

Updated Opioid Conversions! Not Your Mama's Equianalgesic Chart!

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Disclosures



Learning Objectives

- Describe the rationale for rotating patients from one opioid to another when treating pain.
- Interpret recent research on retrospective opioid conversions and its impact on use of an equianalgesic opioid resource.
- Given a simulated patient, calculate a new opioid regimen using the same opioid but with a different dosage formulation or route of administration.
- Given a simulated patient, calculate a new opioid regimen that reflects switching between opioids, dosage formulations and/or routes of administration.

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 health care beliefs

- 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

Opioid	Parenteral	Oral
Morphine	10	25
Fentanyl	0.15	NA
Hydrocodone	NA	25
Hydromorphone	2	5
Oxycodone	10 (not in US)	20

Reprinted with permission from McPherson ML. Demystifying opioid conversion calculations: a guide for effective dosing, 2nd ed. Bethesda: ASHP; ©2018 in press.

*NOTE: Learner is STRONGLY encouraged to access original work to review all caveats and explanations pertaining to this chart. *Note: not available in the US.*

The Problem with “Those Charts”

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

5-Step OCC Process

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

Case 1

- HW is an 84-year-old man in a LTC facility with general debility on oxycodone 5 mg/acetaminophen 325 mg tabs, six 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

1. Pain assessed; stable and controlled
2. Six tabs x 5 mg oxycodone per day = 30 mg TDD oral oxycodone
3. 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
4. Individualization – oxycodone is oxycodone; no need to change dose
5. 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 six 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

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 mg IV morphine per day

25-50% increase → 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 oral morphine solution 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 which 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; divide 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 one opioid to a DIFFERENT opioid
- Set up your ratio, calculate total daily dose of NEW opioid
 - If patient's pain was 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 one formulation or route to another of the SAME opioid

- Account for bioavailability
- Increase if patient in pain

From one 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.

Case 4

- Mrs. Claytor is a 62-year-old woman with pancreatic cancer.
- Her pain is well controlled, but she is unable to swallow the MS Contin tablets (200 mg po q12h) or even the oral morphine solution (40 mg q3h prn breakthrough pain, she uses about one dose per day).
- Her physician would like to switch her to a parenteral SQ morphine infusion. Recommendation?

Case 4

$$\frac{\text{"x" mg SQ morphine}}{440 \text{ mg oral morphine}} = \frac{10 \text{ mg SQ morphine}}{25 \text{ mg oral morphine}}$$

Cross multiply and solve for "x" as follows:

$$(25)(x) = (10)(440)$$

$$25x = 4400$$

$$x = 176 \text{ mg SQ morphine per day}$$

$$176 / 24 \text{ hours} = 7.3 \text{ mg/hour}$$

Recommend 7 mg/hour

Case 4

- Bolus dose?
 - 50-100% of hourly infusion rate
 - 3.5 - 7 mg every 30 minutes SQ (could extend dosing interval once stable)
- When should the continuous infusion start relative to the last dose of MS Contin?

Case 4 To Go Points

- You are switching from oral morphine to IV morphine
 - But you've been asked to calculate a continuous infusion
- No need to dose reduce due to lack of cross-tolerance (morphine to morphine)
- No need to change dose you calculate (no mention of uncontrolled pain)
- Calculate infusion rate, AND bolus dose

Self-Assessment!



- If you're switching a patient from one formulation to a different formulation of the SAME opioid, which of the following should you account for?
 - A. Comparative bioavailability of the two formulations
 - B. Increased sensitivity to the new regimen
 - C. Need to increase calculated dose due to pain control not at goal
 - D. A and C
 - E. A, B and C

Self-Assessment!



- If you're switching a patient from one formulation to a different formulation of the SAME opioid, which of the following should you account for?
 - A. Comparative bioavailability of the two formulations
 - B. Increased sensitivity to the new regimen
 - C. Need to increase calculated dose due to pain control not at goal
 - D. **A and C**
 - E. A, B and C

Case 5

- MJ is a 68-year-old man admitted for total hip replacement.
- He was started on a PCA pump, hydromorphone 0.2 mg IV q10min.
- From hours 49-60 he used a total of 7.2 mg IV hydromorphone
- Convert to shorting-acting AND long-acting oral morphine (at 50% of IV requirements).

Case 5

- 7.2 mg IV hydromorphone over 12 hours = 14.4 mg IV hydromorphone over 24 hours

$$\frac{\text{"x" mg PO morphine}}{14.4 \text{ mg IV HM}} = \frac{25 \text{ mg PO morphine}}{2 \text{ mg IV HM}}$$

$$(2)(x) = (25)(14.4)$$

$$X = 180$$

Reduce by 50% - 90 mg oral morphine a day

90 mg/6 = 15 mg → MSIR 15 mg po q4h

LA MS

MS Contin 45 mg po q12h

Kadian 50 mg po q12h

Oramorph SR 30 mg po q8h

Case 5 To Go Points

- Going from IV to oral opioid
- This is ACUTE pain – should be getting better every day
- Consider giving as short-acting opioid
 - Unless pain expected to last a good while, then consider long-acting opioid

Case 6

- Mr. Crippen is a 58-year-old man who was admitted to an inpatient Hospice facility for pain out of control.
- Several days after admission, his pain is now well-controlled on a PCA IV morphine infusion at 1.5 mg/hour, plus 0.5 mg for breakthrough.
- On average he uses 8 doses of breakthrough per 24 hours.

Case 6

- His physician would like to convert him to an oral opioid for discharge.
- What do you recommend?
- Calculate an equivalent dose of oral morphine.
- How about oral oxycodone?

Case 6

- 1.5 mg/hour IV morphine x 24 hours = 36 mg IV morphine per day
- Plus 8 x 0.5 mg bolus = 4 mg IV morphine
- TOTAL daily IV morphine dose = 40 mg
- Total daily oral morphine dose = 100 mg
 - MS Contin 45 mg po q12h
 - MSIR 15 mg po q2h prn

Case 6

- TOTAL daily IV morphine dose = 40 mg

$$\frac{\text{"x" mg po oxycodone}}{40 \text{ mg IV morphine}} = \frac{20 \text{ mg po oxycodone}}{10 \text{ mg SQ morphine}}$$

80 mg oral oxycodone total daily dose

Reduce 25-50% to 40-60 mg oxycodone per day

Case 6 To Go Points

- This is a patient with advanced illness – pain will NOT be improving (will likely worsen)
- Going from parenteral to oral morphine – account for bioavailability, but otherwise no need to adjust
- Going from parenteral morphine to oral oxycodone – need to account for bioavailability AND dose reduce because his pain was controlled

Case 7

- Mr. Johnson is a 62-year-old cancer pain patient who is unable to swallow tablets or oral solution.
- He refuses rectal administration of medications and is not interested in a parenteral infusion.
- He is currently receiving Oramorph SR 30 mg po q8h with oral morphine solution 10 mg po q3h prn (taking about 4 doses per day).

Case 7

- His pain is well controlled on this regimen.
- What do you need to consider before converting him to transdermal fentanyl (TDF)?
- How do you make this conversion?

Case 7

- Calculate total daily dose of morphine:
 - Oramorph 30 mg po q8h = 90
 - Oral morphine solution 10 mg x 4 per day = 40
 - TDD = 130 mg oral morphine
- Generally give 50% of total daily morphine dose as transdermal fentanyl
 - TDF in mcg/hour ~ 50% of oral morphine TDD
- 65 mcg – need to round up or down
 - Transdermal fentanyl 50 mcg/hour q3days
- Considerations? Timing?

Case 7 To Go Points

- You CANNOT start transdermal fentanyl in an opioid-naïve patient (must meet FDA definition)
- If patient not on oral morphine, convert to oral morphine total daily dose
- Take 50% of oral morphine TDD and that's ~ the mcg/h TDF patch strength

Breakthrough Pain

- Spontaneous
 - Idiopathic, occurring with no known stimulus
- Incident
 - Secondary to a stimulus which the patient may or may not be able to control
- End-of-dose failure
 - Pain at the end of the dosing interval of a long-acting opioid

Types of Breakthrough Pain

	Characteristics	Management Strategies
Spontaneous	<ul style="list-style-type: none"> •Pain that requires no precipitating stimulus. •Can occur without warning and be acutely severe. •Spontaneous pain commonly has a neuropathic component. 	<ul style="list-style-type: none"> •Immediate-release opioid on an as-needed basis. •Consider use of a co-analgesic (particularly if neuropathic).
Incident pain; volitional	<ul style="list-style-type: none"> •Consistent temporal causal relationship with identifiable causes that are under the patient’s control such as patient-precipitated movement, wound, or personal care. 	<ul style="list-style-type: none"> •Non-opioid or immediate-release opioid, on an as-needed basis or prophylactically; rest; ice; patient education.
Incident pain; non-volitional	<ul style="list-style-type: none"> •Consistent temporal causal relationship with identifiable causes that are NOT under the patient’s control such as sneezing, bladder spasm, or coughing. 	<ul style="list-style-type: none"> •Immediate-release opioid on an as-needed basis.
End-of-dose	<ul style="list-style-type: none"> •Pain that recurs before the next scheduled dose of the around-the-clock analgesic. •Likely due to a subtherapeutic dose of analgesic. 	<ul style="list-style-type: none"> •Increase in dose and/or frequency of around-the-clock analgesic.


BTP Assessment Questions

- Do you have episodes of severe pain or BTP?
- How many episodes of BTP do you have each week? Each day?
- How long is it from the time the pain first occurs to when the pain is at its worst?
- How long does each episode of BTP last (minutes, hours)?
- On a scale of 0 to 10, with 0 being no pain and 10 being the worst pain you can imagine, how much does an episode of BTP hurt when it occurs?
- Describe where the BTP occurs. What does it feel like?
- Is the BTP similar to or different from your baseline persistent pain?
- Does your BTP occur with movement or other activity, spontaneously (not associated with any activity), or just before you are supposed to take your next dose of pain medicine?

BTP Assessment Questions

- What impact does BTP have on your daily responsibilities at home/work? Are you able to do the things that you want/need to do?
- Are there any things that you avoid doing or that you are able to do only with severe pain?
- What do you do to relieve the pain?
- What types of treatments have you used? How long did you use them? Were they effective? Are they still effective?
- What drugs have you used to relieve the BTP? What were the doses? Were they effective? Are they still effective?

Pharmacokinetics of IR Opioids

Solubility	IR Opioids	Onset of analgesia	Duration of effect
Hydrophilic	Morphine (oral)	30-40 minutes	4 hours
	Oxycodone (oral)	30 minutes	4 hours
	Oxymorphone (oral)	30 minutes	4-6 hours
	Hydromorphone (oral)	30 minutes	4 hours
	Methadone (oral)	10-15 minutes	4-8 hours
Lipophilic	Fentanyl (transmucosal)	5-10 minutes	1-2 hours

Dose of SA Rescue Opioid

- ONE dose of rescue opioid (e.g., oxycodone, oxymorphone, morphine) should be 10-15% of the TOTAL daily dose of oral long-acting opioid.
 - MS Contin 30 mg q12h
 - TDD = 60 mg
 - 10% - 6 mg; 15% - 9 mg
 - Oral morphine 5 or 10 mg q2h prn breakthrough pain
- Rate pain before and after rescue opioid

Case 8

- Mrs. Hendricks is a 54-year-old woman with end-stage esophageal cancer.
- She is receiving TDF 75 mcg, every 72 hours for persistent pain.
- You would like to use morphine oral solution (20 mg/ml) for breakthrough pain. What dose do you recommend?

Case 8

- TDF 75 mcg ~ 150 mg TDD oral morphine
 - 10% = 15 mg
 - 15% = 22.5 mg
- Morphine oral solution, 20 mg every 2 hours as needed for breakthrough pain
- Keep a pain diary, rate pain before and after rescue opioid

Case 8 To Go Points

- TDF mcg/h x 2 ~ total daily dose oral morphine
- Apply 10-15% rule (10-15% of total daily oral morphine dose = ONE dose of breakthrough short-acting opioid)

Opioid Dosage Escalation Strategies

- For moderate to severe pain, increase opioid TDD by 50-100%, regardless of starting dose.
- For mild-moderate pain, increase opioid TDD by 25-50%, regardless of starting dose.
- BUT USE SOME COMMON SENSE!
- Short-acting, immediate-release single-ingredient opioids (morphine, oxycodone, hydromorphone) can be safely dose-escalated every 2 hours.
- Long-acting, sustained-release opioids can be increased every 24 hours (this does not include TDF or methadone).
- TDD = total daily dose; TDF = transdermal fentanyl

Self-Assessment!



- If a patient is receiving transdermal fentanyl 75 mcg/h (assume good body habitus) what would be an appropriate dose of short-acting morphine for breakthrough pain?
 - A. SA morphine 5 mg po q2h prn
 - B. SA morphine 10 mg po q3h prn
 - C. SA morphine 15 mg po q2h prn
 - D. SA morphine 20 mg po q6h prn
 - E. SA morphine 30 mg po q2h prn

Self-Assessment!



- If a patient is receiving transdermal fentanyl 75 mcg/h (assume good body habitus) what would be an appropriate dose of short-acting morphine for breakthrough pain?
 - A. SA morphine 5 mg po q2h prn
 - B. SA morphine 10 mg po q3h prn
 - C. SA morphine 15 mg po q2h prn
 - D. SA morphine 20 mg po q6h prn
 - E. SA morphine 30 mg po q2h prn

Updated Opioid Conversions! Not Your Mama's Equianalgesic Chart!

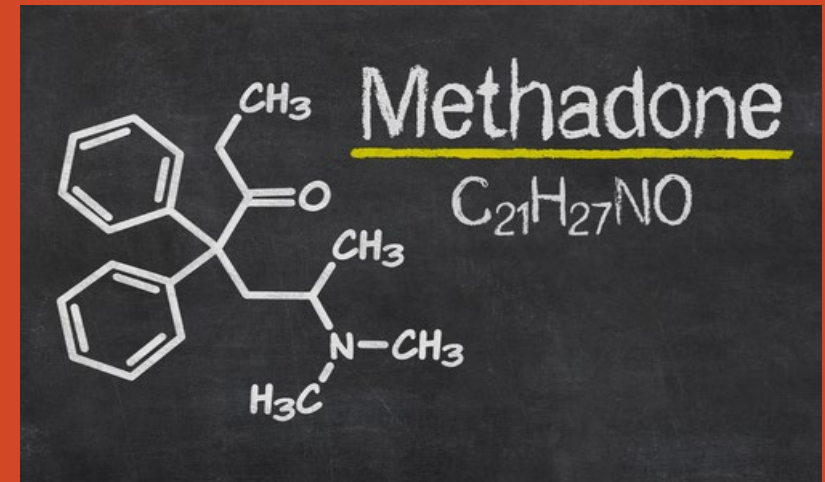
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**Magical, Mystical,
Mischievous Methadone:
She's a Naughty Kitten but
Worth it!**



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Learning Objectives

- Briefly describe the pharmacodynamic effects (all three proposed mechanisms of action) and pharmacokinetic parameters (absorption, distribution, metabolism, excretion) of methadone.
- Describe screening criteria that reflect consideration of therapeutic effectiveness and potential toxicity for an actual or simulated patient.
- Given a simulated opioid-naïve patient, recommend a starting methadone dose that reflects patient- and methadone-specific variables.
- Given a simulated opioid-tolerant patient, recommend a starting methadone dose that reflects patient- and methadone-specific variables.
- Given a simulated case of a patient starting or receiving methadone, recommend a course of action when the patient is taking or will begin taking a medication known to interact with methadone.
- Given a simulated case of a patient receiving methadone, describe best practices to monitor the patient's response to therapy (therapeutic and potential toxicity).

Methadone Stats

- Long and variable half-life
- Potential drug interactions with multiple medications
- Variability in equianalgesic dose ratios
- Association with prolongation of QTc
 - “Proportion of methadone-associated deaths related to arrhythmia is likely to be small relative to the proportion related to accidental overdose, though reliable estimates are not available”

Pharmacodynamics of Methadone

- Synthetic opioid developed over 60 years ago
- Used to treat opioid dependent patients
- Many characteristics making it ideal for chronic pain patients (long duration of action, efficacy, low cost)
- Racemic mixture of R- and S-methadone
 - R-methadone is 8-50 times more potent than S-methadone

So what's the MOA of methadone?



Pharmacodynamics of Methadone

- Mu, kappa, delta agonist
- NMDA receptor antagonist
- Inhibits reuptake of serotonin



Pharmacokinetics of Methadone

- Absorption
 - Oral, rectal, IV, IM, SQ, epidural*, intrathecal*
 - Basic, lipophilic drug
 - Onset 15-45 minutes after oral, peaks in 2.5-4 hours
 - Oral bioavailability 70-80% (range 36-100%)

* Not FDA approved

Pharmacokinetics of Methadone

- Distribution

- Widely and quickly distributed throughout
 - Brain, gut, kidney, liver, muscle, lung
- Retained in tissues and slowly released back into plasma during redistribution and elimination; contributes to long half-life
- Binds to alpha 1-acid glycoprotein; less so to albumin and globulin
 - Free fraction varies four-fold among patients

Whoa....

- Bad news – we've all suffered some tragedy that resulted in opioid-responsive chronic pain
- We've all been started on methadone 2.5 mg po q12h two weeks ago
- We all have a different methadone serum level
- Why is this?



Pharmacokinetics of Methadone

- Metabolism – extensively metabolized
 - N-demethylation
 - Cytochrome P450 – 3A4, 2B6, 2C8, 2C9, 2C19, 2D6
 - Primarily in the liver, also in the gut
 - Pharmacologically-inactive metabolites, eliminated in urine and feces
 - Involved in numerous drug interactions

Pharmacokinetics of Methadone

- Elimination
 - Inactive metabolites are eliminated in urine and feces
 - Elimination half-life is 5-130 hours; AVERAGE 24 hours
 - Takes 4-10 days to achieve steady state
 - When initiating drug therapy
 - With dosage changes

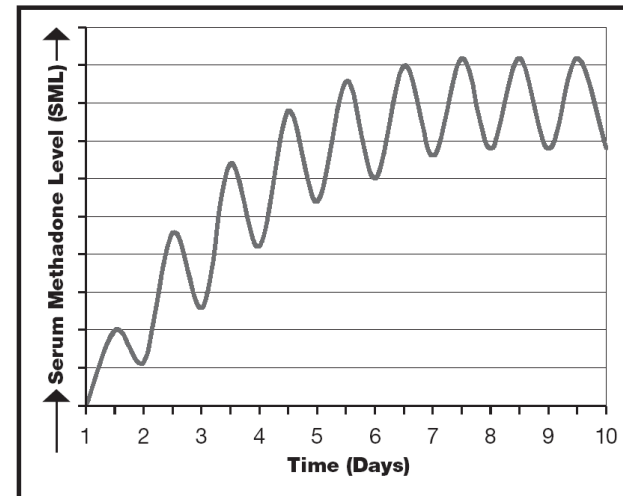
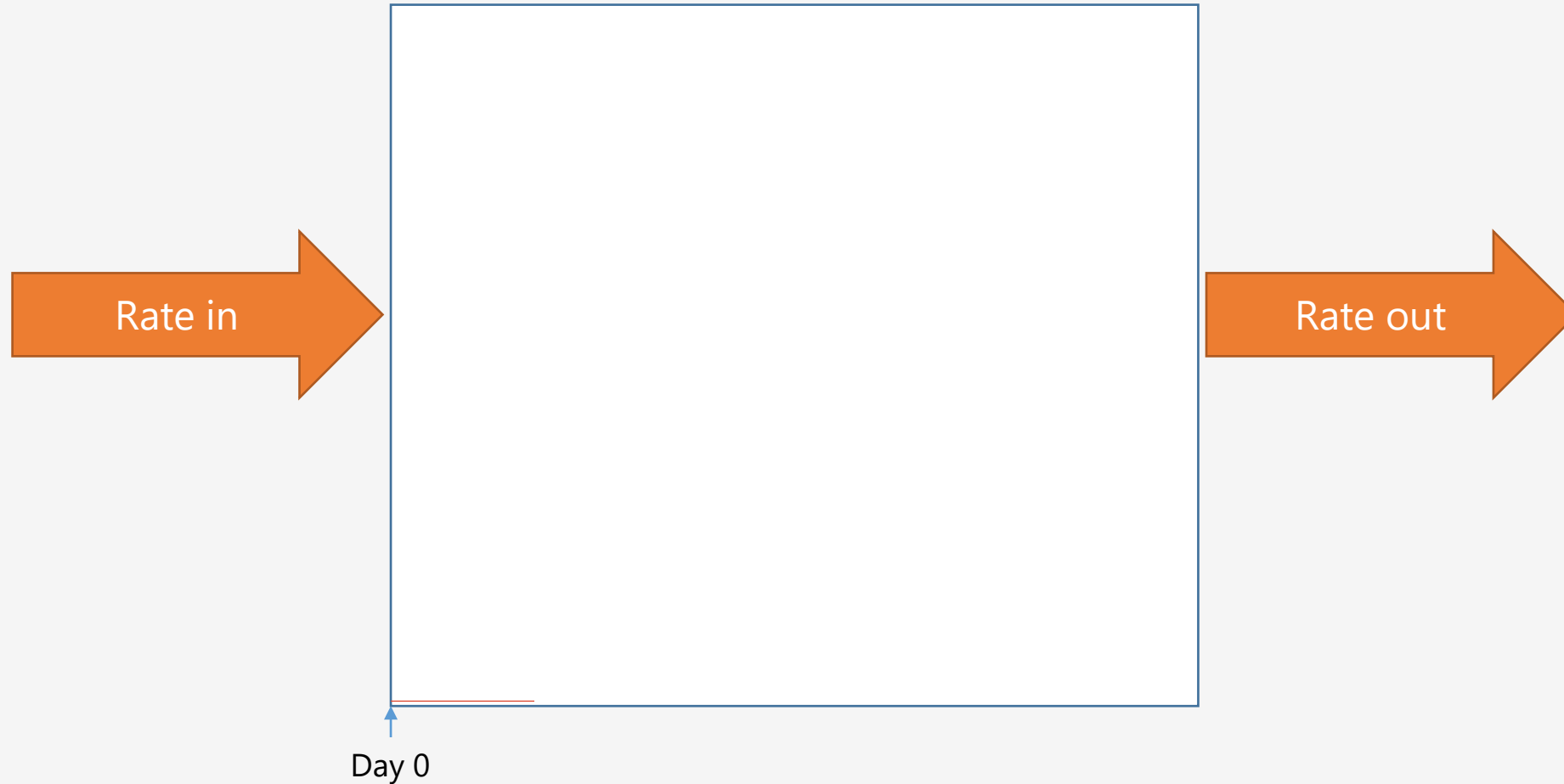


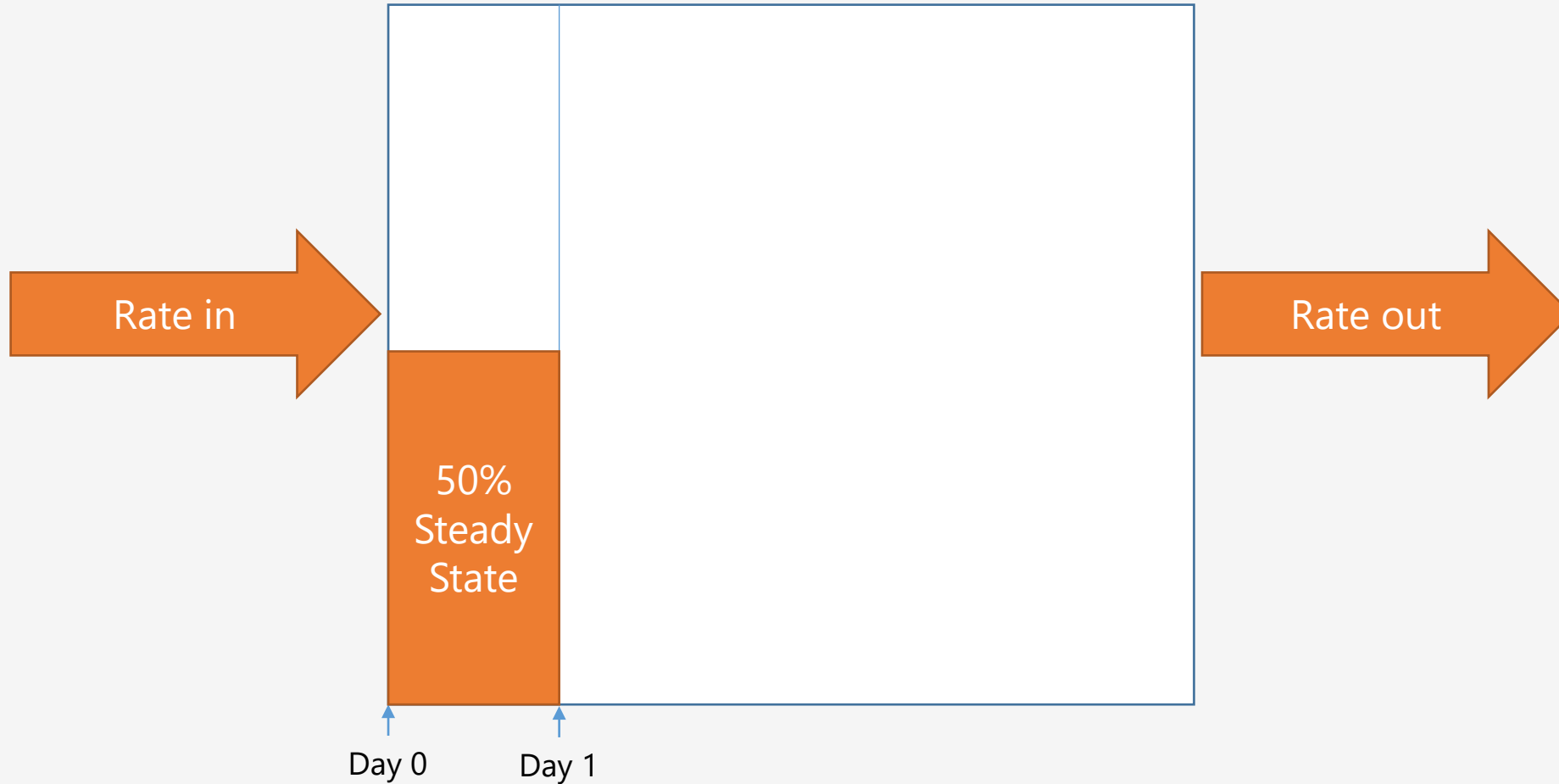
Figure 6-1. Steady-state methadone concentration reached in about 5 days. Source: Addiction Treatment Forum: Methadone Dosing and Safety in the Treatment of Opioid Addiction, Stewart B. Leavitt, PhD.

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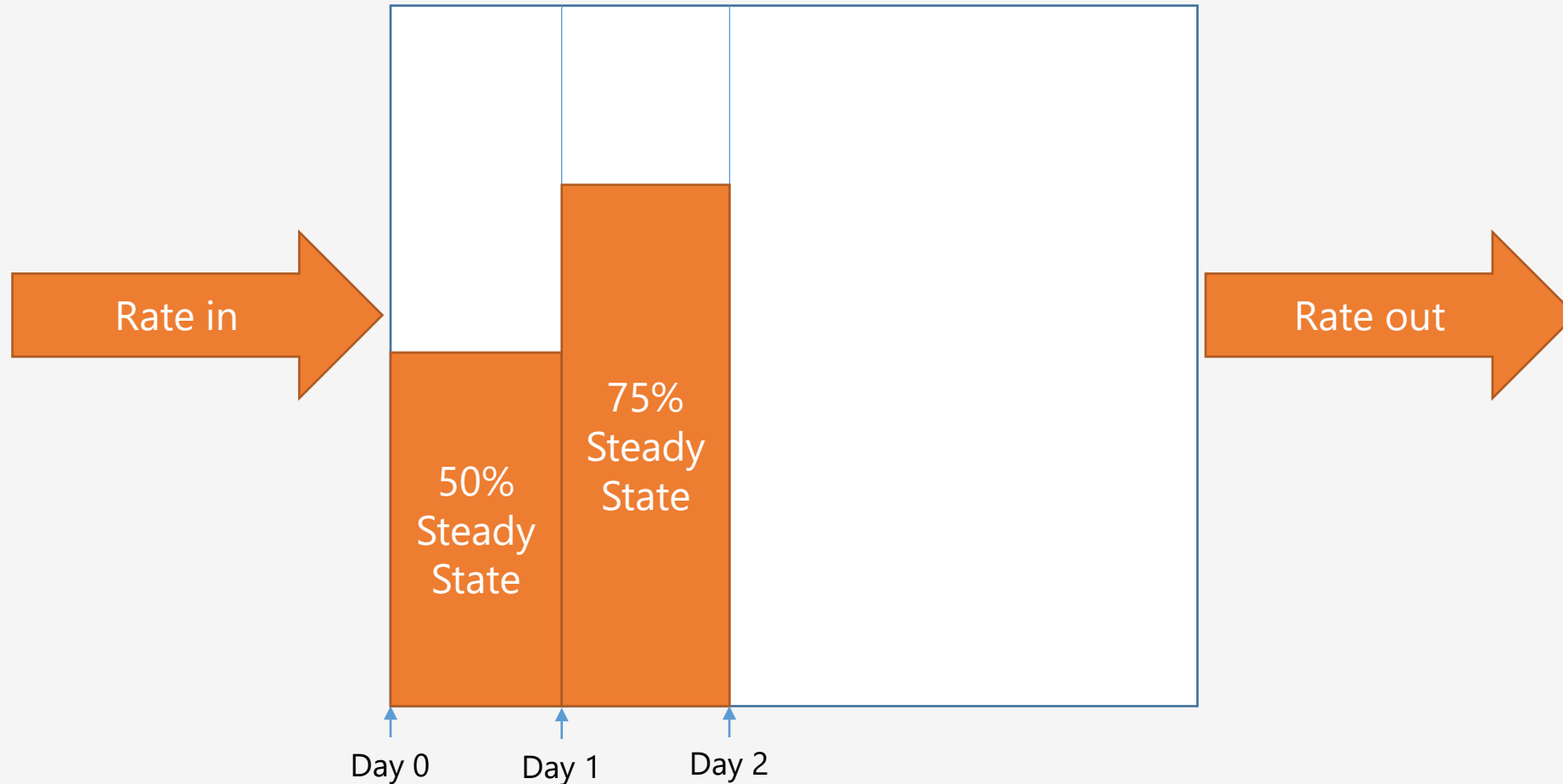
Achieving Steady State



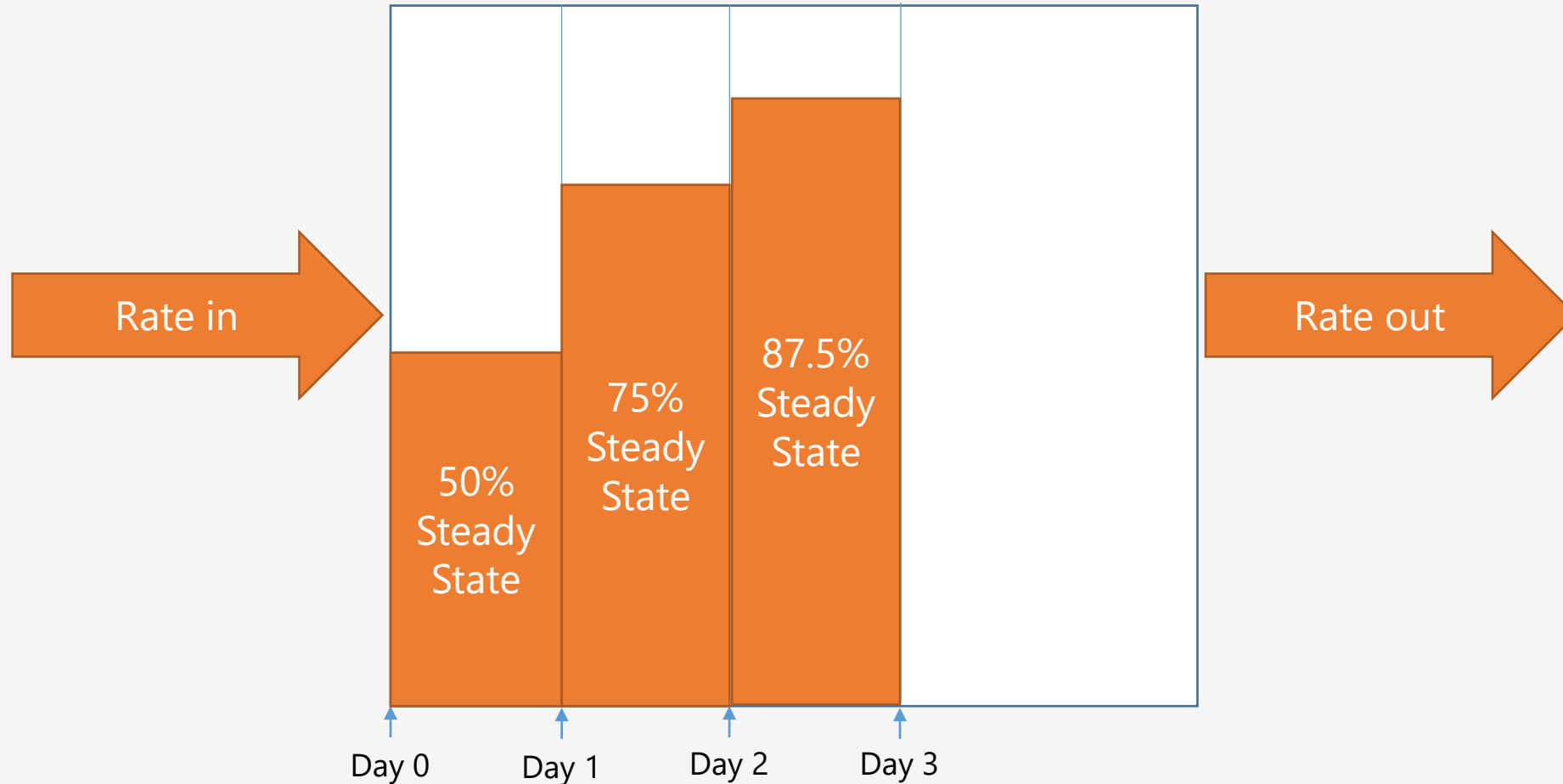
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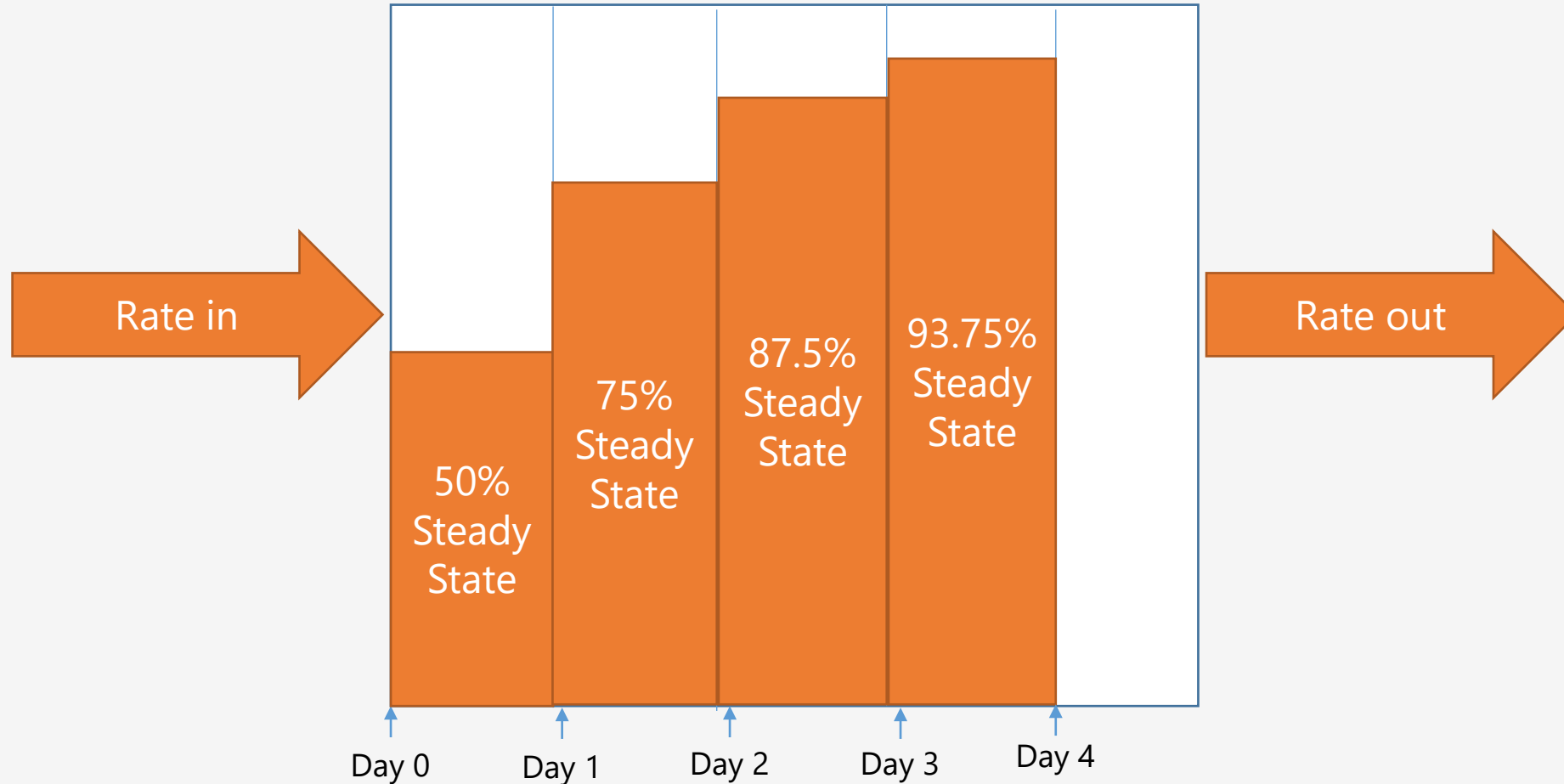
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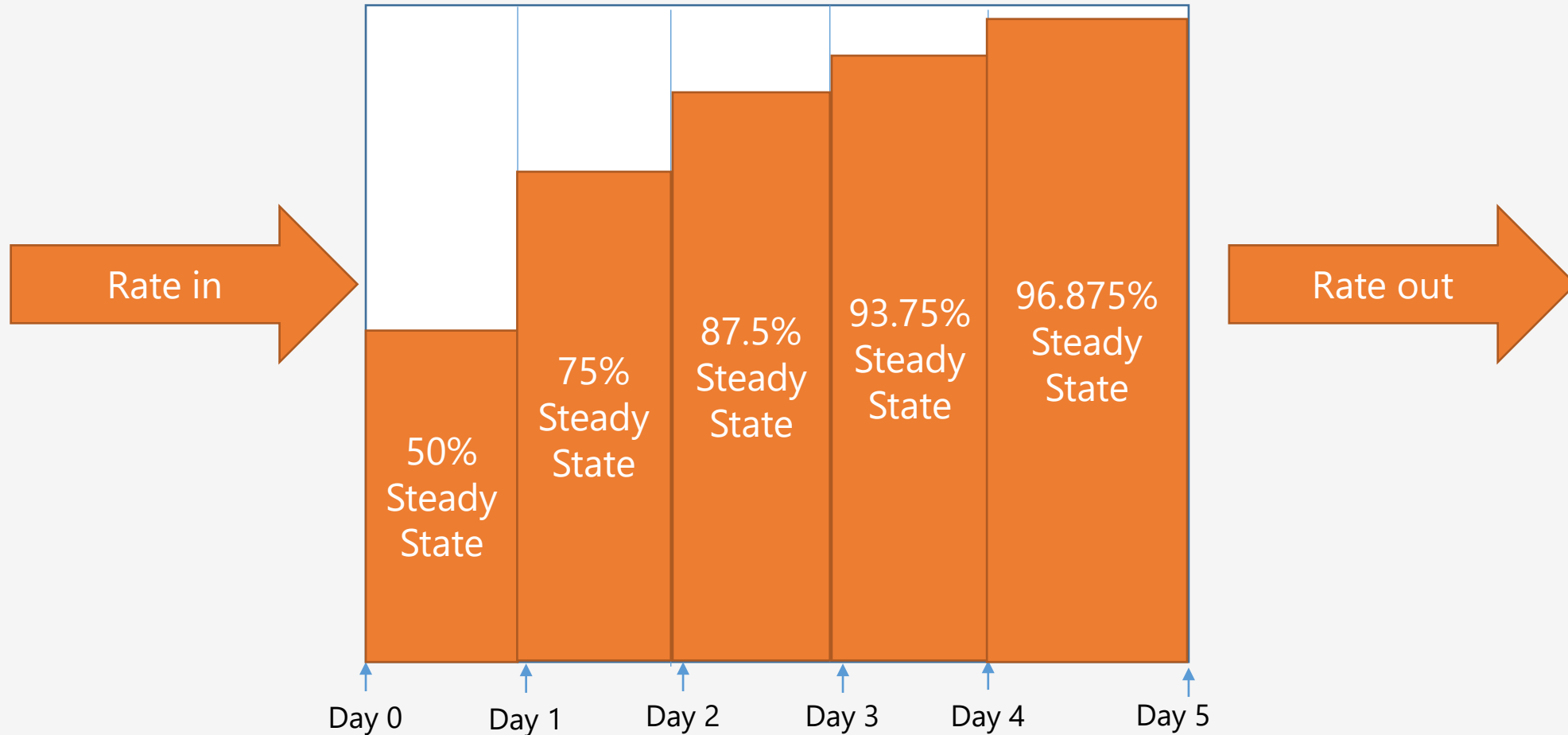
Achieving Steady State



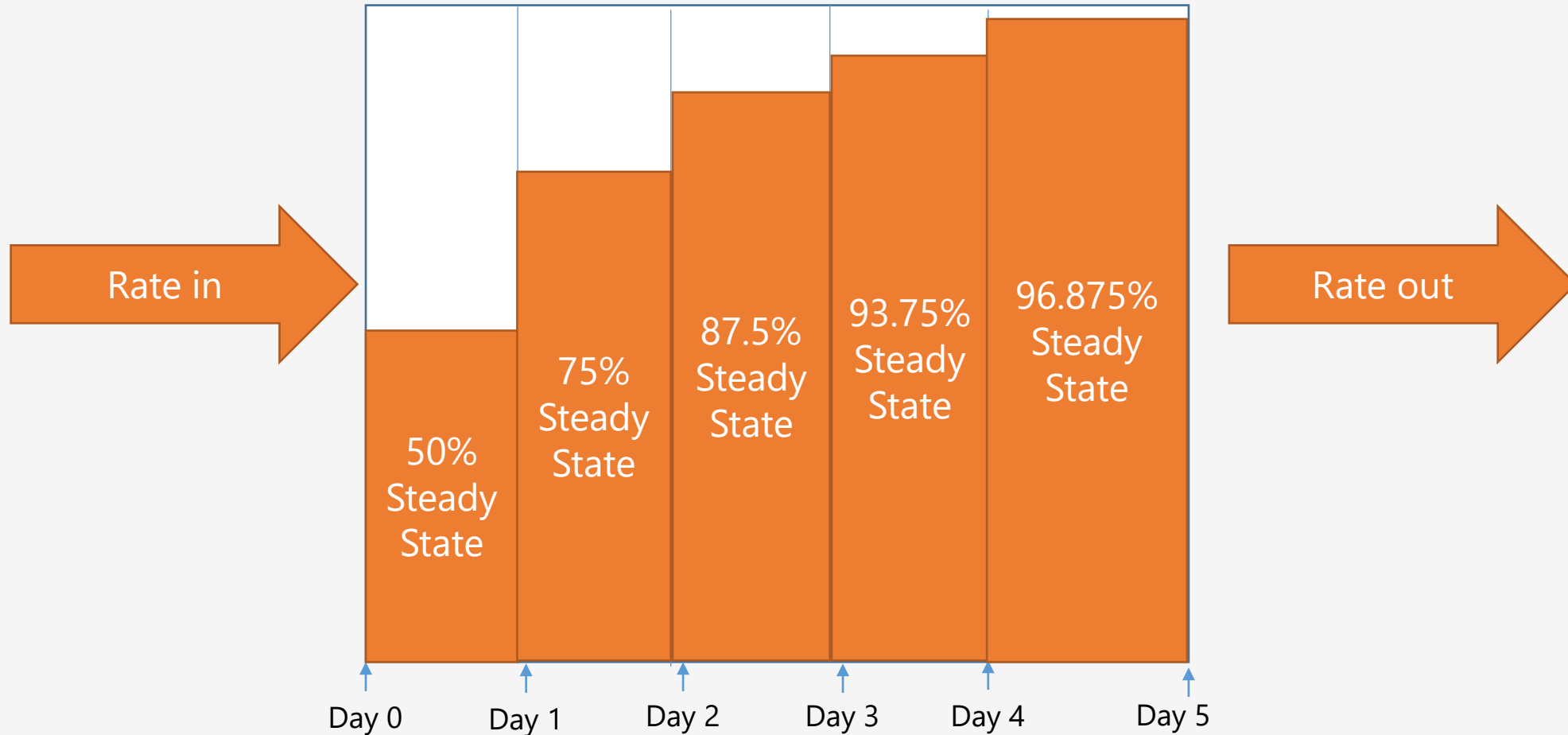
Achieving Steady State



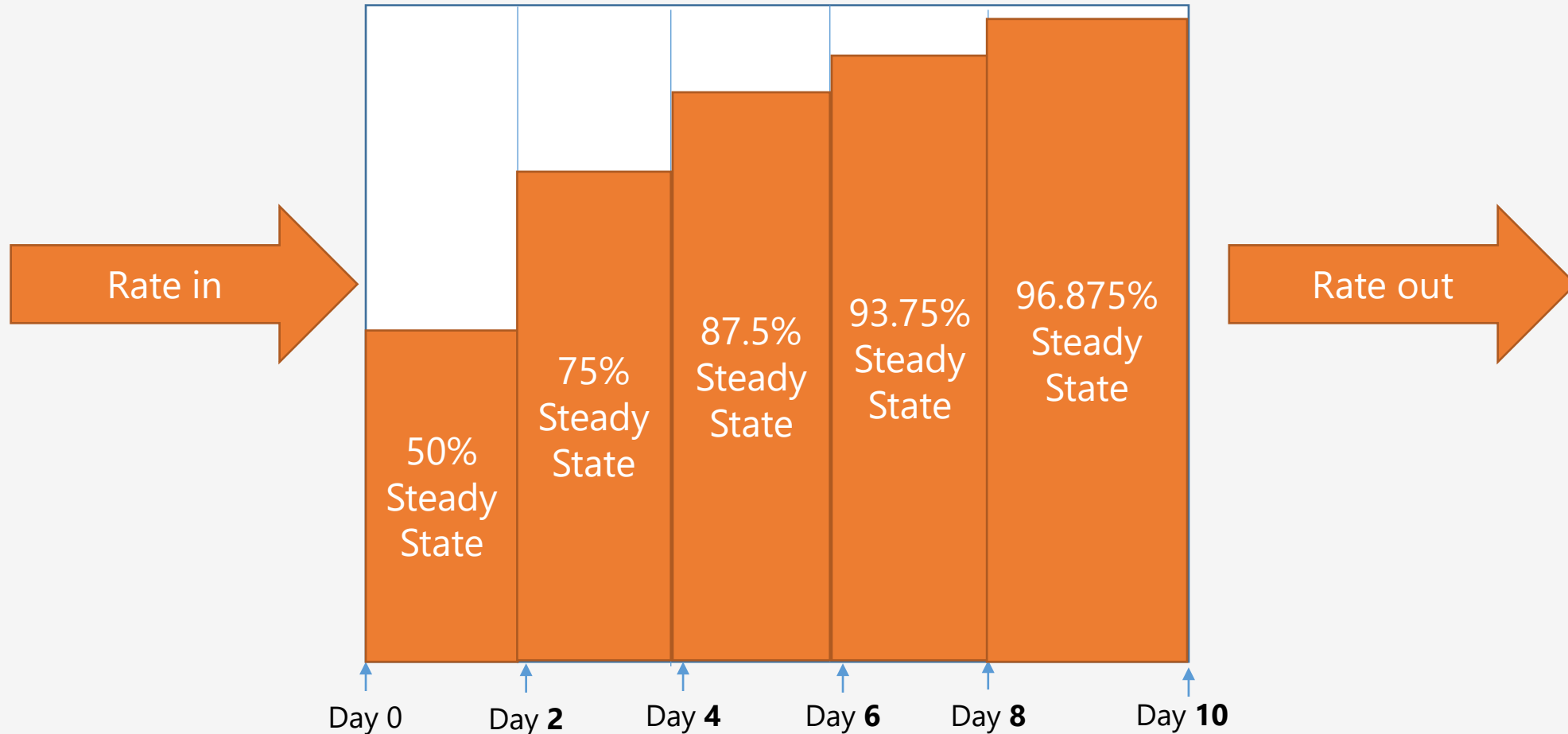
Achieving Steady State



Achieving Steady State ($t_{1/2} = 24$ hours)



Achieving Steady State ($t_{1/2} = 48$ hours)



Drug Interactions with Methadone

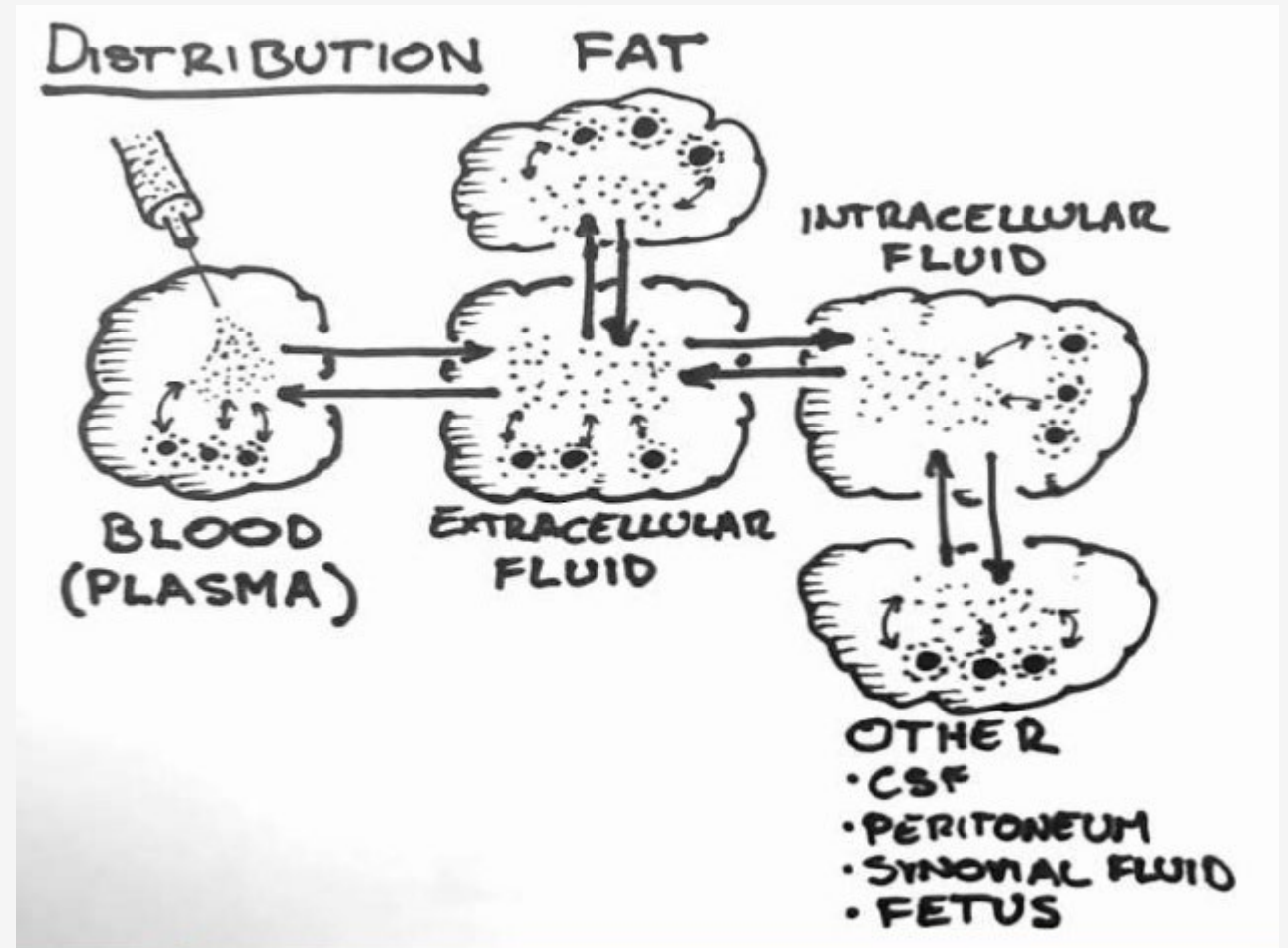
- Drug interaction
 - A clinical scenario where one drug alters the pharmacologic effect of another drug given at the same time (e.g., in the same drug regimen)
 - Drug interactions can alter the pharmacokinetics of a drug
 - Absorption, distribution, metabolism, excretion
 - Drug interactions can alter the pharmacodynamics of a drug
 - Increased or decreased therapeutic effectiveness of either drug
 - Increased or decreased adverse effects of either drug

Pharmacodynamic Drug Interactions

- Methadone and other opioids
 - Increased analgesia
 - Additive toxicities – increased risk respiratory depression and sedation
- Methadone and alcohol, neuroleptics, benzodiazepines, antidepressants, etc.
 - Increased CNS depression
- Methadone and other medications that prolong QT interval (antiarrhythmics, antipsychotics, antidepressants, etc.)

Pharmacokinetic Drug Interactions

- Distribution
 - Competition for protein binding sites
 - May increase methadone free fraction
 - TCA and neuroleptic medications compete with methadone for binding on alpha 1-acid glycoprotein



Pharmacokinetic Drug Interactions

- Metabolism
 - Extensively metabolized in intestines and liver
 - Other medications can *induce* (increase) activity of enzymes
 - Other medications can *inhibit* (reduce) activity of enzymes
 - These other medications affect the serum level of the object drug being metabolized – methadone – known as the *substrate*



How quickly does this happen?

Effect of Enzyme Inhibitors/Inducers

What's the situation?	What happens in this situation?	What does this mean for my patient?	What should I do about it?
Taking methadone with medications known to be enzyme inhibitors	Slowed metabolism of methadone, resulting in increased methadone serum level	The patient may become toxic from a methadone overdose	Reduce calculated methadone dose by 25% or more. Encourage use of rescue opioid.
Taking methadone with medications known to be enzyme inducers.	Increased metabolism of methadone, resulting in decreased methadone serum level	Dose of methadone may be insufficient and patient can experience increased pain	Use calculated methadone dose but strongly encourage use of rescue opioid. Increase methadone if appropriate once at steady-state.

Drugs that Inhibit Methadone Metabolism



Anti-infectives

Antidepressants

Amiodarone

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

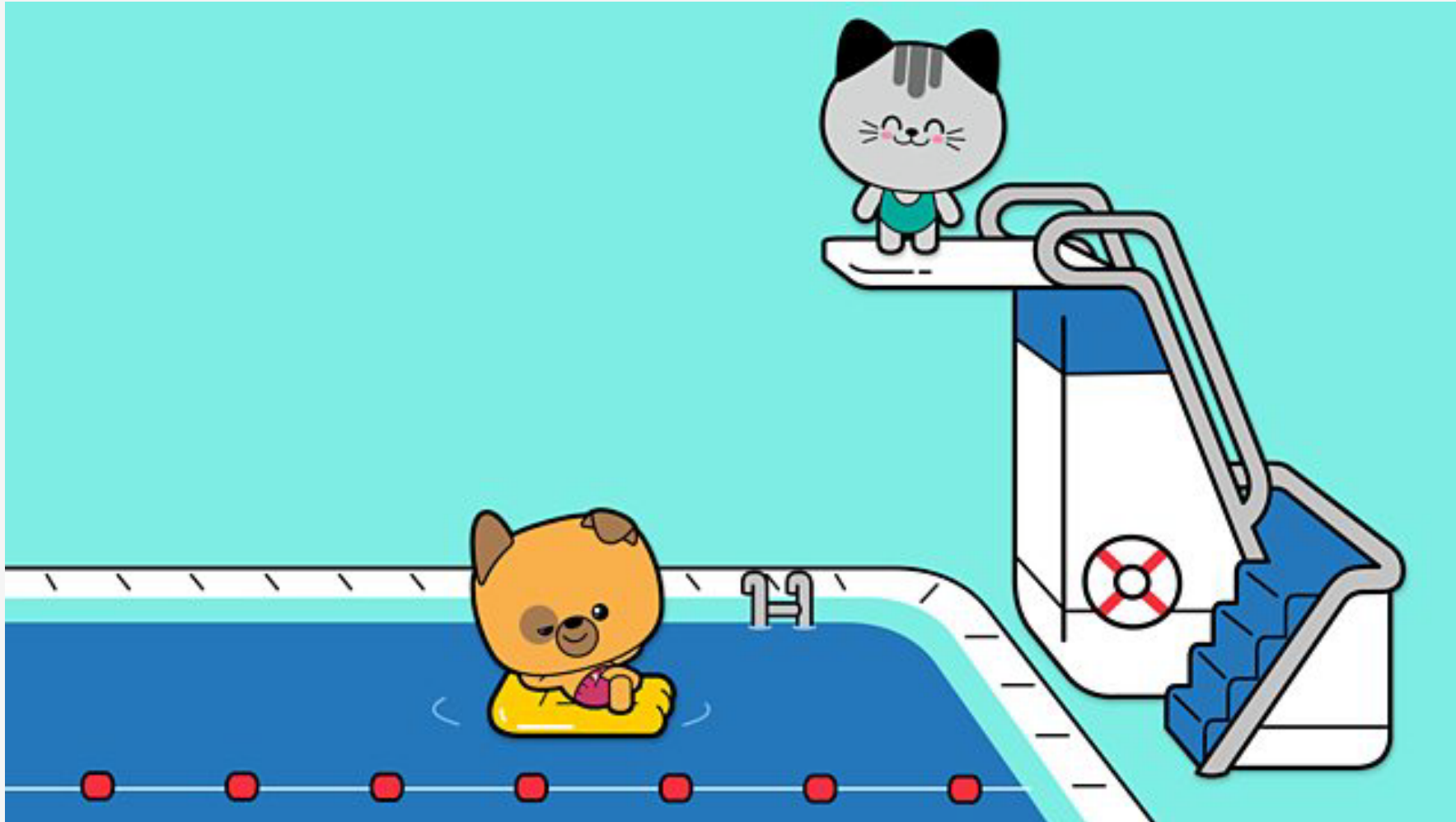
Antidepressants

SSRIs

TCA's

Amiodarone

The good, the bad, and the ugly



Who is a GOOD candidate for methadone? What circumstances favor using methadone?

Who is NOT such a good candidate for methadone? Under what circumstances would you be disinclined to use methadone?

Appropriate Methadone Candidates

- True morphine allergic (or other mu agonist)
- Significant renal impairment
- Neuropathic pain
- Opioid-induced adverse effects
- Pain refractory to other opioids or uncontrolled pain
- Cost is an issue
- Long-acting opioid preferred (especially oral solution)
- Any opioid-requiring patient???

Inappropriate Methadone Candidates

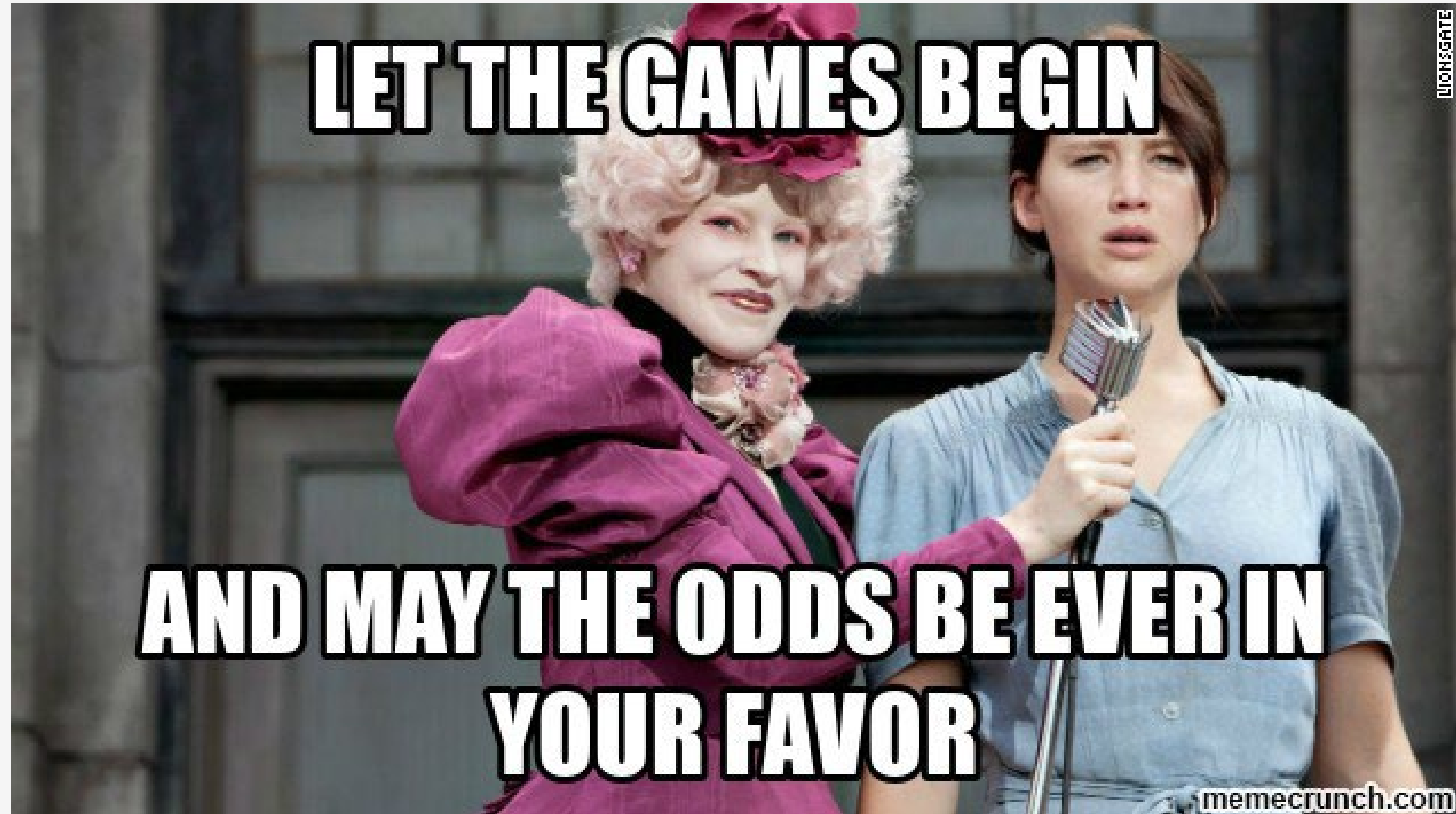
(at least use caution)

- Very limited prognosis (less than a week)
- Numerous drug interactions with methadone
- History of syncope or arrhythmias
- Lives alone, poor cognitive functioning, unreliable, noncomprehending instruction
- History of nonadherence to therapy

ECG Monitoring

Level of Vigilance	Goals of Care; Methadone Role	ECG Monitoring Recommendation
High	Curative, life-prolonging Methadone 1 st line opioid	<ul style="list-style-type: none">• <u>Obtain</u> baseline ECG with positive risk factors, prior QTc > 450 ms, history suggestive of prior ventricular arrhythmia• <u>Consider</u> baseline ECG if no risk factors, prior QTc < 450 ms in previous year
Moderate	Curative, life-prolonging Methadone 2 nd line opioid Or Comfort measures only Methadone 1 st line opioid	<ul style="list-style-type: none">• Discuss risks and benefits with patient/family in light of goals of care• Routine baseline ECG monitoring not recommended; may consider obtaining ECG based on patient's risk status, wishes and goals of care• Document informed consent if no ECG
Low	Comfort measures only Methadone 1 st or 2 nd line opioid	<ul style="list-style-type: none">• No ECG unless compelling indication

To the (dosing) games begin...



Case 1

- BL is a 54 year old woman with a 10 year history of low back pain, now failed back.
 - Did not respond to acetaminophen, NSAID
 - Adverse effects to gabapentin and duloxetine
- Not taking any medications that interact with methadone, and is opioid-naïve.
- Doesn't want a short-acting opioid because she works in an office and is afraid of "peak" effect.
- PCP asks for dosing recommendation.

What do YOU think?

- 54 years old, ambulatory, opioid-naïve
- Starting dose of methadone?
 - A. 1 mg by mouth every 12 hours
 - B. 2.5 mg by mouth every 12 hours
 - C. 2.5 mg by mouth every 8 hours
 - D. 5 mg by mouth every 12 hours
 - E. 5 mg by mouth every 8 hours



Case 1

- No interacting medications, and she is younger (54 years old)
- Possible recommendations:
 - 2.5 mg by mouth q12h (half of a 5 mg tablet)
 - 2.5 mg by mouth q8h (possibly switch to q12h dosing later)
- Rescue opioid?
 - If appropriate, morphine or oxycodone 5 mg by mouth every 4 or 6 hours as needed for additional pain

Case 2

- FA is an 89 year old man admitted to hospice with a diagnosis of protein-calorie malnutrition, complaining of generalized aches and pains.
- Patient is ambulatory and frail.
- Has a history of bleeding ulcer, PCP does not want to prescribe a NSAID. Did not respond to acetaminophen.
- PCP would like you to recommend a methadone dose.
- No interacting medications.

Case 2

- No interacting medications, but he is elderly and frail.
- Possible recommendations:
 - 1 mg by mouth qam or qhs
 - 1 mg by mouth q12h
 - 2.5 mg by mouth qam or qhs
- Rescue opioid?
 - Morphine or oxycodone 2.5 to 5 mg by mouth every 2, 3 or 4 hours as needed for additional pain

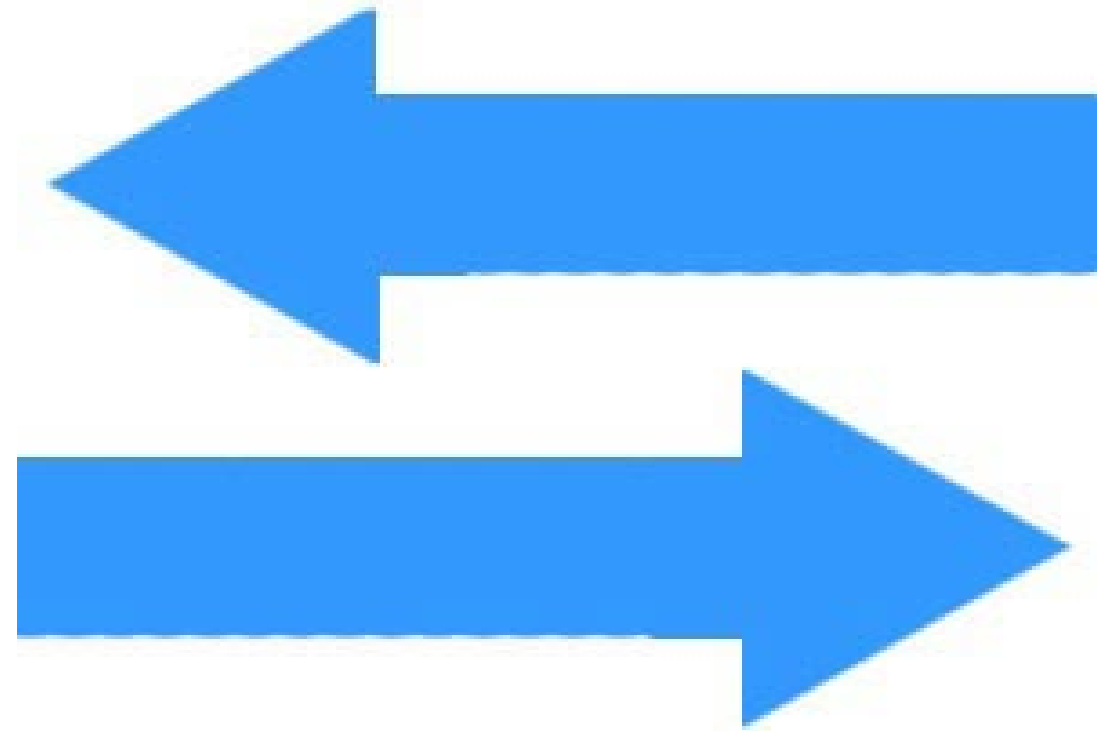
Initiating Methadone (Chou, APS)

- Start at low dose
 - In opioid-naïve patients, or converting from low doses of other opioids (e.g., < 40-60 mg OME/day) – do not exceed methadone 2.5 mg by mouth every 8 hours
 - Dose increases no more than 5 mg/day every 5-7 days
 - Converting from higher doses of other opioids, start methadone at 75-90% less than calculated equianalgesic dose
 - Do not exceed methadone 30-40 mg by mouth qd
 - Dose increases no more than 10 mg/day every 5-7 days

Initiating Methadone

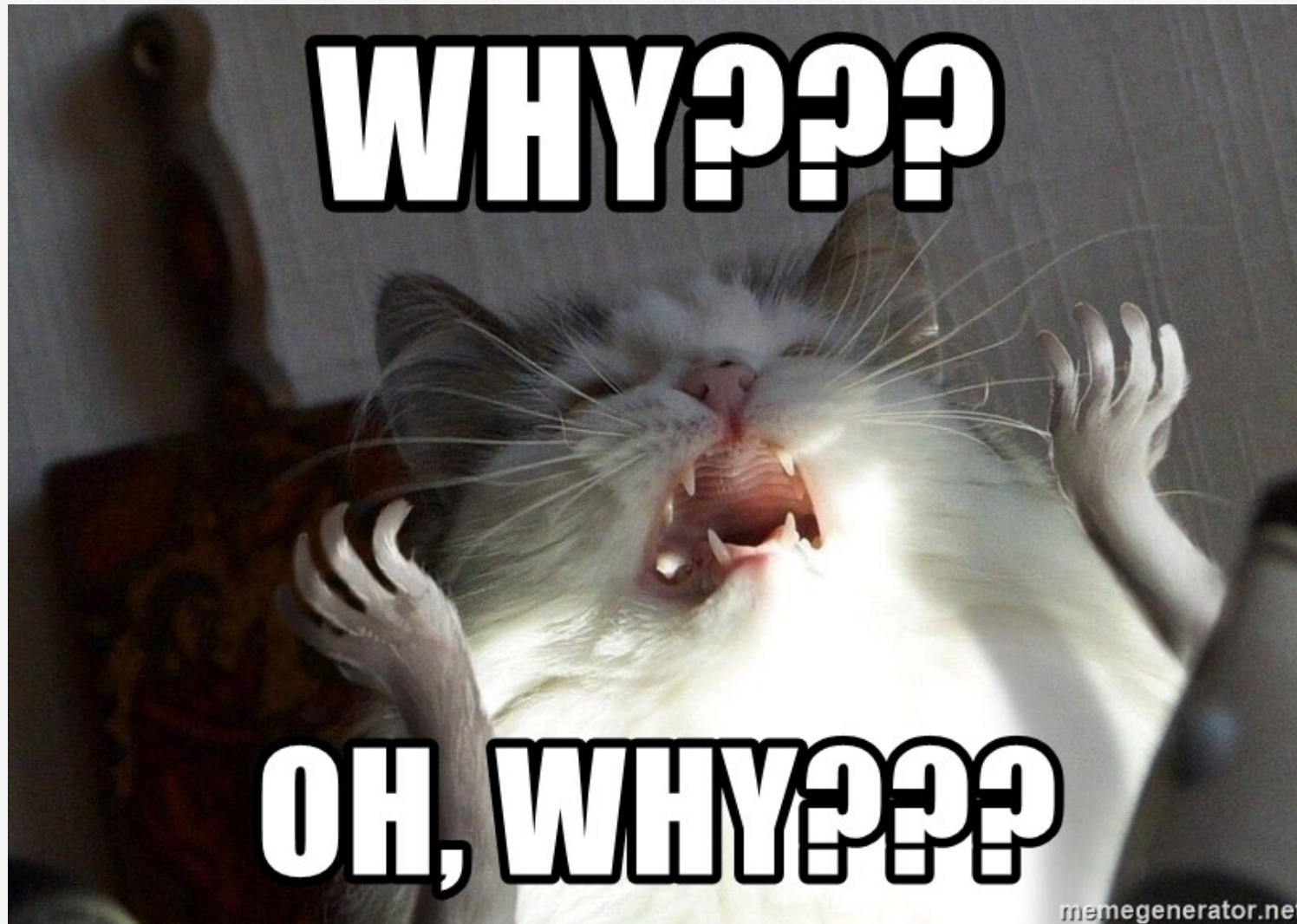
- In opioid-naïve patients, or ≥ 40 -60 mg OME/day – do not exceed methadone 2-7.5 mg by mouth per day in 2-3 divided doses
 - 1 mg by mouth q12h (oral solution)
 - 2 mg by mouth q12h (oral solution)
 - 2.5 mg by mouth q12h (tablet or oral solution)
 - 2.5 mg by mouth q8h (tablet or oral solution)
- Reduce calculated dose by 25-33% if enzyme inhibiting medication on board
- Dose increase no more than 5 mg/day every 5-7 days

OME – oral morphine equivalent



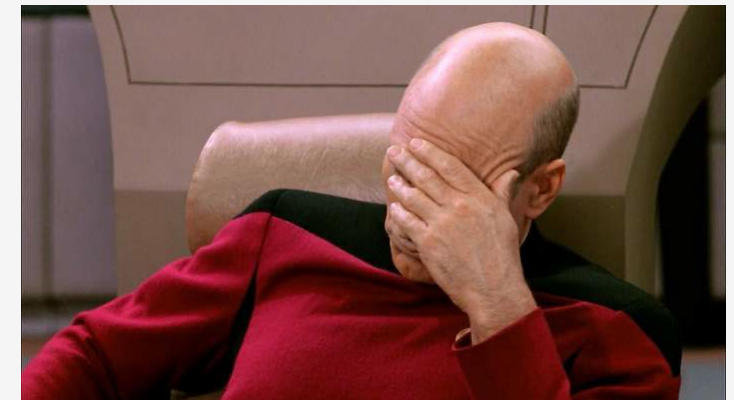
CONVERSION

Why is the conversion to methadone NOT linear?



25 mg oral morphine ~
20 mg oral oxycodone

250 mg oral morphine ~
200 mg oral oxycodone



Summary of Main Methods of Rotation to Methadone

Rotation Method	Description
3DS	<ul style="list-style-type: none"> Day 1—30% of original opioid replaced with an equianalgesic dose of methadone given in three daily divided doses. Days 2 and 3—dose of methadone is increased by 30% and dose of original opioid reduced by 30% each day.
RC stop and go	<ul style="list-style-type: none"> Original opioid is discontinued. Daily methadone dose is calculated according to evidence-based conversion ratios and given in three regular divided daily doses. Regular methadone dose titrated to achieve effective analgesia. It has been argued that a higher priming dose of methadone (20%–30% higher than as calculated using published conversion ratios) may be required initially.
AL stop and go	<ul style="list-style-type: none"> Original opioid is discontinued. A fixed dose of methadone that is one-tenth of the actual or calculated morphine equivalent oral daily dose up to a maximum of 30 mg is calculated. The fixed dose is taken orally as required but not more frequently than three hourly. On day 6, the methadone requirement of the previous two days is noted and converted into a regular every 12-hour regime.
German model	<ul style="list-style-type: none"> Original opioid is discontinued. Methadone is prescribed at a dose of 5–10 mg orally every 4 hours and every 1 hour as needed. On days 2–3, the dose of methadone is titrated up by 30% until analgesia is achieved. After 72 hours, methadone dosing is changed to an every 8-hour and every 3-hour as-needed regime as the same dose as prescribed on days 2–3. Methadone dose is titrated up until analgesia is achieved.
Outpatient titration	<ul style="list-style-type: none"> Original opioid continued at same dose. Methadone commenced at 5 mg orally every 4 hours and increased by 5 mg/dose every 3 days until improved analgesia is noted. Original opioid then reduced by one-third, and the methadone dose increased according to breakthrough requirements. The original opioid dose is reduced, and the methadone dose increased accordingly over a variable period.

3DS = 3 day switch; RC = rapid conversion; AL = ad libitum (as needed)

Source: Reprinted from McLean S, Twomey F. Methods of rotation from another strong opioid to methadone for the management of cancer pain: A systematic review of the available evidence. *J Pain Symptom Manage.* 2015;50:248-259. ©2015, with permission of Elsevier.

Ripamonti, 1998 ⁵¹						
Morphine dose (mg/day)	30–90	90–300	Greater than 300			
Morphine: methadone EDR	4:1	6:1	8:1			
Mercadante, 2001 ⁵²						
Morphine dose (mg/day)	30–90	90–300	>300			
Morphine: methadone EDR	4:1	8:1	12:1			
Ayonrinde, 2000 ⁵³						
Morphine dose (mg/day)	Less than 100	101–300	301–600	601–800	801–1,000	1,001 or more
Morphine: methadone EDR	3:1	5:1	10:1	12:1	15:1	20:1

EDR = equianalgesic dose ratio

Fast Facts – 50% of Ayonrinde Dolophone prescribing info - < 5% to 30% OME Plonk method ([OME + 15]/15) APS – “pick whatever method y’all like, but after you calculate your answer, reduce it by 75-90%!”

$$\text{Methadone (mg)} = \frac{X}{21} \left\{ 5.7 - 3 \sin \left[\frac{90}{\left[\frac{110}{X} \right]^5 + 1} \right] - \sin \left[\frac{90}{\left[\frac{320}{X} \right]^7 + 1} \right] \right\}$$

Let X=Morphine (mg)

Fudin Factor (fear the Fudin)

Initiating Methadone

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

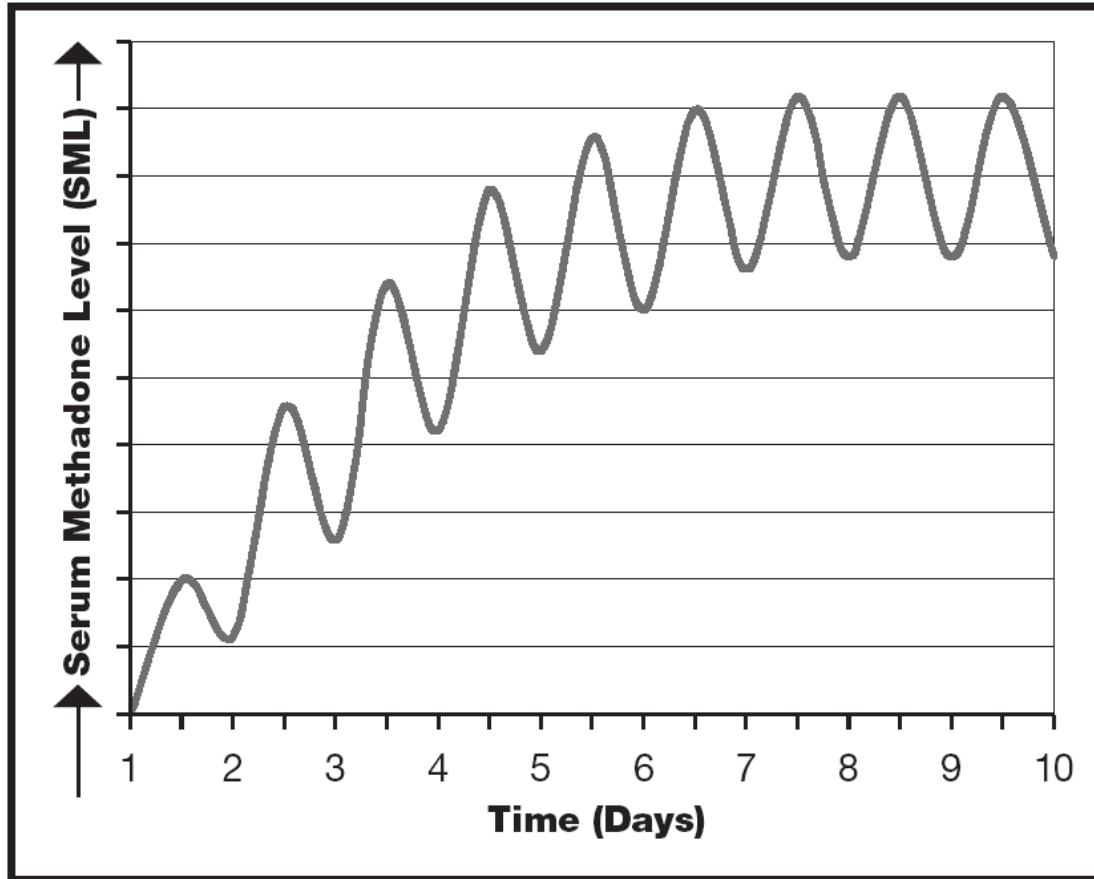


Figure 6-1. Steady-state methadone concentration reached in about 5 days. *Source:* Addiction Treatment Forum: Methadone Dosing and Safety in the Treatment of Opioid Addiction, Stewart B. Leavitt, PhD.

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

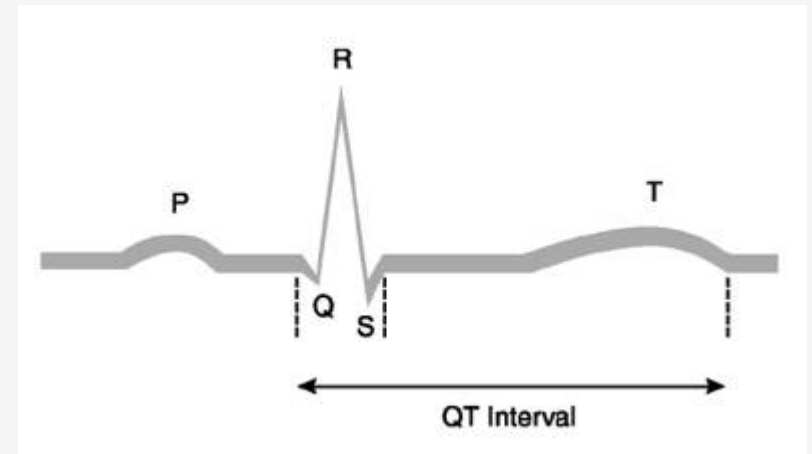
SSRIs

TCA's

Amiodarone

Drugs that prolong QTc

- Clarithromycin, erythromycin
- Quetiapine, haloperidol
- TCA's
 - Amitriptyline, desipramine, imipramine, nortriptyline
- Cocaine



Case 3

- 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 3 – 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

Case 3 – 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 3 – Step 5: 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 4

- 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. The 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.

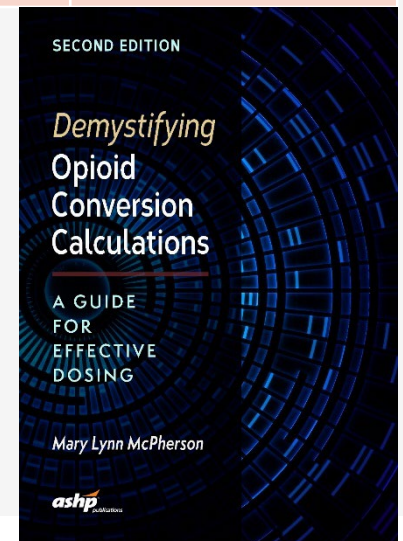
Case 4

- 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
Oxycodone	10 (not in US)	20
Oxymorphone	1	10



Case 4

- 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 4

- 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

OME – oral morphine equivalent

Case 5

- 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 5

- 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 5

- 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 five doses of morphine 20 mg a day = 100 mg
 - TDD oral morphine ~ 250 mg

Case 5

- 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 which COULD give you a significant opioid-sparing effect
 - Be conservative with scheduled methadone, but generous with breakthrough

Case 5

- 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 5

- 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 5

- Patient's opioid log

Day	Methadone	Morphine	Avg Pain Rating
1	Removed TDF at 8 am, one 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 5

- 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 Adverse Effects

- More common

- Constipation – anticipate!
- Nausea and vomiting
- Sedation
- Dizziness/light-headedness

- Less common

- Prolongation of the QTc interval
- Serotonin syndrome
- Hyperalgesia
- Respiratory depression / sleep apnea
- Edema
- Diaphoresis, dry mouth
- Urinary retention, rash, pruritus
- Hypogonadism

Overdose signs and symptoms:

Somnolent, unarousable

Respiratory rate < 8/min

SBP < 90 mmHg or 20% less than baseline

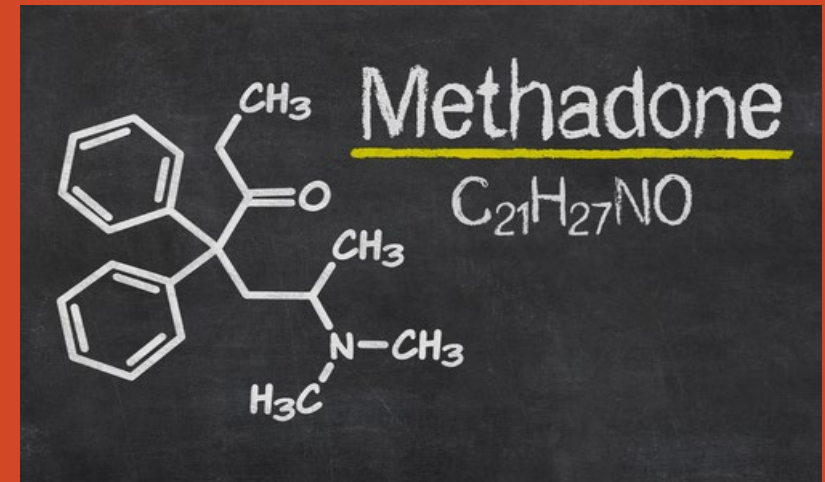
Snoring/sleep-disordered breathing

Pinpoint pupils

Instructions for the Caregiver

- For the first 4-5 days after starting methadone, or after increasing the dose, observe patient every 2-3 hours while awake (for example, 4-5 times per day)
- Is the patient asleep? Is s/he easily awakened?
 - If this is a change and the patient is becoming more and more sleepy and harder to wake up, contact nurse
- Is the patient snoring?
 - If the patient's snoring is new or worsening, contact the nurse or doctor.

**Magical, Mystical,
Mischievous Methadone:
She's a Naughty Kitten but
Worth it!**



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