration
- Utilize traditional immediate-release opioid
  - Morphine IR, oxycodone IR, hydromorphone IR
    - Dosed q2-4h PRN breakthrough pain
  - One breakthrough dose = 10% - 15% of total daily dose of oral morphine equivalents (OME)
- If methadone must be used for breakthrough pain, start low and limit to 3 PRN doses per day.
- Be conservative with daily methadone dose and more aggressive with breakthrough pain regimen.

METHADONE DOSING: CLINICAL CONSIDERATIONS

- If more than 3 breakthrough doses are needed per day to treat baseline pain, contact prescriber with recommendation to increase methadone.
- If breakthrough pain is caused by movement or is episodic, pre-treat with short acting opioids.
- Hold methadone for lethargy, respirations < 9/min, decreased responsiveness, or other signs of opioid toxicity.
- Although it is as effective as other opioids, do not use methadone PRN for shortness of breath.
  - Use short-acting, traditional opioid

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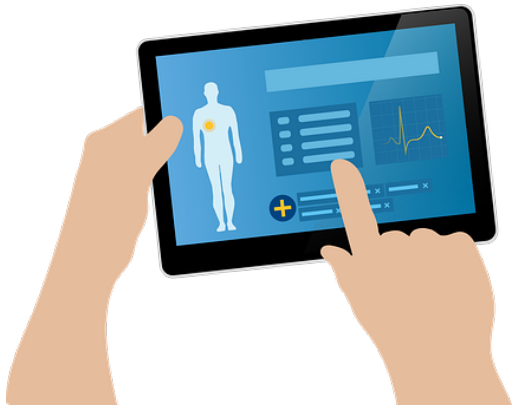
EXAMPLE

MRS. C

- 64-year-old female admitted to hospice
  - Primary Dx: breast cancer with mets
  - Complains of increasing back pain
    - Intensity: 10/10
    - Describes as stabbing and burning
  - PMH: Diabetes, Non-smoker
- Current analgesic regimen:
  - Morphine ER 45 mg PO q12h
  - Morphine IR 7.5 mg PO q2h PRN BTP (using 6 doses/day)
  - Total Oral Morphine/day: 135 mg



MRS. C

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MRS. C

- Methadone Equianalgesic dosing ratio: 10:1
- 135 mg ÷ 10 = 13.5 mg methadone per day
- Consider dose reduction
  - 25% = 10 mg methadone
  - 50% = 7 mg methadone
- Round up or down based on pain severity and individual patient factors.

Mrs. C's Plan:

- Discontinue Morphine ER
- Begin Methadone 5mg po q12h
- Increase Morphine
  - 20 mg/mL: Take 0.5 mL (10 mg) to 1 mL (20 mg) po q2h PRN pain
- Monitor analgesic response and methadone toxicity
- No changes for 5-7 days!

MRS. C: CONTINUED

- Today is methadone day 3
  - Current regimen: Methadone 5 mg PO q12h
- Reports pain intensity: 9/10
- Has taken two morphine 10 mg doses in the last 24 hours
- Patient insists the methadone dose should be increased
- What do we do?

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ADVERSE EFFECTS

MANAGEMENT OF ADVERSE EFFECTS

Common Adverse Effects	First Line Medication(s)	Comments
Opioid-induced constipation (stasis)	Senna-S Metoclopramide	Induces motility Avoid "all mush, no push!" Less severe/frequent with methadone
Opioid-induced nausea/vomiting	Haloperidol Prochlorperazine Metoclopramide	Dopamine-mediated Less severe/frequent with methadone
Sedation	Oral steroid Methylphenidate	Reduces with continued use Less severe/frequent with methadone
Opioid-induced itching/rash	Oral diphenhydramine *Hydroxyzine	Uncomplicated itching/rash is a common side effect, not an allergy. Switching opioids may or may not be effective

TOXICITY

- Signs and symptoms:
  - Extreme somnolence
  - Stupor
  - Muscular flaccidity
  - Cold, clammy skin
  - Constricted pupils
  - Respiratory depression
- Synergistic toxicity: benzodiazepines
  - Examples: lorazepam, diazepam

PATIENT MONITORING

Counseling and Monitoring:

- Drowsiness
- Decreased level of arousal
- Apnea/loud snoring
- Decreased respirations
- Slurred speech
- Pinpoint pupils

Clinicians Should Consider:

- EKG
- Counseling
- High starting dose
- Interacting medications
- Co-administration of medications that may also decrease the respiratory rate

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ADJUVANT DOSING

ADJUVANT DOSING

- Patients may be unable or unwilling to switch completely to methadone.
- Consider adding a smaller dose of methadone to a patient's existing pain regimen:
  - Improves pain control
  - Reduces side effects
  - Cost
- Current regimen is usually decreased
- Evaluate adjunct medication regimen:
  - Steroids
  - Gabapentin

MR. P

- 42-year-old male with pancreatic cancer and significant metastases
- Still able to swallow pills whole
- Currently taking: Morphine IV via continuous infusion
  - 25 mg per hour continuous
  - 10 mg bolus q 10 min PRN breakthrough pain
  - Has used 39 breakthrough doses with 51 attempts in the last 24 hours
- Pain is still 10/10 and he states: "Everything hurts! Even the blanket!"
- Refuses to switch outright to methadone

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SUMMARY

SUMMARY: HOSPICE

Good Methadone Candidate

- True morphine allergy
- Intolerable opioid adverse effects
- Renal disease
- Neuropathic pain
- Refractory pain
- Cost burden
- Dysphagia

Poor Methadone Candidate

- Limited prognosis
- Numerous drug-drug interactions
- History of arrhythmia
- Lives alone
- Cognitively impaired
- Adherence issues

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HOSPICE

QUESTIONS?

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