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ADVANCED EDUCATION

CERTIFICATION SERIES



PALLIATIVE CARE

Methadone Madness: Part 2

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Titles and Affiliations

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Disclosures



Learning Objectives

- Review how to perform opioid conversion calculations
- Calculate a methadone starting dose for an opioid-tolerant patient
- Describe a strategy to use methadone as an adjuvant analgesic
- Explain conversion between oral, rectal, and parenteral methadone
- Describe a strategy for increasing methadone, including magnitude of increase and speed of increase

Reasons for Changing Opioids

- Lack of therapeutic response
- Development of adverse effects
- Change in patient status
- Other considerations
 - Opioid/formulation availability
 - Formulary issues
 - Patient/family healthcare beliefs



A Rose By Any Other Name...

- Opioid rotation
- Opioid substitution
- Opioid switching
- Opioid Conversion Calculation!



Equianalgesic Dosing Terminology

- Opioid responsiveness
 - The degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or the occurrence of acceptable analgesia
- Potency
 - Intensity of the analgesic effect of a given dose
 - Dependent on access to the opioid receptor and binding affinity
- Equipotent doses = equianalgesic
- Equianalgesic opioid dosing

Converting Among Routes: Same Opioid

- Bioavailability
 - The rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action
- Oral bioavailability
 - Morphine 30%-40% (range 16%-68%)
 - Hydromorphone 50% (29%-95%)
 - Oxycodone 80%
 - Oxymorphone 10%

Equianalgesic Opioid Dosing

Drug	Equianalgesic Doses (mg)	
	Parenteral	Oral
Morphine	10	25
Codeine	100	200
Fentanyl	0.15	NA
Hydrocodone	NA	25
Hydromorphone	2	5
Meperidine	100	300
Oxycodone	10*	20
Oxymorphone	1	10
Tapentadol	NA	100
Tramadol	100*	120

*Not available in the US

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NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

www.fda.gov/media/150396/download.

The Problem with “Those Charts”

- Source of equianalgesic data
- Patient-specific variables
- Unidirectional vs bidirectional equivalencies



5-Step OCC Process

- Globally assess pain complaint (PQRSTU)
- Determine TDD current opioid (LA and SA)
- Decide which opioid analgesic will be used for the new agent and consult established conversion tables to determine new dose
- Individualize dosage based on assessment information gathered in Step 1
- Patient follow-up and continual reassessment (7-14 days)

TDD – total daily dose

www.ncbi.nlm.nih.gov/books/NBK535402/

Case 1

- HW is an 84 year old man in a LTC facility with general debility on oxycodone 5 mg/acetaminophen 325 mg tabs, 6 per day, pain well controlled
- He can no longer swallow the tablets and his physician asks you convert him to an oral solution of oxycodone 5 mg per 5 ml

Case 1

- Pain assessed; stable and controlled
- 6 tabs x 5 mg oxycodone per day = 30 mg TDD oral oxycodone
- Switching to 5 mg oxycodone by oral solution (5 mg/5 ml).
Dose is 5 mg; volume is 5 ml (5 mg oxycodone/5 ml) q4h
- Individualization – oxycodone is oxycodone; no need to change dose
- Monitor response

Case 1 To Go Points

- Ignore contribution of acetaminophen
- You're going from oral oxycodone tablet (as oxycodone/acetaminophen) to oral oxycodone (oral solution)
 - The only thing you have to consider is the bioavailability difference between oxycodone as a tablet, and oxycodone as an oral solution
 - It's the same, so it's a 1:1 conversion

Case 2

- WP is a 62 year old man with multiple myeloma and diffuse bony mets admitted to hospice
- Current analgesic regimen extended-release oral morphine 30 mg po q12h plus oral morphine solution 10 mg prn (takes 6 times per day), plus dexamethasone
- Admitted to inpatient to switch to IV morphine due to continued pain

Case 2

- Pain assessed
- TDD oral morphine = 30 mg po q12h = 60
- Oral morphine solution 10 mg x 6 = 60 mg
- TDD = 120 mg oral morphine
- Consult equianalgesic dosing chart for equivalency

TDD – total daily dose

Case 2

- $\frac{\text{"x" mg new opioid}}{\text{mg of current opioid}} = \frac{\text{equivalent mg new opioid}}{\text{equivalent mg current opioid}}$
- $\frac{\text{"x" mg IV morphine}}{120 \text{ mg oral morphine}} = \frac{10 \text{ mg (IV morphine)}}{25 \text{ mg (oral morphine)}}$
- $(x)(25) = (10)(120)$
- $X = 48 \text{ mg IV morphine per day}$
- 25%-50% increase \rightarrow morphine 10 mg IV q4h (TDD 60 mg)

Case 2 To Go Points

- You're converting from morphine to morphine, BUT you're converting between routes of administration (oral to IV)
 - Morphine IV dose = $\sim 1/3$ of morphine PO dose
 - So, morphine IV dose is $\sim 1/3$ morphine PO dose (work in total daily doses for ease of calculation)

Case 2 To Go Points

- When you do a conversion calculation if you are SWITCHING from one opioid to a DIFFERENT opioid, you usually need to reduce the dose you calculated
 - This patient was going from morphine to morphine so you don't have to do that
- BUT he is in pain, so you need to increase the dose

Case 3

- Mrs. Smith is a 92 year old woman with breast cancer, currently receiving MS Contin 60 mg po q12h, plus MSIR 20 mg po q4h prn, taking on average 3 doses per day
- She has been on this dose for about 2 weeks, and her pain is well controlled, but she has developed visual hallucinations that she finds quite frightening

Case 3

- She has significant renal impairment (serum creatinine of 2.0 mg/dl) and this adverse effect may be due to accumulation of morphine metabolites
- Her physician would like to switch her to long-acting oxycodone
- What are the steps necessary to make this conversion?

Setting Up the Conversion Equation

1. Calculate total daily dose of current opioids
2. Set up conversion ratio between old opioid (and route of administration) and new opioid (and route of administration) as follows:

$$\frac{\text{"x" mg new opioid}}{\text{mg of current opioid}} = \frac{\text{equivalent mg new opioid}}{\text{equivalent mg current opioid}}$$

Case 3

$$\frac{\text{"x" mg new opioid}}{\text{mg of current opioid}} = \frac{\text{equivalent mg new opioid}}{\text{equivalent mg current opioid}}$$

$$\frac{\text{"x" mg new opioid}}{180 \text{ mg morphine}} = \frac{20 \text{ mg (oxycodone)}}{25 \text{ mg (morphine)}}$$

$$(x)(25) = (20)(180)$$

$$X = 144 \text{ mg oral oxycodone per day}$$

Solving the Equation

- Cross multiply, solve for “x”
- Individualize dose for patient
 - Pain controlled; developed adverse effect
 - Reduce 25%-50%
 - Calculated oxycodone 144 mg po qd
 - Reduce to 72-108 mg po qd

Solving the Equation

- Reduce to 72-108 mg po oxycodone qd
- Decide how many times per day you're going to dose the new opioid; divided by the appropriate dosing interval, and select a dosage that is available in that strength
- Oxycodone extended-release 30 mg po q12h (or 40 mg po q12h) with oxycodone IR 10 mg po q2h prn

Case 3 To Go Points

- In this case you are switching from 1 opioid to a DIFFERENT opioid
- Set up your ratio, calculate total daily dose of NEW opioid
 - If patient's pain is well controlled, REDUCE your calculated dose by 25%-50%
 - If patient was in pain at the time of the switch, go with calculated dose (or round down a little)
- Make sure you can GIVE the dose you recommend
 - With available tablets, capsules or oral solution

Switching

From 1 formulation or route to another of the SAME opioid

- Account for bioavailability
- Increase if patient in pain

From 1 opioid to another opioid

- Use ratios from equianalgesic chart
- If pain controlled, REDUCE calculated dose by 25%-50%
- If patient in pain, use calculated dose, or a little less

Self-Assessment!

WHAT HAVE YOU LEARNED?











OME – oral morphine equivalent

- JR is a 52 year old man admitted to hospice with a diagnosis of end-stage lung cancer. He is taking a nonformulary long acting oral oxycodone tablet, 20 mg po q12h and oxycodone 5 mg every 2 hours as needed for additional pain (he uses about 4 doses per day). This regimen controls his pain, but the hospice would prefer to use methadone. You know the first step is converting the total daily oral oxycodone to the total daily oral morphine equivalent. Which of the following oral morphine equivalent (OME) is correct?
 - A. OME is 60 mg
 - B. OME is 75 mg
 - C. OME is 90 mg
 - D. OME is 120 mg

Self-Assessment!

WHAT HAVE YOU LEARNED?





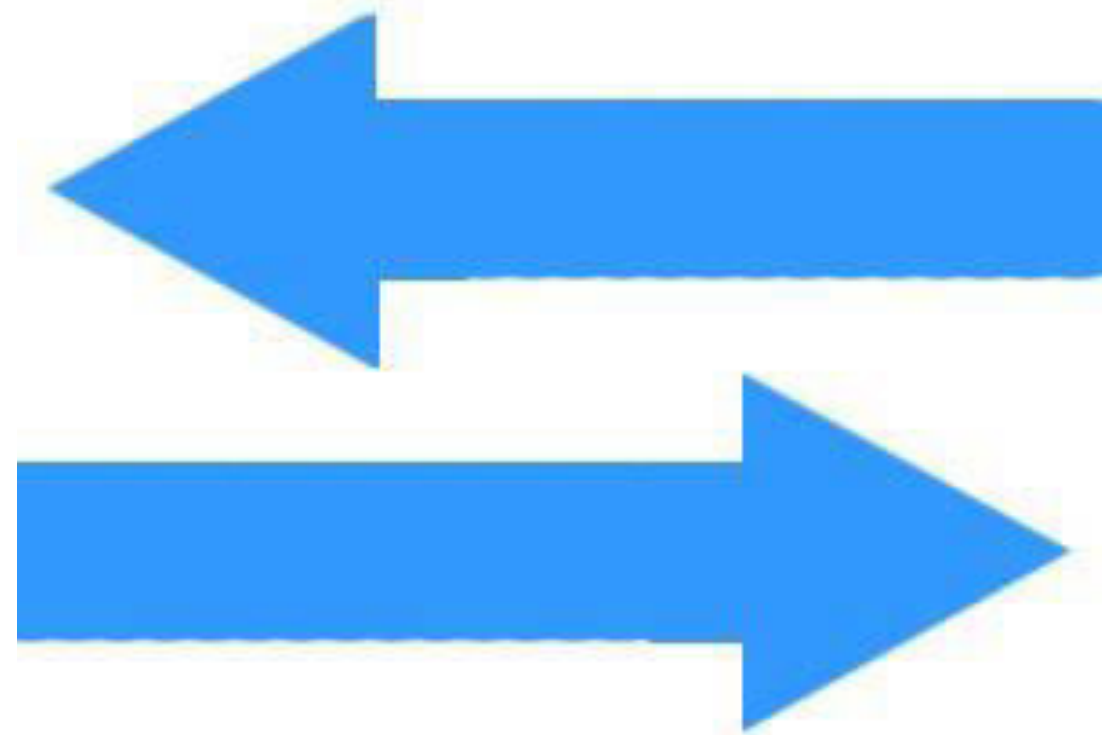






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- A. OME is 60 mg
- B. OME is 75 mg
- C. OME is 90 mg
- D. OME is 120 mg



CONVERSION

Initiating Methadone (HPM)

OME per day	Recommended Methadone Starting Dose
< 40 – 60 mg	2-7.5 mg po qd in 2-3 divided doses
> 60 – 199 mg (and <65 yo)	10:1 (morphine : methadone)
> 200 mg (+/or ≥65 yo)	20:1 (morphine : methadone)

- Do not exceed 30 mg methadone per day as a starting dose
- Reduce calculated dose by 25%-33% if enzyme inhibiting medication on board
- Do not adjust dose for 5-7 days (or per clinical judgement)

The Road to Steady-State

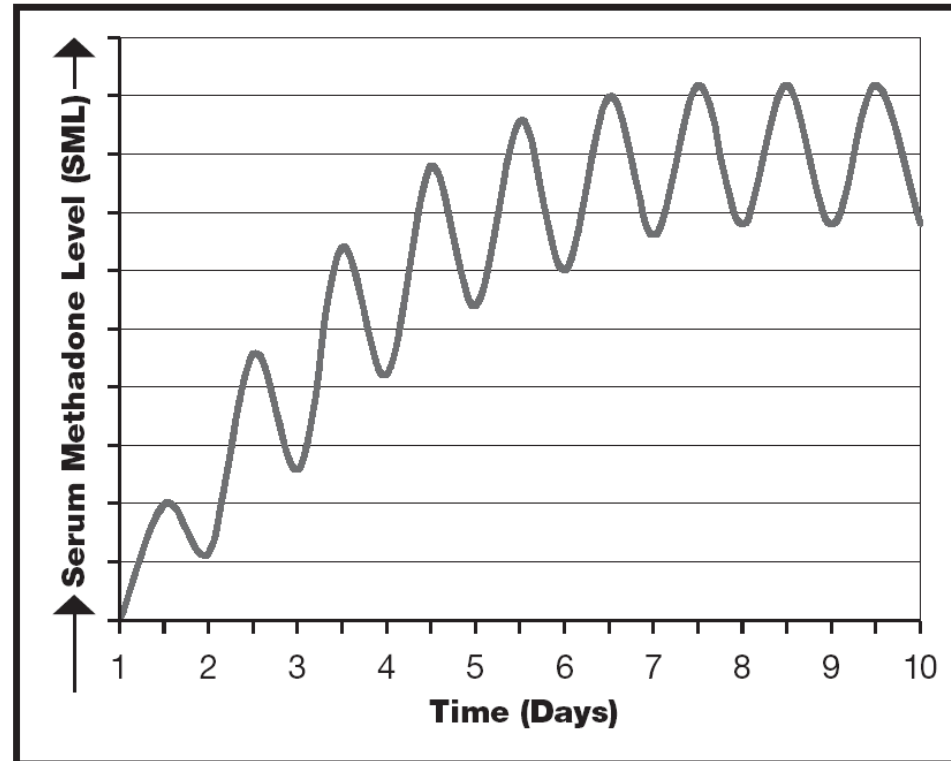


Figure 6-1. Steady-state methadone concentration reached in about 5 days. *Source:* Addiction Treatment Forum: Methadone Dosing and Safety in the Treatment of Opioid Addiction, Stewart B. Leavitt, PhD.

Used with permission *Pain Topics*.

Maximum TDD Conversion

TABLE 2. DIFFERENCES IN PAIN SCALE AND METHADONE DOSE

<i>Pt</i>	<i>Prior MPSS</i>	<i>Stabilized MPSS</i>	<i>Initial methadone dose</i>	<i>Stabilized methadone dose</i>
1	9.0	6.0	5 mg po q6h	10 mg po q8h
2	1.0	2.0	15 mg po q8h	20 mg po q8h
3	4.0	0	10 mg po q8h	10 mg po q8h
4	5.0	5.0	10 mg po q8h	15 mg po q8h
5	6.0	5.5	10 mg po q8h	10 mg po q8h
6	7.5	6.5	10 mg po q8h	10 mg po q8h
7	8.0	5.0	10 mg po q8h	10 mg po q8h
8	0	0	10 mg po q8h	10 mg po q8h
9	8.0	4.5	10 mg po q8h	10 mg po q8h
10	7.0	0	10 mg po q8h	10 mg po q8h

Pt, patient; MPSS, median pain scale score.

Enzyme Inducers

Rifampicin /
rifampin
Rifabutin
Phenobarbital
Phenytoin
Spironolactone
Nevirapine
Efavirenz
Amprenavir
Nelfinavir
Ritonavir
Carbamazepine
St. John's Wort

Enzyme Inhibitors

Amiodarone
Fluconazole
Fluoxetine
Paroxetine
Sertraline
Ciprofloxacin
Fluvoxamine
Amitriptyline

Ketoconazole
Erythromycin
Troleandomycin
Citalopram
Desipramine
Clarithromycin
Telithromycin
Itraconazole

Anti-infectives

Antibiotics

Antifungals

Antivirals

Antidepressants

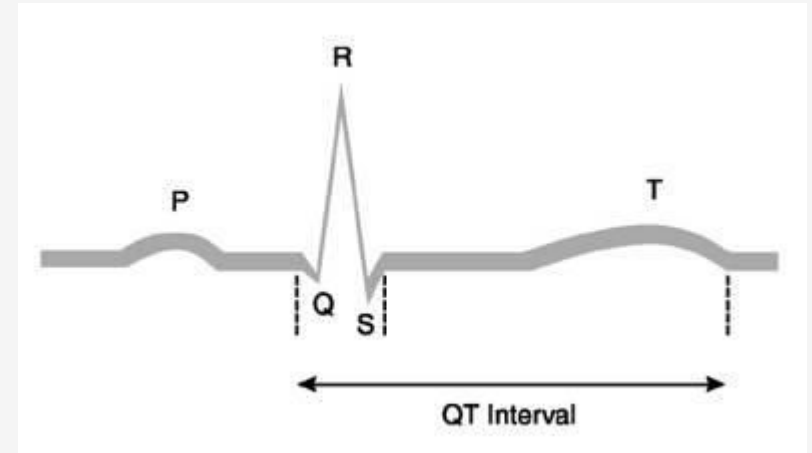
SSRIs

TCA's

Amiodarone

Drugs that Prolong QTc

- Clarithromycin, erythromycin
- Quetiapine, haloperidol
- TCAs
 - Amitriptyline, desipramine, imipramine, nortriptyline
- Cocaine



Chou. *J Pain*. 2014;15(4):321-337.

Case 4

- AO is a 64 year old woman with end-stage breast cancer. She is taking extended-release morphine 60 mg by mouth q12h with morphine oral solution 20 mg by mouth q2h prn breakthrough pain (using about 2 doses qd)
- The morphine makes her itch, and diphenhydramine makes her too sleepy. Her physician would like to switch her to methadone. AO not taking any interacting medications
- Step 1: PQRST
- Pain is nociceptive and neuropathic; pain in chest area, numbness and tingling from axilla, down arm

Case 4 – Step 2 (TDD Opioid)

- She is taking extended-release morphine 60 mg by mouth q12h with morphine oral solution 20 mg by mouth q2h prn breakthrough pain (using about 2 doses qd)
- TDD = 60 mg x 2 = 120 mg PLUS 20 x 2 = 40 mg for a TDD of 160 mg oral morphine
- If patient is not already taking oral morphine, convert to oral morphine
 - Refer to equianalgesic dosing chart
 - Consider LA and SA opioid use
 - Do not reduce for lack of complete cross-tolerance

Opioid	Equianalgesic Equivalence (mg)	
	Parenteral	Opioid
Morphine	10	25
Fentanyl	0.15	NA
Hydrocodone	NA	25
Hydromorphone	2	5
Oxycodone	10 (not in US)	20
Oxymorphone	1	10

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NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

Case 4 – Step 3: Conversion

- Patient's TDD oral morphine is 160 mg; <65 years old
- Use 10:1 conversion
 - Methadone 16 mg TDD
 - Recommendation: 8 mg po q12h (or 5 mg po q8h)
- No interacting medications
 - No need to reduce methadone dose
- What to do for rescue medication?
 - Methadone?
 - Morphine or oxycodone – 10%-15% TDD
 - Morphine (MSIR) 15 mg by mouth q4h prn breakthrough pain
- Rapid switch or gradual?

Case 4 – Step 4: Patient Monitoring

- Ask AO's husband to observe AO several times a day for changes in her respirations (depth, rhythm, rate), difficulty awakening her, snoring, and other signs of opioid overdose
- We will see or speak to AO/husband daily over the next week
- Do not adjust therapy before 5-7 days

Case 5

- Mrs. Juniper is an 84 year old woman residing in a long-term care facility, admitted to hospice with a diagnosis of Alzheimer's dementia
- She also has a long history of chronic low back pain (spinal stenosis) and osteoarthritis of both knees and hips
- She is bedbound for much of the day, and shifts about restlessly; nurse case manager believes this is due to physical discomfort
- The patient was admitted to hospice on OxyContin 20 mg by mouth every 12 hours, and oxycodone oral solution 5 mg every 2 hours as needed for additional pain (not receiving)
- You decide to switch her to methadone. Not receiving any interacting drugs

Case 5

- The patient was admitted to hospice on OxyContin 20 mg by mouth every 12 hours, and oxycodone oral solution 5 mg every 2 hours as needed for additional pain (not receiving).
- Her total daily dose of oral oxycodone is 40 mg
- How do you convert this to oral morphine equivalents per day?

Opioid Conversion Calculations

1. Assess patient's pain complaint thoroughly; is pain controlled (at goal?)
2. Determine average total daily dose of current opioid use (long- and short-acting)
3. Set up ratio using equianalgesic equivalence chart; calculate new dose
4. Individualize calculated dose based on patient assessment in step 1
5. Monitor patient closely; adjust as needed.

	Equianalgesic Equivalence (mg)	
Opioid	Parenteral	Opioid
Morphine	10	25
Fentanyl	0.15	NA
Hydrocodone	NA	25
Hydromorphone	2	5
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NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart.

Case 5

- Total daily dose of oxycodone is 40 mg
- $\frac{\text{"x" mg oral morphine}}{40 \text{ mg oral oxycodone}} = \frac{25 \text{ mg oral morphine}}{20 \text{ mg oral oxycodone}}$
- $(20)(x) = (25)(40)$
- $X = 50$ mg oral morphine
- Because you are using this number to convert to methadone, no need to adjust

Case 5

- 84 years old (>65 years old)
- Receiving 50 mg OME per day
- Defaults to opioid naïve dosing
- Methadone 1 mg by mouth every 8 OR 12 hours
- Methadone 2 mg by mouth every 12 hours
- Oral morphine solution 5 mg by mouth as needed for additional pain every 2 hours

Case 6

- Mr. J. is a 62 year old man admitted to home-based hospice with a diagnosis of end-stage prostate cancer, with widespread metastases to the bone
- He is 5'8" and weighs 165 pounds (normal body habitus)
- Mr. J. is on a transdermal fentanyl patch 75 mcg/h, changed every 72 hours
- He also has an order for oral morphine solution 20 mg every 2 hours as needed for additional pain (about 5 doses/day)
- His pain is not well managed on this regimen and he wants to switch to a different opioid. Not on any interacting medications

Case 6

- You decide to switch him from transdermal fentanyl to methadone, and to add dexamethasone for the metastatic bone pain (no history of diabetes or serious gastrointestinal issues)
- How do you determine the oral morphine equivalent of his current regimen?
- What dose of methadone do you recommend starting?
- How would you time removing the transdermal fentanyl patch and starting oral methadone?
- All EXCELLENT questions!

Case 6

- How do you determine the oral morphine equivalent of his current regimen?
 - TDF in mcg/h ~ 50% of total daily dose oral morphine
 - TDF 75 mcg/h ~ 150 mg oral morphine
 - Plus 5 doses of morphine 20 mg a day = 100 mg
 - TDD oral morphine ~ 250 mg

Case 6

- What dose of methadone do you recommend starting?
 - 62 years old
 - >200 mg oral morphine per day (he's receiving 250 mg oral morphine)
 - 20:1 (20 mg OME:1 mg oral methadone) → 12.5 mg oral methadone per day
- Considerations
 - He's not that much > 200 mg oral morphine a day
 - Is he a "young" 62 year old or an "old" 62 year old?
 - But you're adding a co-analgesic that COULD give you a significant opioid-sparing effect
 - Be conservative with scheduled methadone, but generous with breakthrough

Case 6

- Recommendation:
 - Methadone 7 mg by mouth every 12 hours (methadone 10 mg/ml)
 - Patient tells you a 20 mg dose of oral morphine brings pain down about 2 points
 - Morphine solution 20 mg by mouth every 2 hours as needed for moderate pain, OR
 - Morphine solution 30 mg by mouth every 2 hours as needed for severe pain
- How would you time removing the transdermal fentanyl patch and starting oral methadone?

Case 6

- How would you time removing the transdermal fentanyl patch and starting oral methadone?
- Once the oral methadone solution is IN THE HOME, remove the transdermal fentanyl patch
- Start methadone 8 hours later
- Use oral morphine solution (at 20 or 30 mg q2h prn)

Case 6

Patient's opioid log

Day	Methadone	Morphine	Avg Pain Rating
1	Removed TDF at 8 am, 1 dose methadone 7 mg at 8 pm	4 doses x 30 mg 2 doses x 20 mg = 160 mg OME	8
2	Methadone 7 mg at 8 am and 8 pm	5 doses x 30 mg 2 doses x 20 mg = 190 mg OME	7
3	Methadone 7 mg at 8 am and 8 pm	3 doses x 30 mg 3 doses x 20 mg = 150 mg OME	7
4	Methadone 7 mg at 8 am and 8 pm	2 doses x 30 mg 2 doses x 20 mg = 100 mg OME	6
5	Methadone 7 mg at 8 am and 8 pm	4 doses x 20 mg = 80 mg OME	5
6	Methadone 7 mg at 8 am and 8 pm	4 doses x 20 mg = 80 mg OME	4-5

- What would you like to do at this time? Pain goal ≤ 3

Case 6

- Do not increase methadone before 5 days
- Do not increase by more than 5 mg/day (until TDD methadone >30 mg)
- Patient currently on methadone 7 mg by mouth every 12 hours
- Increase methadone to 9 mg (or even 10 mg) by mouth every 12 hours
- Maintain oral morphine as prescribed for breakthrough pain

Methadone As a Co-analgesic

- Patients with advanced illness may experience opioid dosage escalation
 - Disease progression
 - Tolerance to opioid
 - Development of opioid-induced hyperalgesia
 - Poorly opioid-responsive pain
- May in part be due to NMDA receptor activation
- Methadone is an NMDA receptor antagonist
- Using methadone as a co-analgesic may be beneficial, especially with patients close to death

Jamero. *U.S. Pharmacist*. Emerging Role of NMDA Antagonists in Pain Management.

Methadone As a Co-analgesic

- 146 cancer pain patients on chronic opioid therapy
- Median oral morphine dose was 120 mg/day
- Added methadone, median dose was 3 mg a day
- 72/146 patients (49.3%) had $\geq 30\%$ reduction in pain
- Median time to first significant response was 7 days

Courtemance. *J Pall Med.* 2016;19(2):972-978.

Methadone As a Co-analgesic

- 20 cancer patients in an outpatient palliative care clinic
- Mean daily routine oral morphine:
 - 338 +/- 217.8 mg at initiation of study
 - 332 +/- 191 mg at evaluation (one month or closest available date)
- Methadone added as co-analgesic:
 - 4.4 +/- 1.4 mg/day at initiation
 - 15.5 +/- 5.9 mg at evaluation
- 15/20 patients achieved decrease in pain score by 2 points at 1 month or first evaluation

Methadone by Different Routes

- Oral methadone = transmucosal methadone = rectal methadone
- Switching from oral methadone to parenteral methadone
 - TDD oral methadone → divide in half for TDD parenteral methadone
- Switching from parenteral methadone to oral methadone
 - TDD parenteral methadone → multiply by 1.3 for TDD oral methadone

achcu.com/media.ashx/achcumethadonebasicsforhospiceproviders03172020final.pdf

Self-Assessment!

WHAT HAVE YOU LEARNED?











- MR is a 78 year old woman residing in a long-term care facility. She has a diagnosis of advanced Alzheimer's disease, and she has been taking methadone 2.5 mg po q12h for generalized aches and pains with good success
- She is likely within days of death and the staff are having a hard time getting her to take the methadone tablet (half of a 5 mg tablet). What would be the equivalent dose of oral methadone solution administered in the buccal cavity?
 - A. Methadone 1 mg po q12h
 - B. Methadone 2 mg po q12h
 - C. Methadone 2.5 mg po q12h
 - D. Methadone 2.5 mg po q8h



Self-Assessment!

- MR is a 78 year old woman residing in a long-term care facility. She has a diagnosis of advanced Alzheimer's disease, and she has been taking methadone 2.5 mg po q12h for generalized aches and pains with good success
- She is likely within days of death and the staff are having a hard time getting her to take the methadone tablet (half of a 5 mg tablet). What would be the equivalent dose of oral methadone solution administered in the buccal cavity?
 - A. Methadone 1 mg po q12h
 - B. Methadone 2 mg po q12h
 - **C. Methadone 2.5 mg po q12h**
 - D. Methadone 2.5 mg po q8h

Conclusion

- Methadone offers many advantages as an opioid
- Methadone also require special attention in dosing

OME per day	Recommended Methadone Starting Dose
< 40 – 60 mg	2-7.5 mg po qd in 2-3 divided doses
> 60 – 199 mg (and <65 yo)	10:1 (morphine : methadone)
> 200 mg (+/or ≥65 yo)	20:1 (morphine : methadone)

- Methadone requires close attention in follow-up monitoring

Additional Resources

- McPherson ML, Walker KA, Davis MP, et al. Safe and Appropriate Use of Methadone in Hospice and Palliative Care: Expert Consensus White Paper. *J Pain Symptom Manage*. 2019;57(3):635-645.e4. doi:10.1016/j.jpainsymman.2018.12.001
- Courtemanche F, Dao D, Gagné F, Tremblay L, Néron A. Methadone as a Coanalgesic for Palliative Care Cancer Patients. *J Palliat Med*. 2016;19(9):972-978. doi:10.1089/jpm.2015.0525
- Haumann J, van Kuijk SMJ, Geurts JW, et al. Methadone versus Fentanyl in Patients with Radiation-Induced Nociceptive Pain with Head and Neck Cancer: A Randomized Controlled Noninferiority Trial. *Pain Pract*. 2018;18(3):331-340. doi:10.1111/papr.12609
- Salpeter SR, Buckley JS, Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. *J Palliat Med*. 2013;16(6):616-622. doi:10.1089/jpm.2012.0612
- Bruera E, Palmer JL, Bosnjak S, et al. Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. *J Clin Oncol*. 2004;22(1):185-192. doi:10.1200/JCO.2004.03.172

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