OPIOID MANAGEMENT

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DISCLOSURES

None

PRESENTATION OBJECTIVES

- 1. Review how to select an appropriate opioid for patients based on medical and psychosocial information.
- 2. Review when and how to titrate opioids.
- 3. Review when and how to change (rotate) opioids.

Take a good pain history

- Location and radiation
- Severity (different pain scales available)
- Timing, duration, and context
- Quality
- Modifying factors
  - Alleviating factors: how long does relief last? How much does pain go down?
- Associated signs and symptoms
  - Numbness, tingling, electric shooting pains, burning

Things I should know before I Rx

Type of pain

- Nociceptive
- Neuropathic
- Emotional/Spiritual

Patient-specific factors

- Medical comorbidities
- Psychosocial issues
- Available routes for administration

System issues

- Refills
- Further management (follow-up)
- Pharmacy (stock and availability)

Pain scale: Subjective or Objective?

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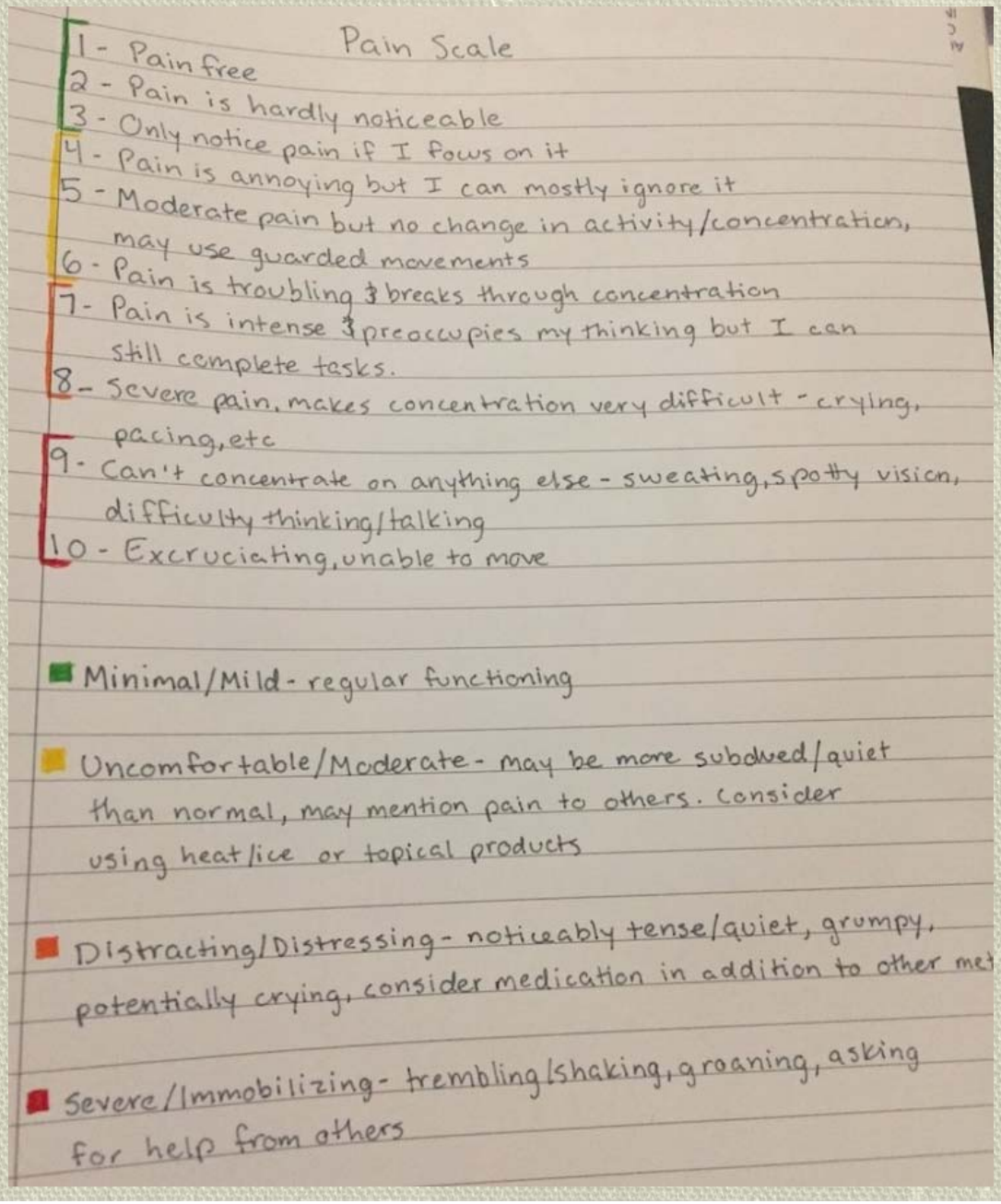
Pain scale: Subjective



Pain Scale

1 - Pain free
2 - Pain is hardly noticeable
3 - Only notice pain if I focus on it
4 - Pain is annoying but I can mostly ignore it
5 - Moderate pain but no change in activity/concentration, may use guarded movements
6 - Pain is troubling & breaks through concentration
7 - Pain is intense & preoccupies my thinking but I can still complete tasks.
8 - Severe pain, makes concentration very difficult - crying, pacing, etc
9 - Can't concentrate on anything else - sweating, spotty vision, difficulty thinking/talking
10 - Excruciating, unable to move

Minimal/Mild - regular functioning

Uncomfortable/Moderate - may be more subdued/quiet than normal, may mention pain to others. Consider using heat/ice or topical products

Distracting/Distressing - noticeably tense/quiet, grumpy, potentially crying, consider medication in addition to other me

Severe/Immobilizing - trembling/shaking, groaning, asking for help from others

Set a FUNCTIONAL goal

Example

- "At what level of pain control do you think you could enjoy life and focus on things other than the pain?"
- What things are you not able to do because of pain?

Usually 1-3/10

- some patients may quote higher numbers

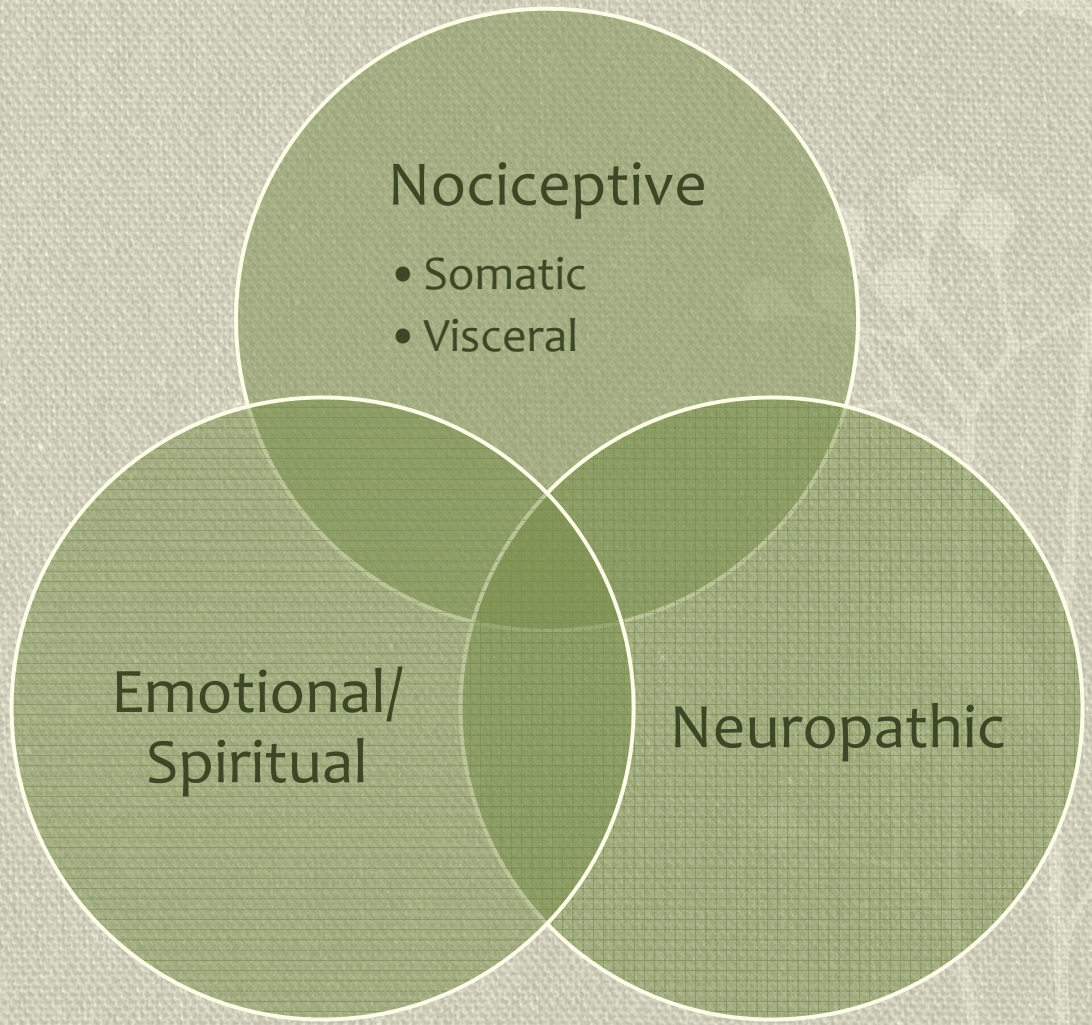
0/10 all the time is not a realistic goal

- Medication side effects would be too burdensome

For some patients, titration toward functional status rather than pain scale is best

- "Chemical copers"

What kind of pain is it?



Neuropathic pain

- Oral medications
  - Antiepileptics
    - Gabapentin (NNT 4.1)
    - Pregabalin
  - Tricyclic antidepressants
    - Amitriptyline (NNT 2.3)
    - Nortriptyline contraindicated: epilepsy, CHF, heart block
  - Opioids (especially methadone) (NNT 2.7)
  - SNRIs
    - Duloxetine (NNT 5.0)
    - Venlafaxine
- Topical medications
  - Capsaicin cream (NNT 6.6)
  - Lidocaine patch (NNT 4.4)

Emotional and Spiritual Pain

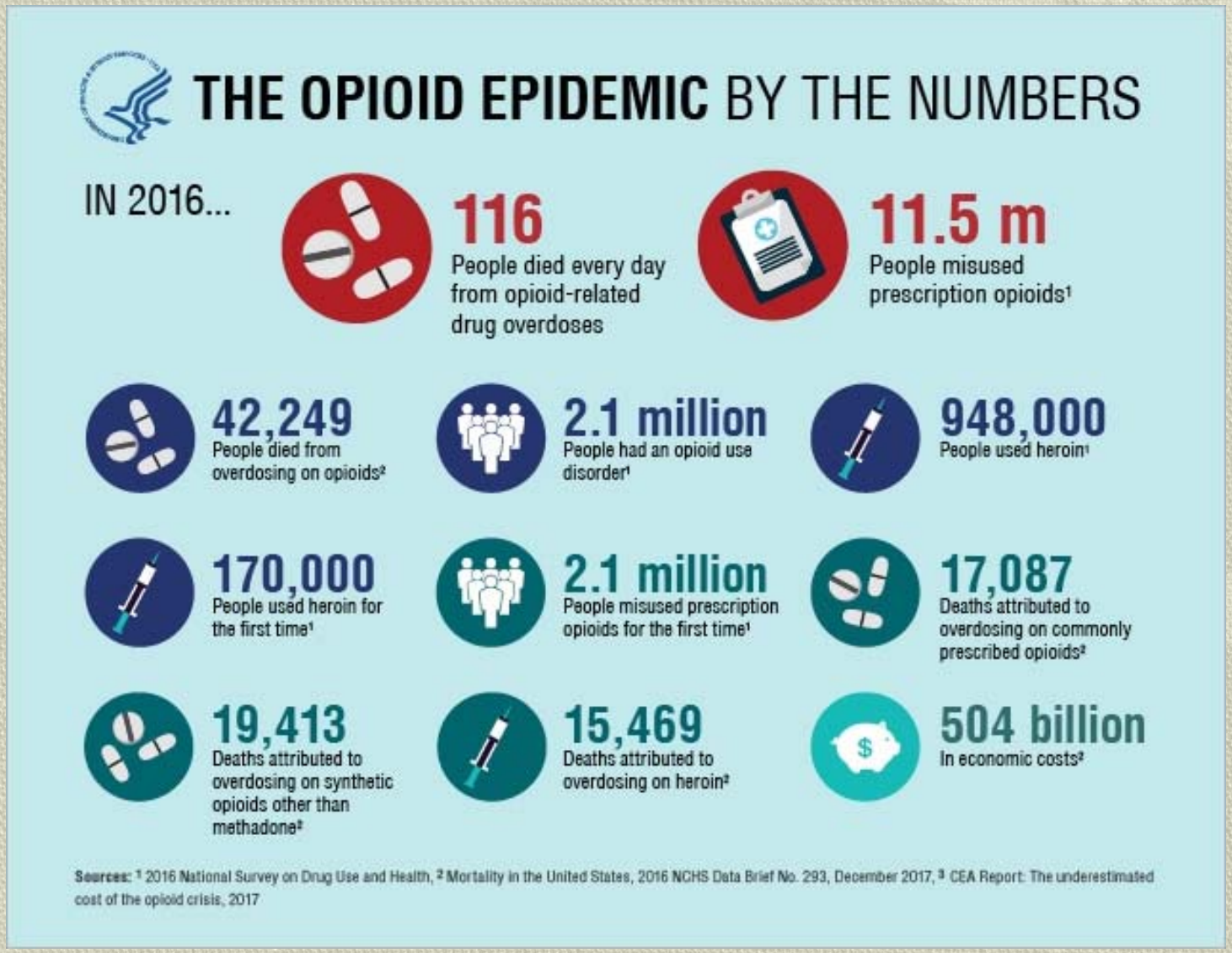
Appropriate interventions

- Counseling
- Social work consultation for financial/care support
- Chaplaincy consultation for spiritual support
- Antidepressants, if meeting criteria for diagnosis

Inappropriate interventions

- Opioids
- Procedures (e.g. nerve blocks, intrathecal pumps) and surgeries

The Opioid Epidemic



The Opioid Epidemic and You

The Opioid Epidemic in America

The Research Behind Understanding, Preventing and Treating Addiction

ELSEVIER

Data from the U.S. National Institute on Drug Abuse indicates:*

Roughly
21-29%
of patients prescribed opioids for chronic pain misuse them

Between
8-12%
develop an opioid use disorder

An estimated
4-6%
who misuse prescription opioids transition to heroin

Approximately
80%
of people who use heroin first misused prescription opioids

* National Institute on Drug Abuse. (2017). Opioid Crisis. Retrieved May, 2017, from https://www.drugabuse.gov/drugs-abuse/opioids/opioid-crisis

Abuse deterrents

- Physical/chemical deterrents: gelling agents or solvents to limit crushing, grinding, cutting, chewing, etc.
- Antagonists: interfere with euphoria
- Aversion: substances added to produce an unpleasant effect upon manipulation (e.g. nasal irritants to prevent snorting)
- Delivery system deterrents: e.g. sustained release depots

Winiecki, SK. Understanding abuse deterrent opioids.
fellowshipinternshipgraduatefacultyprograms/pharmacystudentexperientialprogramcder/ucm532123.pdf

Abuse deterrents

- Can still be crushed, snorted, injected, smoked, or dissolved for abuse
- The most common form of opioid abuse is by swallowing
- All are currently brand-name only (no generics)

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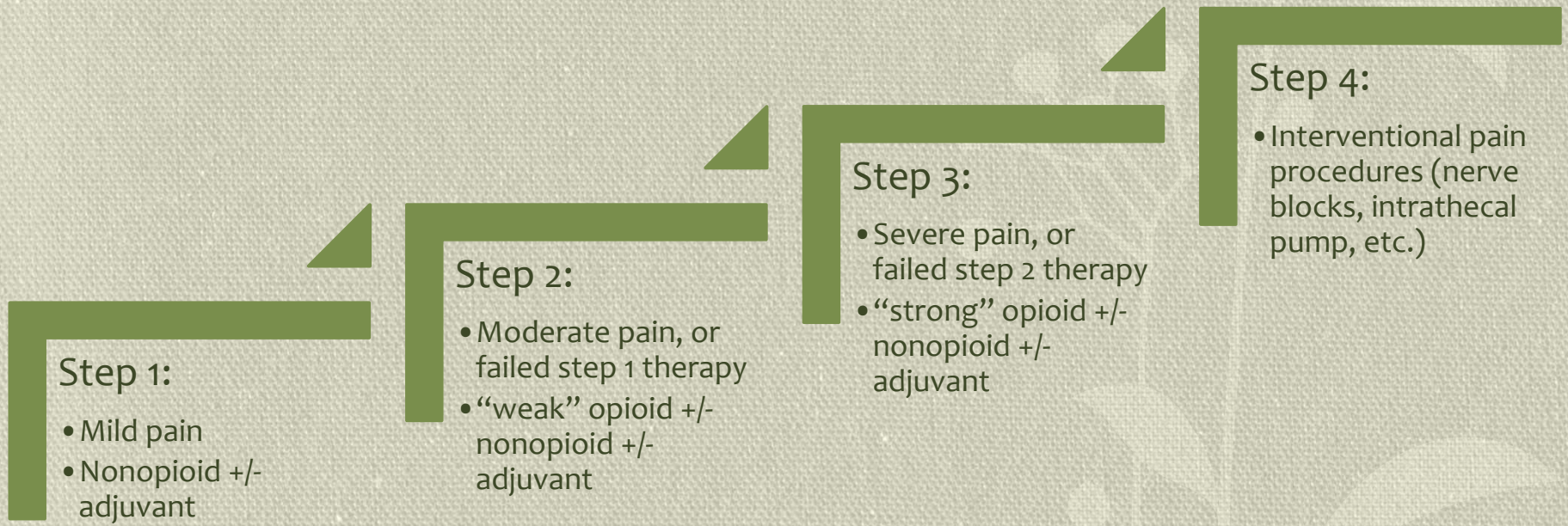
WHO analgesic ladder for cancer pain



Non-opioids and “Weak” Opioids

Over the counter (non-opioids)

- acetaminophen
- NSAIDs

Adjuvants

Prescription (“weak opioids”)

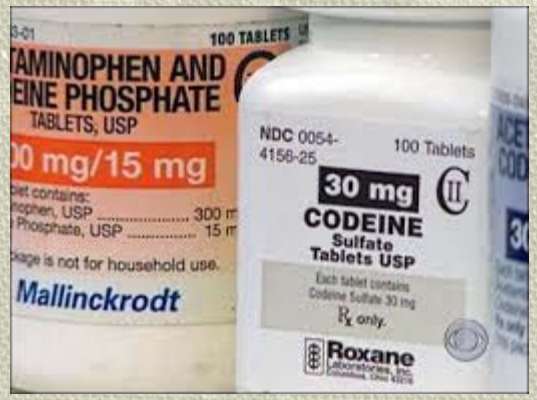
- Codeine/APAP: schedule III
- Tramadol: schedule IV

Codeine

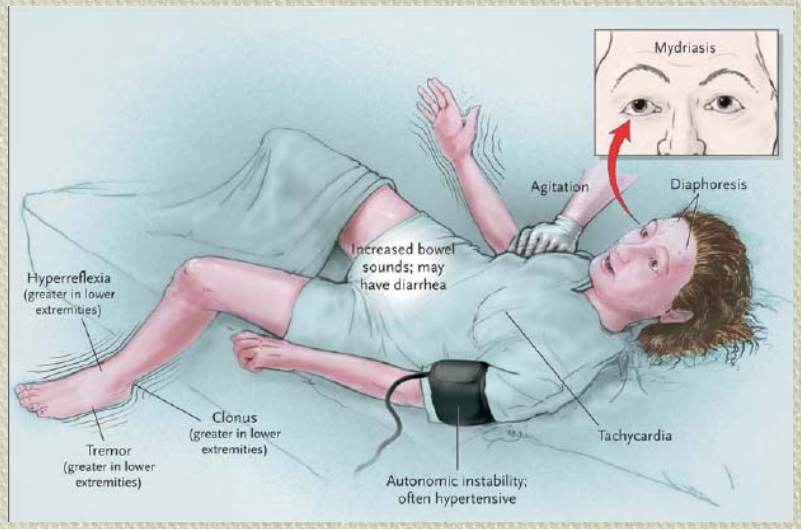
Used for pain, cough, and diarrhea

Oral bioavailability variable (12-84%)

Codeine binds weakly to mu receptors; efficacy depends on conversion to morphine by P450 CYP2D6



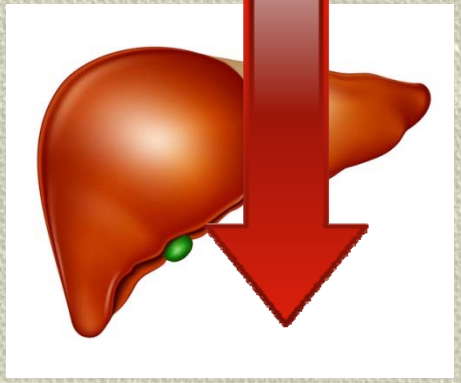
Tramadol



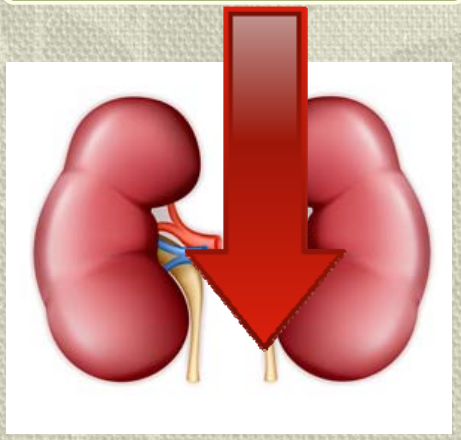
Inhibits noradrenaline and serotonin reuptake (risk: serotonin syndrome)

Increases seizure risk

Max: 50mg Q12h



Max: 200 mg/day



“Strong” Opioids

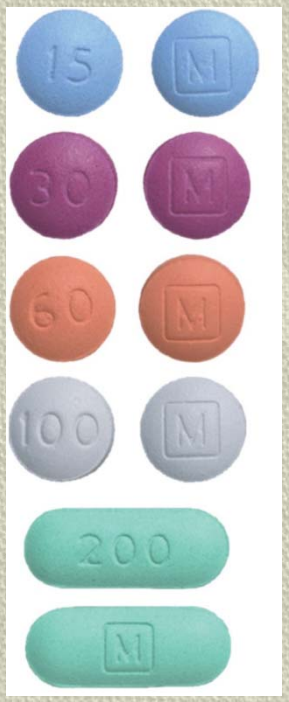
Triplicate prescription (schedule II):

- Morphine
- hydrocodone
- oxycodone
- oxymorphone
- hydromorphone
- methadone
- fentanyl

Morphine

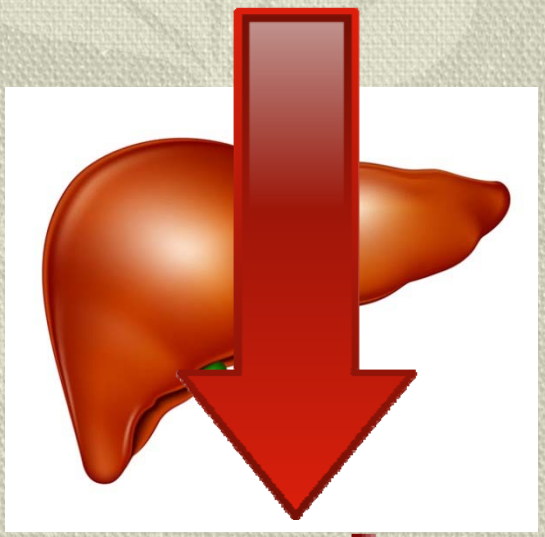
MEDD (morphine equivalent daily dose) = opioids converted to the equivalent dose of PO morphine

IV morphine x 2.5 to 3 = PO morphine



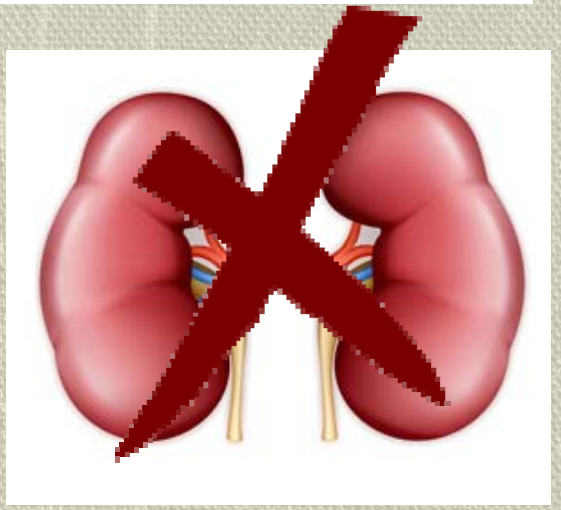
Morphine

Extensively metabolized in liver to renally cleared active metabolites



M3G: opioid-induced neurotoxicity

- Myoclonus → seizures (treatment: benzodiazepines)
- Hyperalgesia/allodynia
- Delirium



M6G: analgesia and respiratory depression

- Effects reversed by naloxone

Hydrocodone

Daily doses limited by acetominophen content (<3g/day) or NSAID content (risk of adverse effects such as gastritis)

- <2g/day in cirrhosis

Equianalgesic ratio (morphine:hydrocodone):

- 1.5:1 at low doses of hydrocodone (<40mg/day)
- 1:1 at high doses (>40mg/day)

Oxycodone

- Popular drug of abuse
- no IV form available
- PO Oxycodone x 1.5 = PO morphine

Hydromorphone

metabolized to H3G in liver, which is also excreted by kidneys

- Generally still better to use in renal insufficiency than morphine

Equianalgesic ratios:

- **4-8 times stronger than morphine**
- IV Hydromorphone x 2 to 5 = PO hydromorphone
- IV Hydromorphone x 10 = PO morphine
- IV hydromorphone x 5 = IV morphine

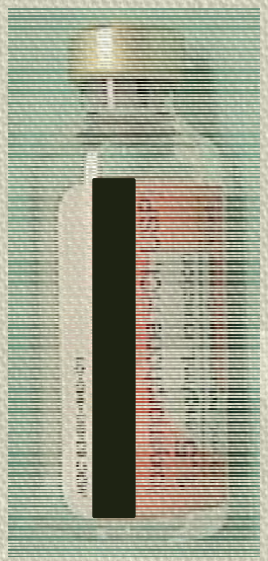
Oxymorphone

Much longer half-life (8h) compared to morphine (1.5h)

- Oxymorphone IR should be dosed Q6h
- Oxymorphone ER should be dosed Q12h

Has metabolites that accumulate in renal insufficiency

Taking with food can increase serum levels by up to 50%; must take 1-2 hours before eating

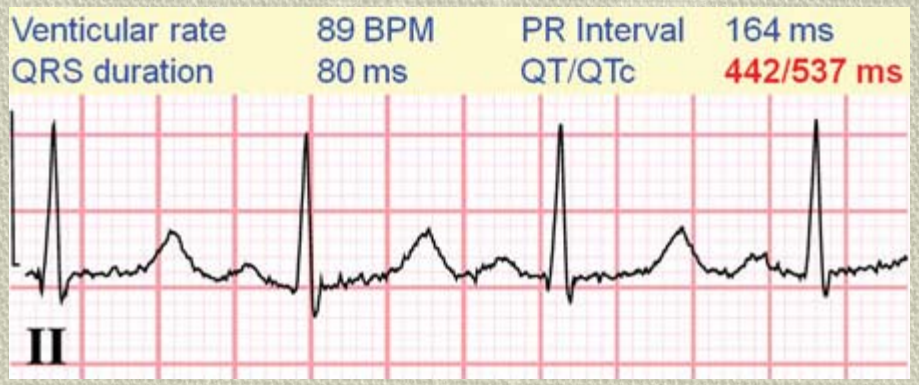


Equianalgesic ratios:

- PO oxymorphone x 3 = PO morphine
- IV oxymorphone x 10 = IV morphine (lipophilic)

Methadone

- Good opioid for neuropathic pain
- Takes 48-72 hours to reach maximum analgesia
- All forms (pills, liquid, IV solutions) are long-acting!
- QTc prolongation generally insignificant until doses >200 mg/day



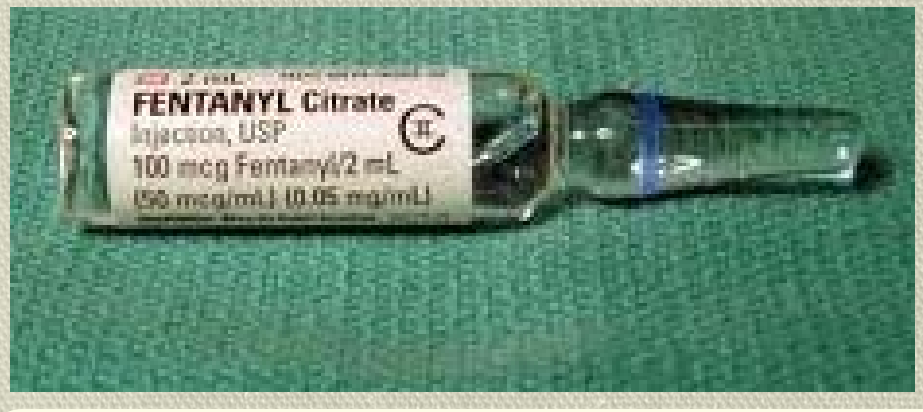
Methadone

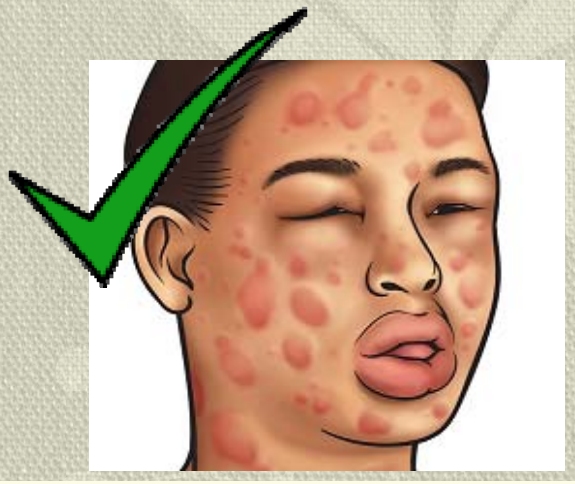
Equianalgesic ratios:

- Methadone becomes more potent at higher doses!
- Get a pain specialist (acute or chronic pain, palliative) to manage

Total 24-hour Morphine Dose	Conversion ratio (oral morphine : oral methadone)	Percent Reduction
<30 mg/d	2:1 (2mg morphine to 1mg methadone)	50% reduction
30-100 mg/d	4:1	75% reduction
100-300 mg/d	8:1	87.5% reduction
300-500 mg/d	12:1	92% reduction
>500 mg/d	20:1	95% reduction

Fentanyl IV



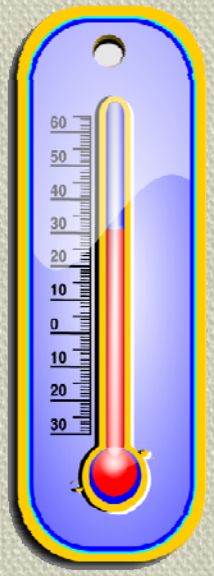


Safest option to try in true morphine or codeine allergy

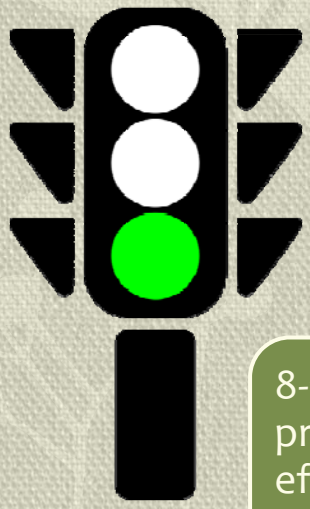
IV fentanyl has duration of action of 0.5 to 1 hour (rapidly redistributed)

morphine IV (mg) x 10 = fentanyl IV (mcg)

Fentanyl transdermal patch

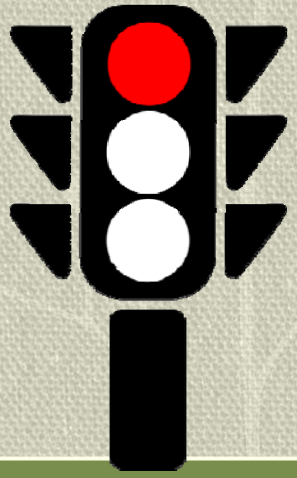


Absorption increases with body temperature!



8-12 hours to provide effective analgesia

Can only be titrated Q48-72h due to dosing → not ideal for patients with acute or unstable pain



12-24 hours for 50% reduction

Equianalgesic ratio: fentanyl patch (mcg/h) x 2 = MEDD (mg)

Fentanyl transmucosal

www.TIRFREMSaccess.com

Onset to analgesia 5-10 minutes

Somnolence, nausea, dizziness, falls

Doses START at 100 mcg!!!

Effective doses unpredictable, not based on MEDD

Transmucosal Immediate-release Fentanyl Risk Evaluation and Mitigation Strategy (TIRF REMS)

Patient-prescriber agreement form required, renewed Q2 years

CONTRAINDICATED for opioid-naïve patients

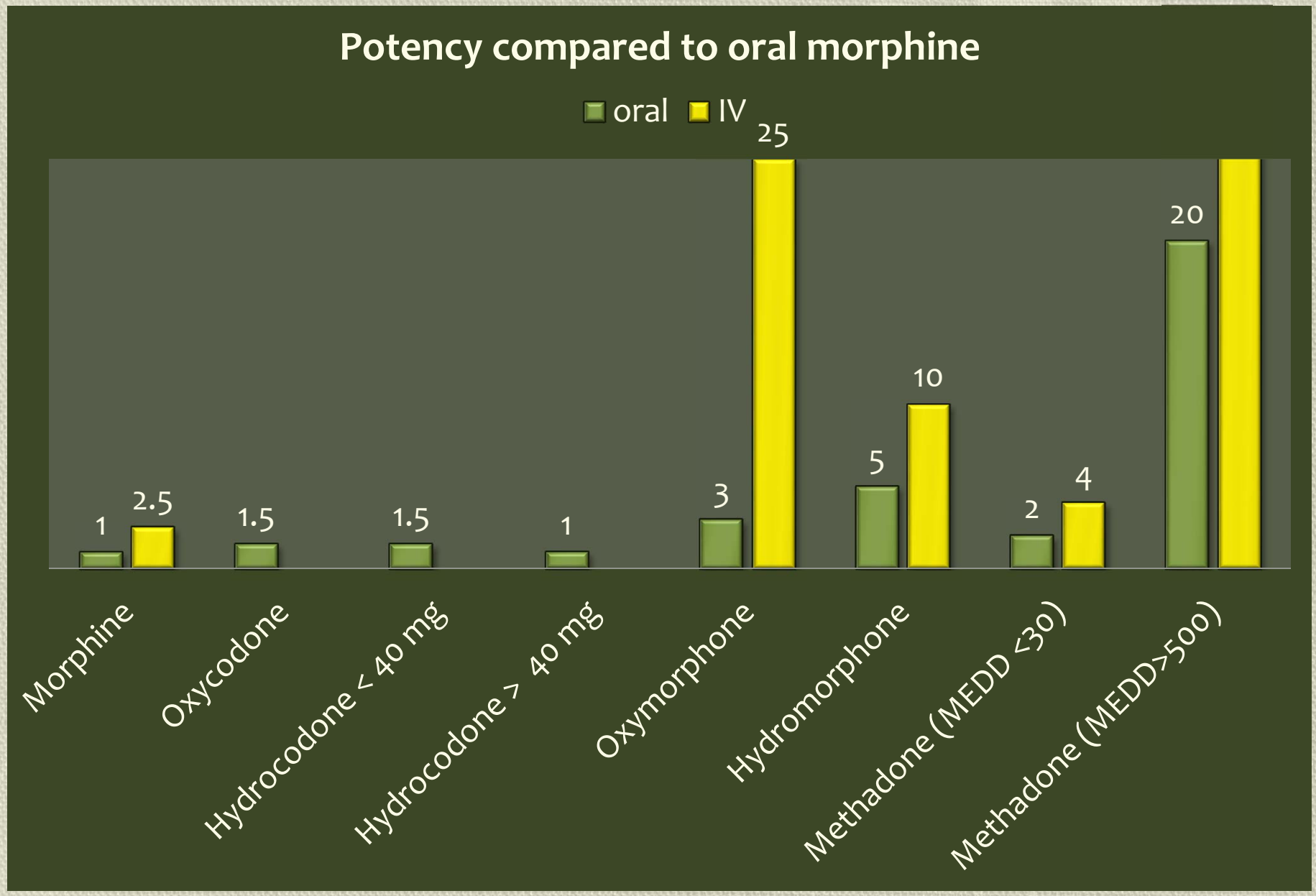
ALL patients should be initiated at the lowest dose

Opioid-tolerant cancer patients ONLY

NOT for acute or post-op pain

Different TIRF brands CANNOT be converted mcg for mcg

Opioid potency comparison chart



Tailoring therapy:

OPIOID SELECTION

QUESTION

- A 48-year-old man with advanced head and neck cancer comes to palliative care clinic for the evaluation and treatment of chronic pain. He has facial nerve neuropathy as well as chronic right jaw pain. He also has chronic renal insufficiency from diabetes, with a baseline serum creatinine of 2.5 mg/dL. Trials of nonopioid pain medication and adjuvants for neuropathic pain have been unsuccessful, and today he tells you that he has resumed using heroin in an effort to control his pain.
- Which of the following opioid analgesics is safest and most likely to be effective for this patient?

a. Hydromorphone

b. Oxycodone

c. Extended-release morphine

d. Acetaminophen with codeine

e. Methadone

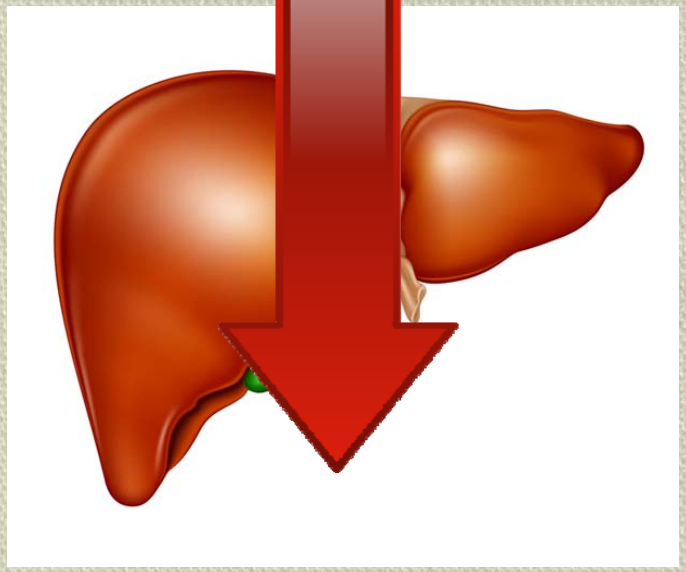
Things I should know before I Rx

Type of pain	• Nociceptive • Neuropathic • Emotional/Spiritual
Patient-specific factors	• Medical comorbidities • Psychosocial issues • Available routes for administration
System issues	• Refills • Further management (follow-up) • Pharmacy (stock and availability)

Factors affecting pharmacokinetics

CNS sensitivity to opioids

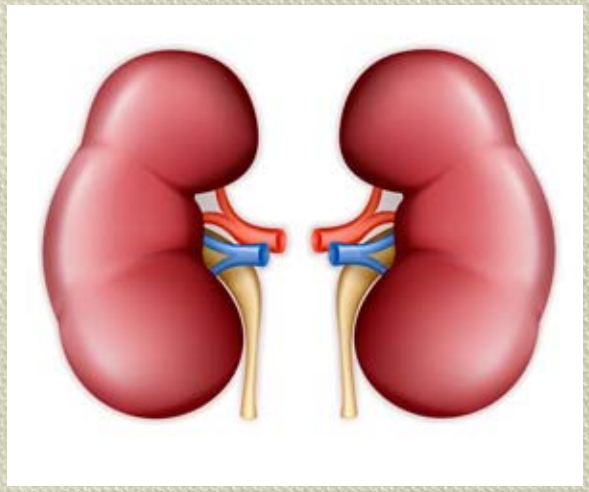
Hepatic clearance of opioids by ~50% by age 70



Unpredictable effects

Reduce opioid doses if concerned

Factors affecting pharmacokinetics



Preferred: fentanyl, methadone

Caution: hydromorphone, oxycodone, oxymorphone, hydrocodone

Avoid: morphine, codeine

Opioid selection: patient factors

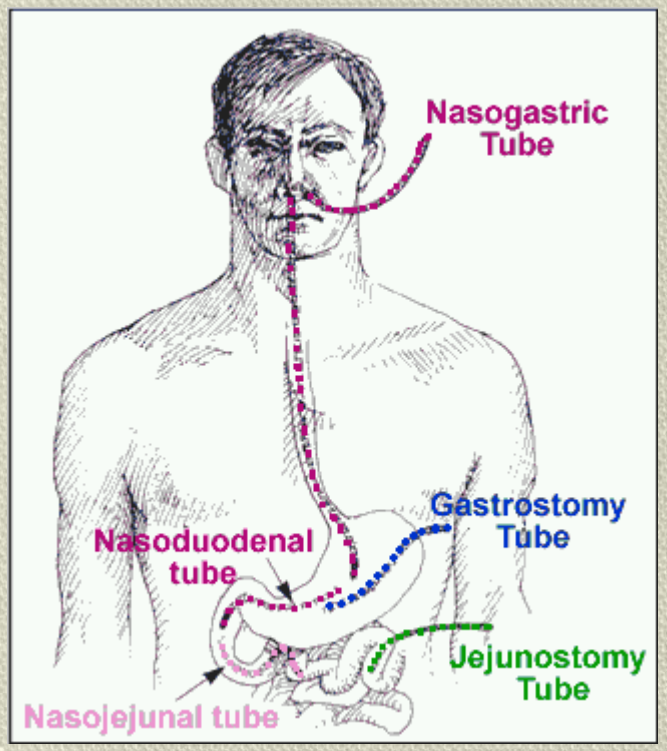
History of "chemical coping" or drug abuse

- Limit-setting

Available routes of administration

- PO
  - Preferred whenever patient is able to swallow
- IV
  - Available in hospitals and LTACs only
  - Oxycodone does not have IV form
- IM
  - Available in most settings except home
  - Not preferred due to pain of administration
- PR
  - Most opioids can be used PR effectively

Patients with NGT/PEG tube



Most long-acting oral opioids CANNOT be crushed!

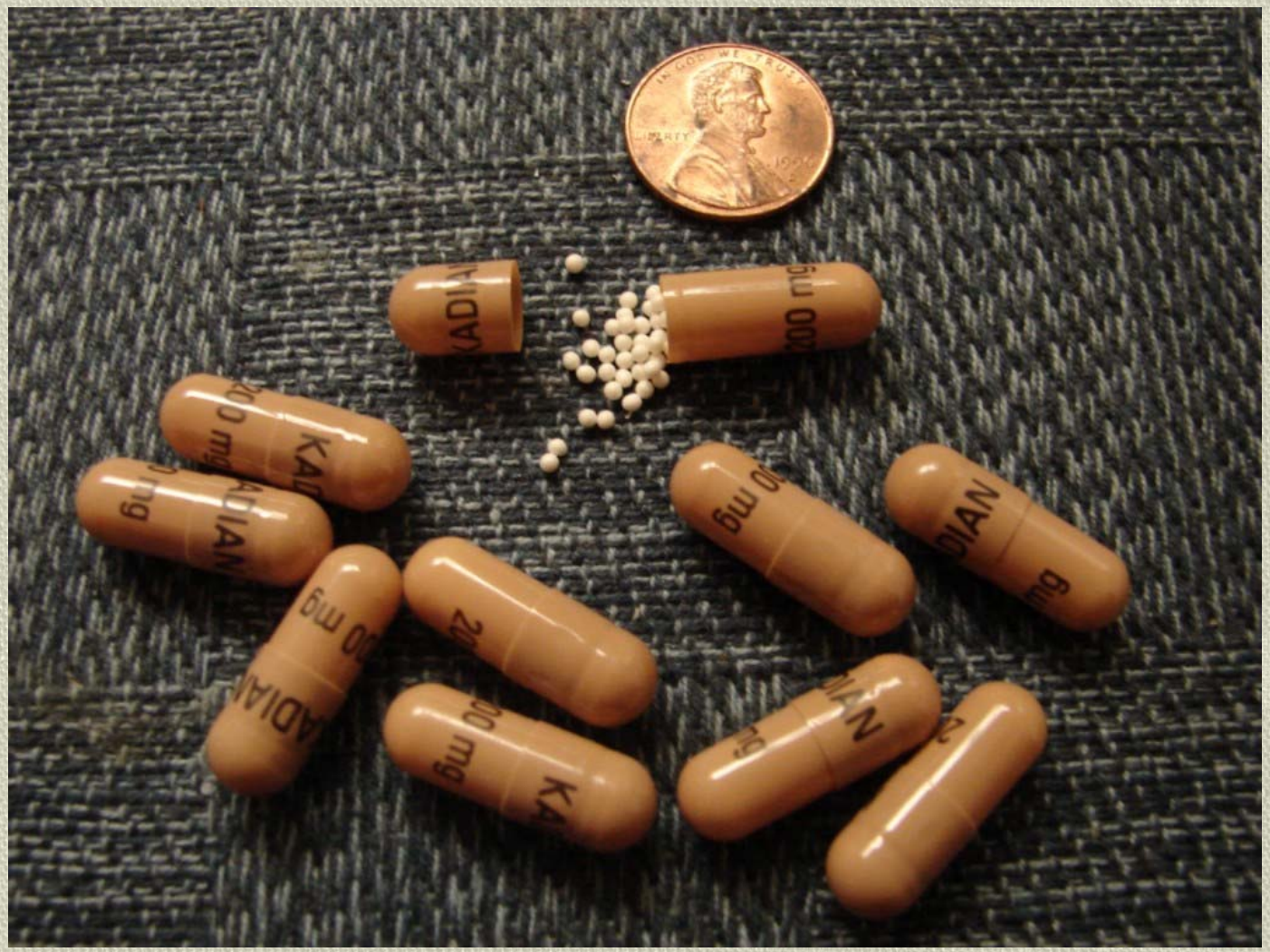
- Only long-acting due to formulation

Long-acting opioid options for NGT/PEG patients:

- Methadone: elixir or crush tablets
- Morphine extended-release pellets with capsule: unscrew capsule and put pellets in liquid or soft solids
- Fentanyl transdermal patch

Short-acting opioids: can use elixir or crush

Morphine extended-release pellets



Subcutaneous route

Available in some hospitals, most hospice settings (including home)

- Family members can be trained to give SQ meds through a SQ catheter

Not available in most nursing homes (require RN to give)

SQ depot prolongs duration of action

- Intermittent administration of opioids SQ Q4h approximates the effect of IV PCA
- Exception: fentanyl SQ is still short-acting, and must be given as a fentanyl IV PCA
- Exception: methadone SQ still has duration of 8-12h (also, beware possible skin toxicity)

Many comfort medications and hydration can be given subcutaneously at home with hospice services

Opioid selection: system issues

Refills

- No refills can be given on triplicate prescriptions
- Refills cannot be faxed or called in to pharmacy

Follow-ups

- Travel to appointments may be burdensome
- Monthly follow-ups needed to refill strong opioids

Pharmacy stocks

- Limited dosages or formulations available
- Limited amounts available

QUESTION

- A 48-year-old man with advanced head and neck cancer comes to palliative care clinic for the evaluation and treatment of chronic pain. He has facial nerve neuropathy as well as chronic right jaw pain. He also has chronic renal insufficiency from diabetes, with a baseline serum creatinine of 2.5 mg/dL. Trials of nonopioid pain medication and adjuvants for neuropathic pain have been unsuccessful, and today he tells you that he has resumed using heroin in an effort to control his pain.

a. Hydromorphone

b. Oxycodone

c. Extended-release morphine

d. Acetaminophen with codeine

e. Methadone

Prescribing:

OPIOID INITIATION

QUESTION

- A 56-year-old woman with widely metastatic lung cancer presents to the emergency department (ED) in severe respiratory distress. She was initially wheezing and had O2 saturation of 85% on arrival. Her current medications include sustained-release morphine, 100 mg every 12 hours, and immediate-release morphine, 20 mg every hour as needed for pain control. She has required 5 doses of her rescue morphine in the past 24 hours for pain control. The ED physician provided the patient with nebulized beta-agonists, IV steroids, and oxygen at 100% FiO2. Her oxygen saturations have improved to 92%, but the patient is still tachypneic and in distress. The patient and her husband are clear that intubation is not an option. The ED physician calls an urgent palliative care consultation.
- What initial dose and route of morphine would you recommend?

  a. 2 mg oral solution

  b. 10 mg oral solution

  c. 2 mg nebulized

  d. 10 mg nebulized

  e. 2 mg IV push

  f. 10 mg IV push

IV PRN medications

- In general: morphine IV equivalent of 1 or 2mg is a good starting dose for MOST people
  - Geriatric starting dose is 0.5mg IV
  - Reduce doses by 50% in high risk patients

Scheduling IV medications

- IV medications:
  - typically schedule Q6h or Q4h
  - Use a smaller dose than your PRN (your PRN should be 10-15% of the total scheduled medication they receive throughout the day at most)
  - Add up how much PRN they received and make sure you schedule less than that
  - Example: morphine sulfate 2mg IV Q4h PRN, received 8 doses in last 24 hours
    - 2mg x 8 doses = 16mg
    - 16/6 = 2.67 mg Q4h (max you would want to schedule)
    - Schedule 2mg IV Q4h

Scheduling oral medications

- Immediate release (IR) medications:
  - typically schedule Q6h or Q8h (Q4h in PEG/NGT only)
  - Use a smaller dose than your PRN (your PRN should be 10-15% of the total scheduled medication they receive throughout the day at most)
  - Add up how much PRN they received and make sure you schedule less than that
  - Example: morphine sulfate 2mg IV Q4h PRN, received 8 doses in last 24 hours
    - 2mg x 8 doses = 16mg
    - 16/4 = 4 mg Q4h (max IV you would want to schedule)
    - 4mg IV x 3mg PO/1 mg IV = 12
    - Schedule 10mg PO Q6h (this would be liquid) OR 15mg PO Q6h (pills)

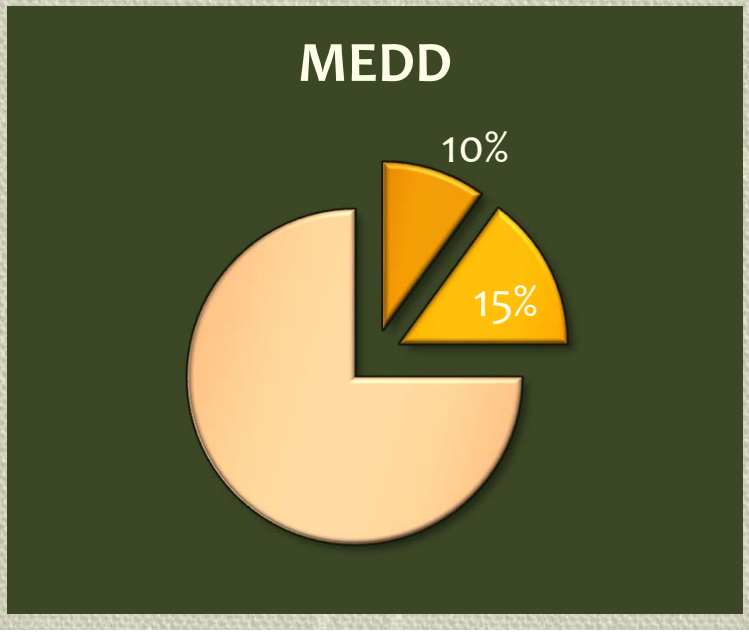
Opioid initiation

A good starting dose for an opioid naïve patient is an MEDD of 30 (long-acting)

- Morphine sulfate ER 15mg PO Q12h (MEDD 30)
- Oxycodone ER 10mg PO Q12h (MEDD 30)
- Fentanyl patch 12mcg (MEDD 25)
- Morphine sulfate 0.5 mg/h drip (MEDD 30)
- Hydromorphone 0.1 mg/h drip (MEDD 24)

Breakthrough pain medication (short-acting)

- 10-15% of total long-acting daily dose every ___ hours PRN
- Dosing interval based on expected duration of action

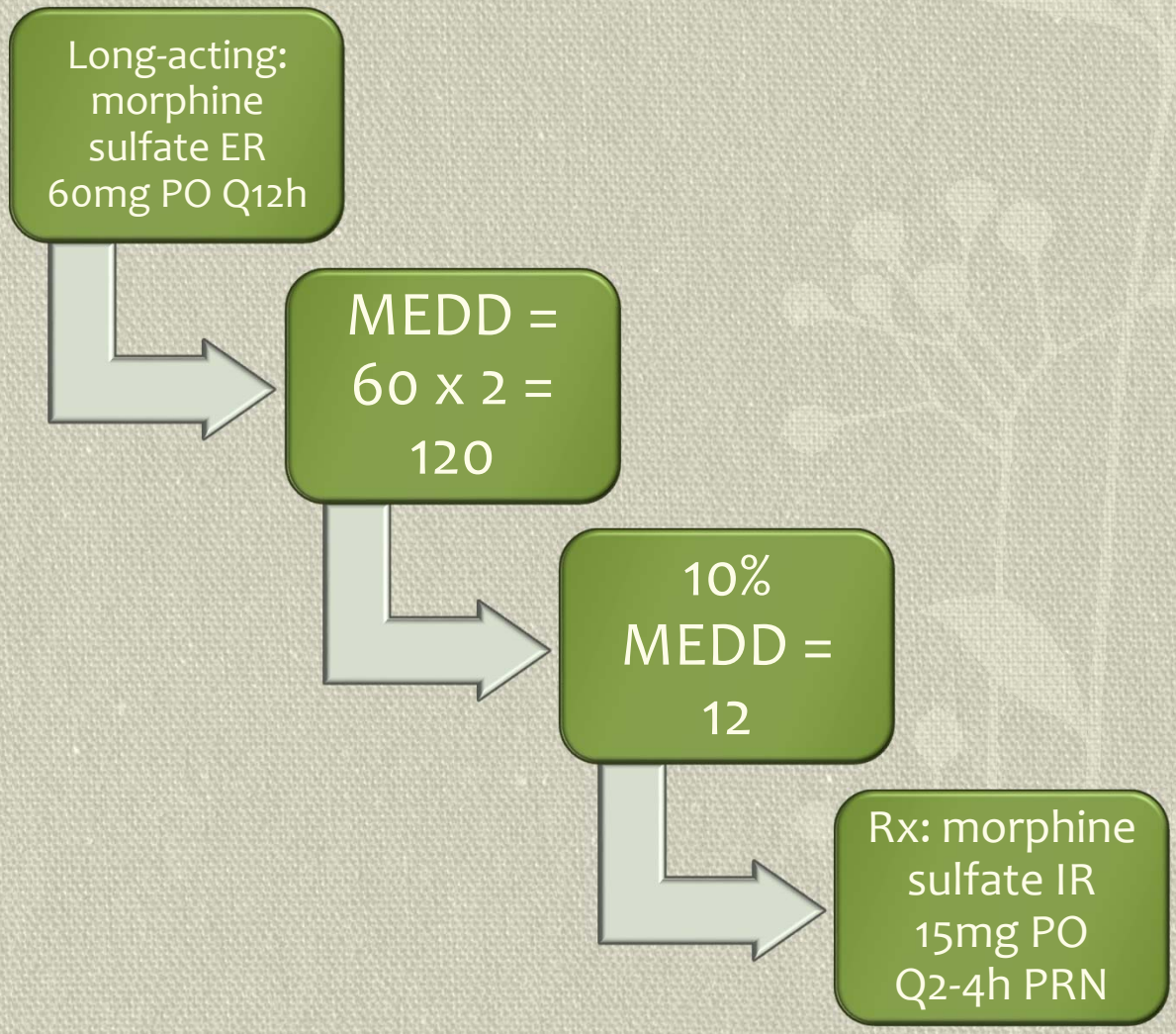


Onset and duration of action

Route	Onset	Duration	Dosing interval
IV*	15 minutes	1-2 hours	Q1-2h
SQ*	15 30 minutes	2 4 hours	Q2 4h
PO*	30-45 minutes	2-4 hours	Q2-4h (short-acting) Q8-12h (ER/CR/SR)
Methadone	30-45 mins (IV/PO)	72 hours	Q8-12h
Fentanyl patch	6-12 hours	72 hours	Q48-72h
Fentanyl lozenge	5-10 minutes	30 minutes	Depends on brand

*Except methadone (longer half-life) and fentanyl (shorter half-life)

Breakthrough dose example:



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a. 2 mg oral solution
b. 10 mg oral solution
c. 2 mg nebulized
d. 10 mg nebulized
e. 2 mg IV push
f. 10 mg IV push

MEDD: 100 x 2

=200 [morphine PO]

Breakthrough dose = 10-15% MEDD:

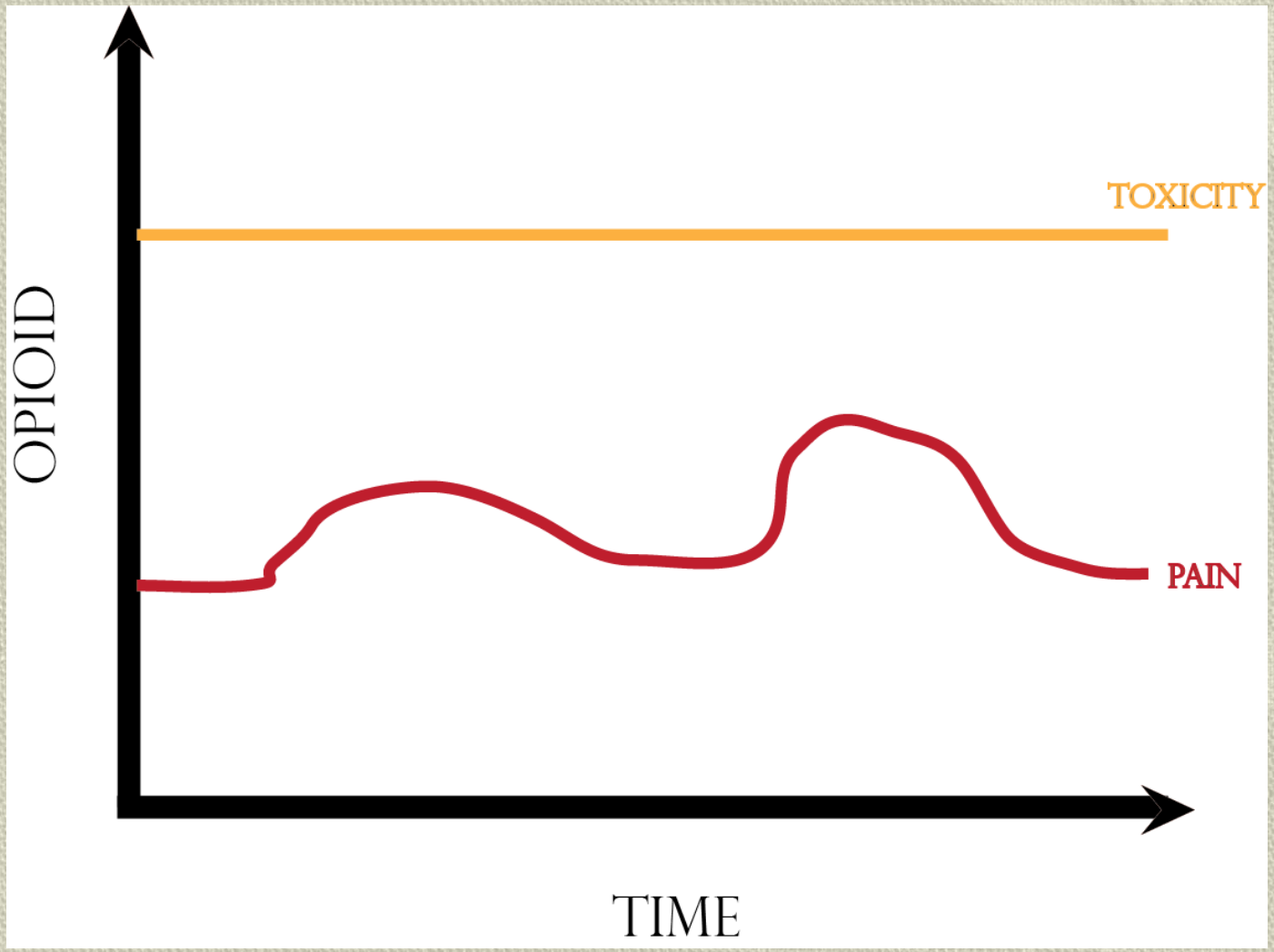
=20-25 [morphine PO]

Morphine IV = morphine PO ÷ 2.5 or 3

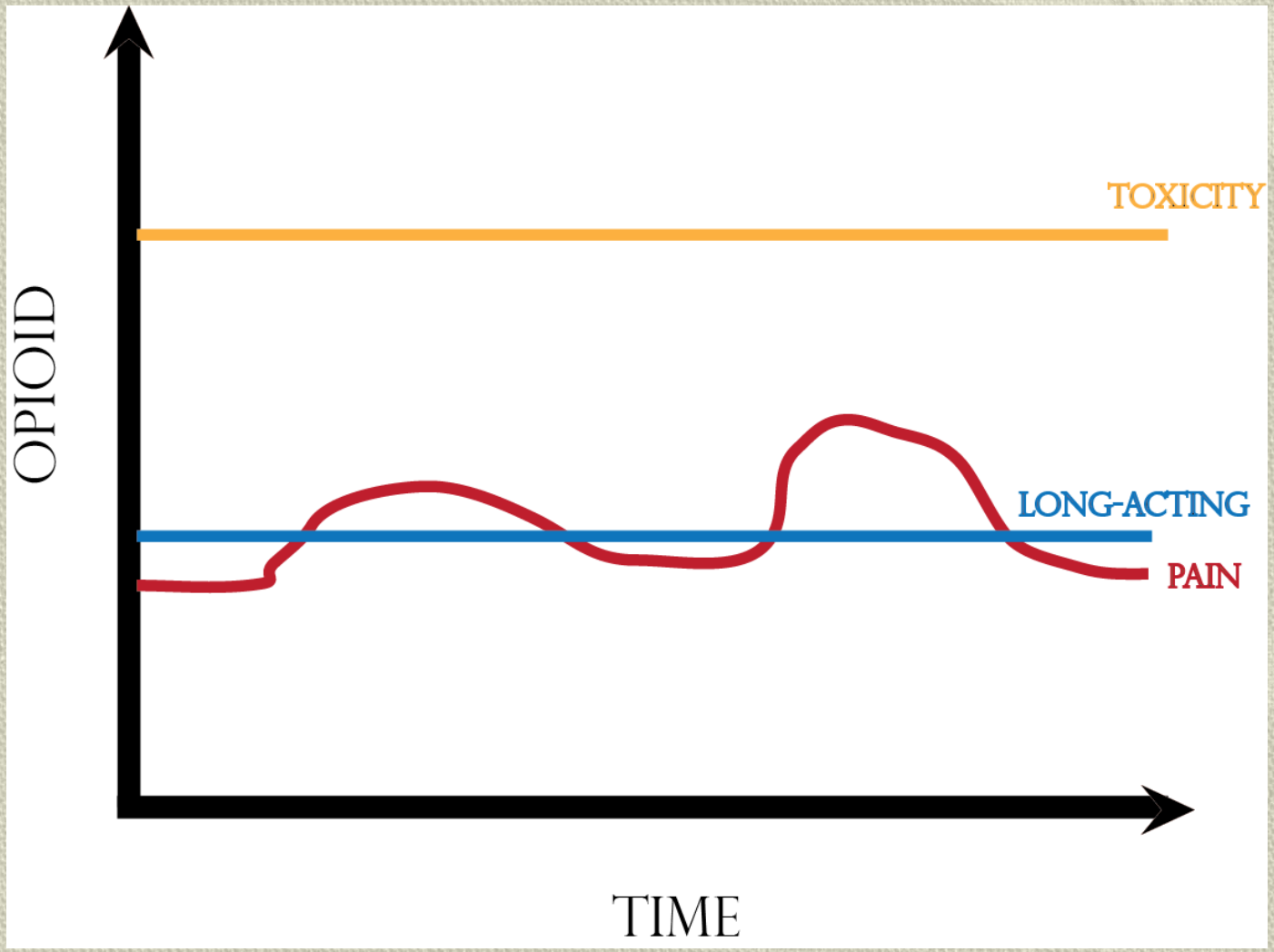
Refining therapy:

OPIOID TITRATION

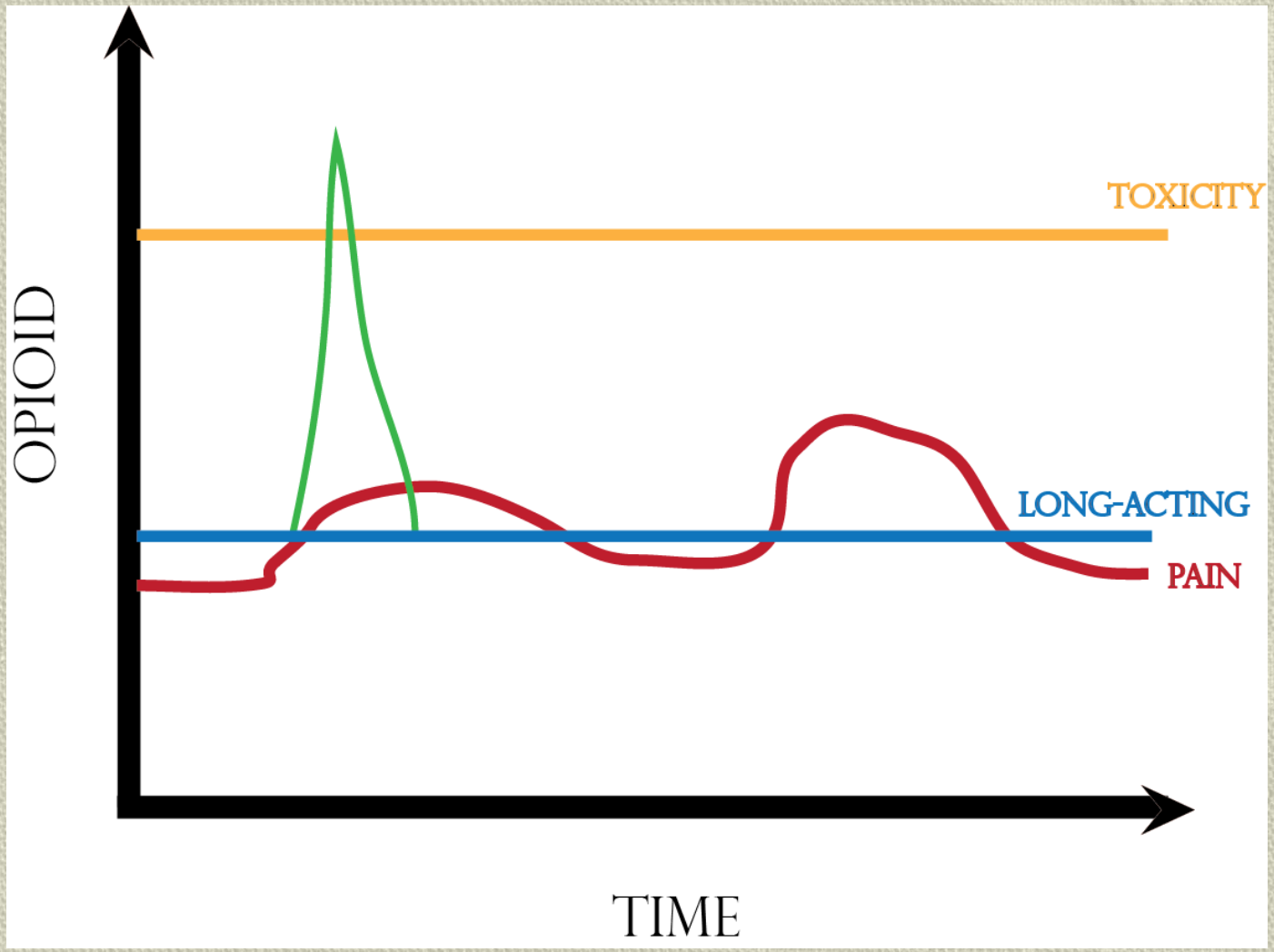
Pain management strategy



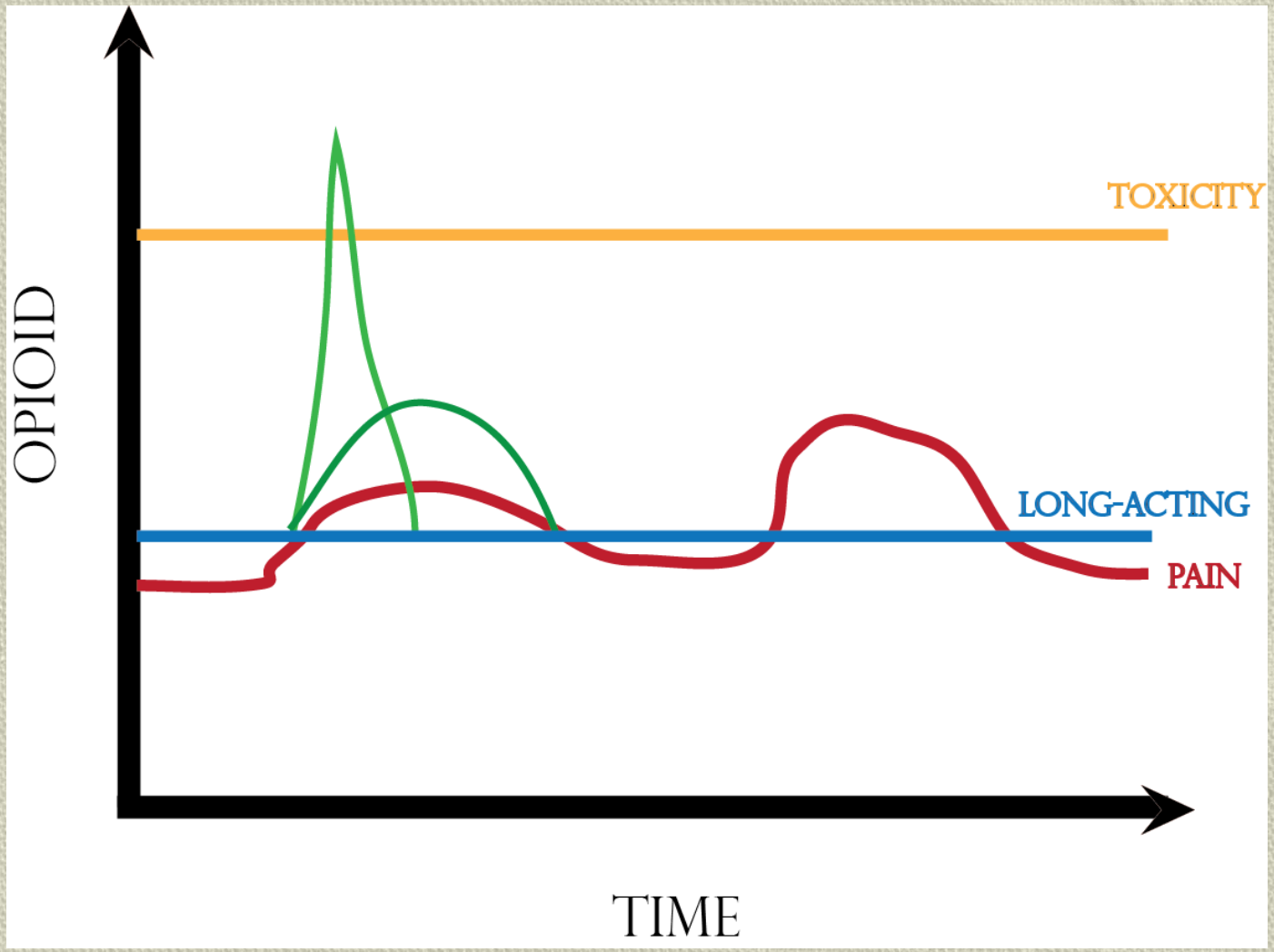
Role of long-acting opioid



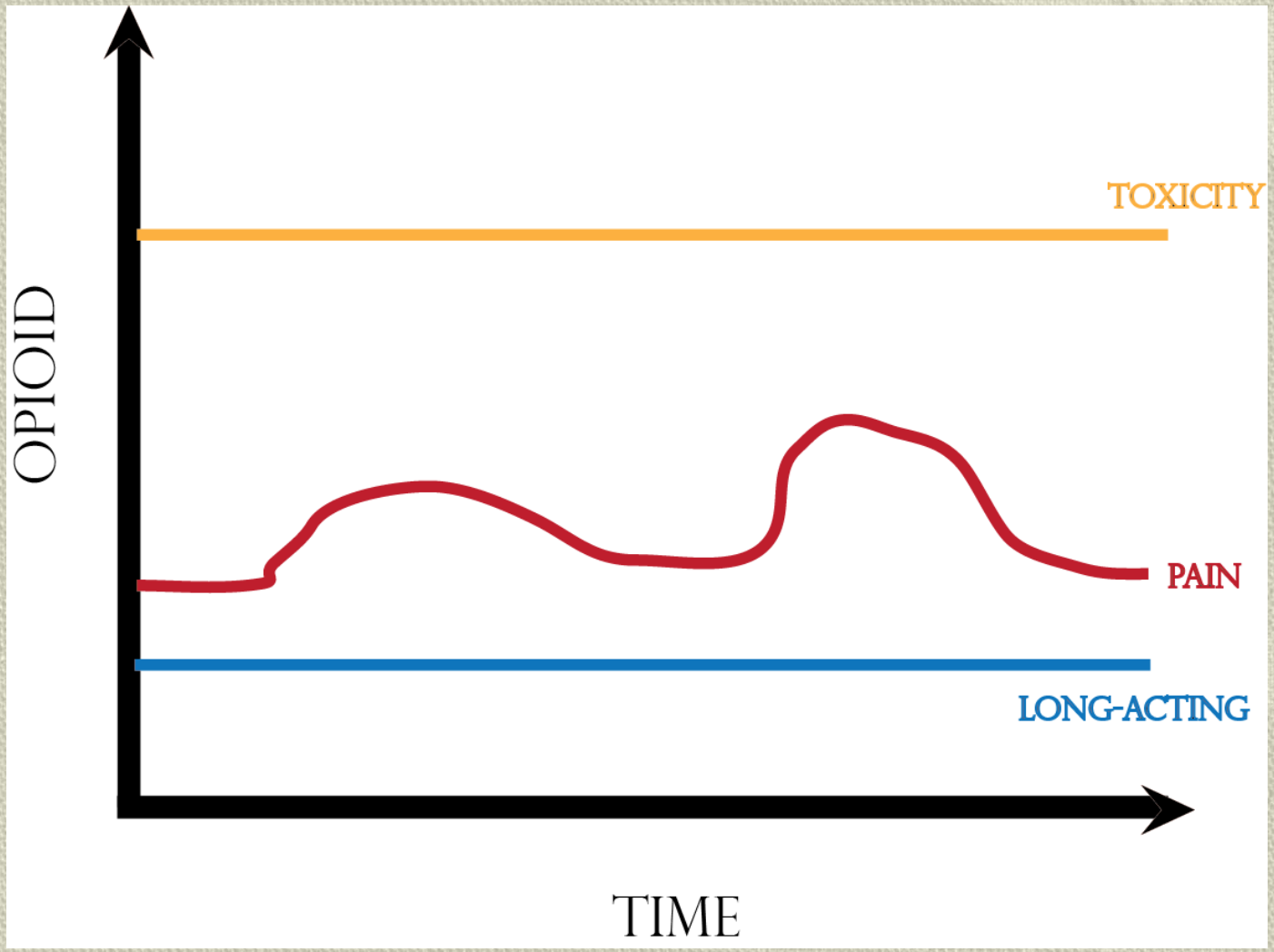
Breakthrough: IV



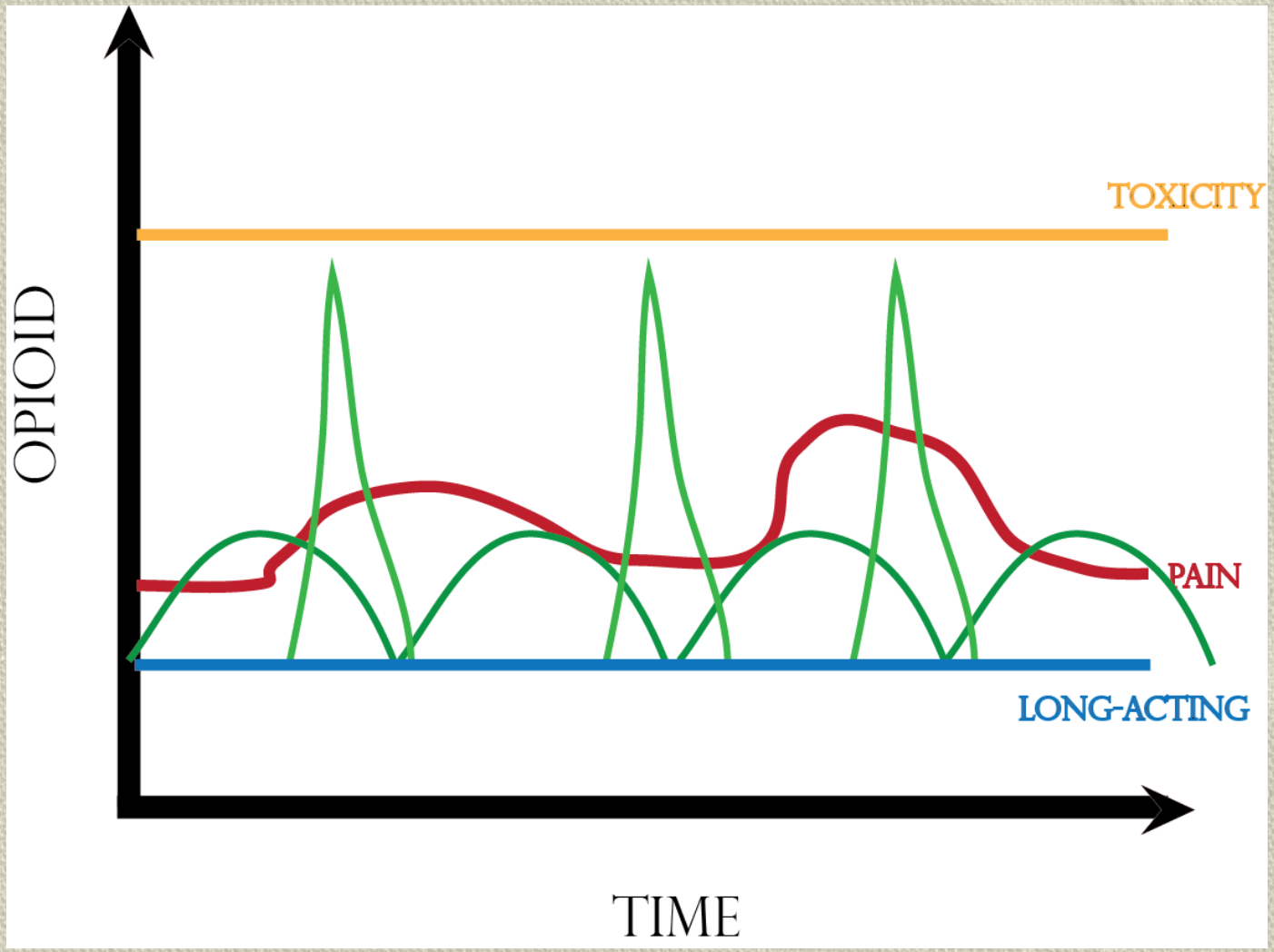
Breakthrough: PO



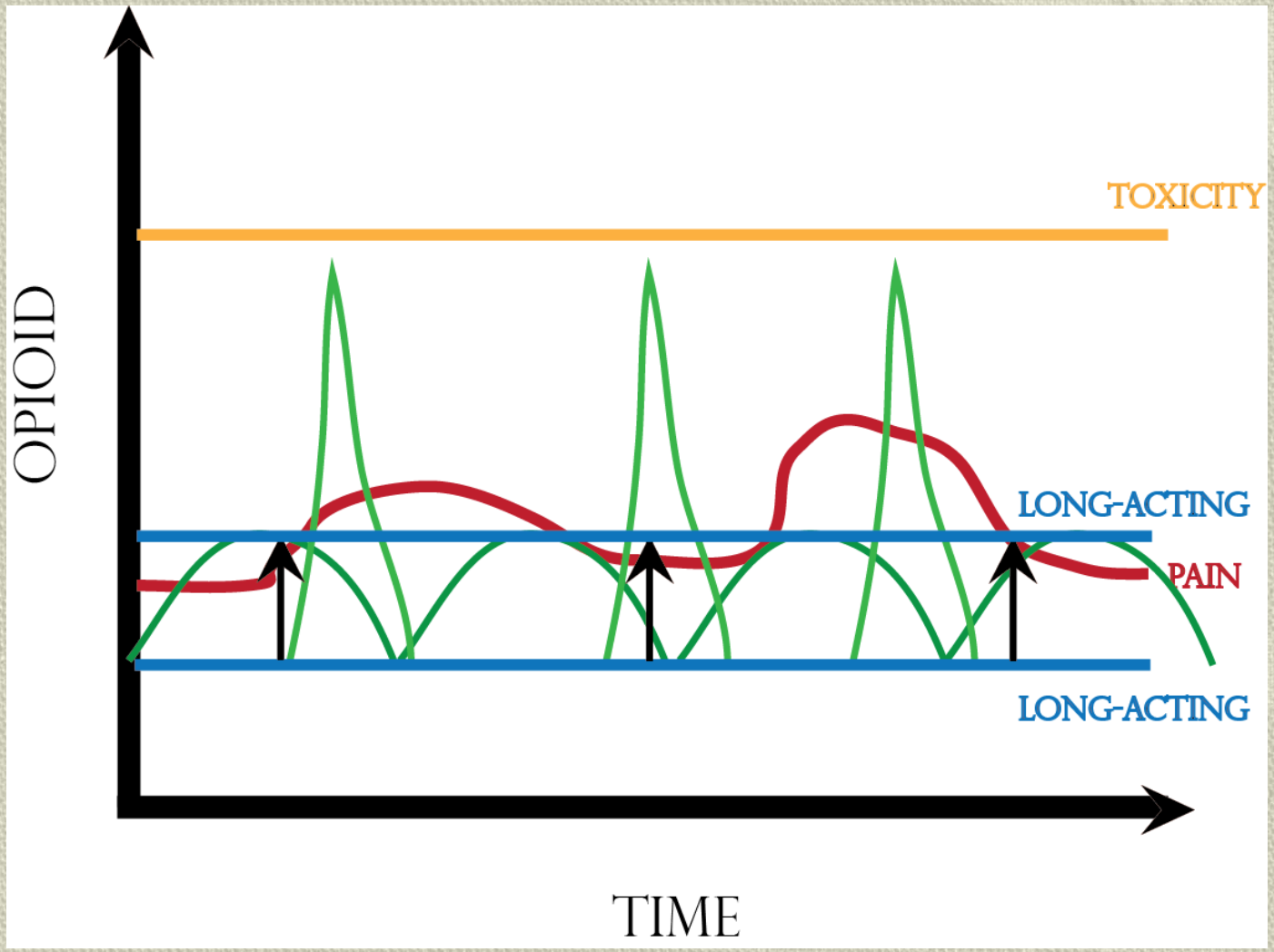
Long-acting dose too low…



Multiple breakthroughs needed



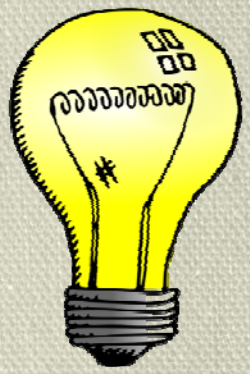
Solution: titrate long-acting dose!



Opioid titration

Rule of thumb:

of MEDD



or more breakthroughs per day

Adjust breakthrough dose after titrating!

Opioid titration

How often can I titrate?

- Depends on half-life of the opioid
- Reach close to maximal analgesic effect before titrating
  - Short-acting oral opioids: can titrate daily
  - Most oral long-acting opioids: can titrate daily with caution, otherwise around 48 hours
  - Fentanyl and methadone: typically titrate after 72 hours
  - IV PCAs/drips: reach steady state after 8 hours and can be titrated Q8h

Opioid withdrawal

Dose needed to prevent opioid withdrawal is 25% of MEDD

- Some sources quote 75% of MEDD

Withdrawal symptoms:

- Anxiety, nervousness, irritability, insomnia
- Chills and hot flushes, gooseflesh
- "Wetness": salivation, lacrimation, rhinorrhea, sweating, sneezing
- Nausea/vomiting, cramping, diarrhea
- Multifocal myoclonus (rare)

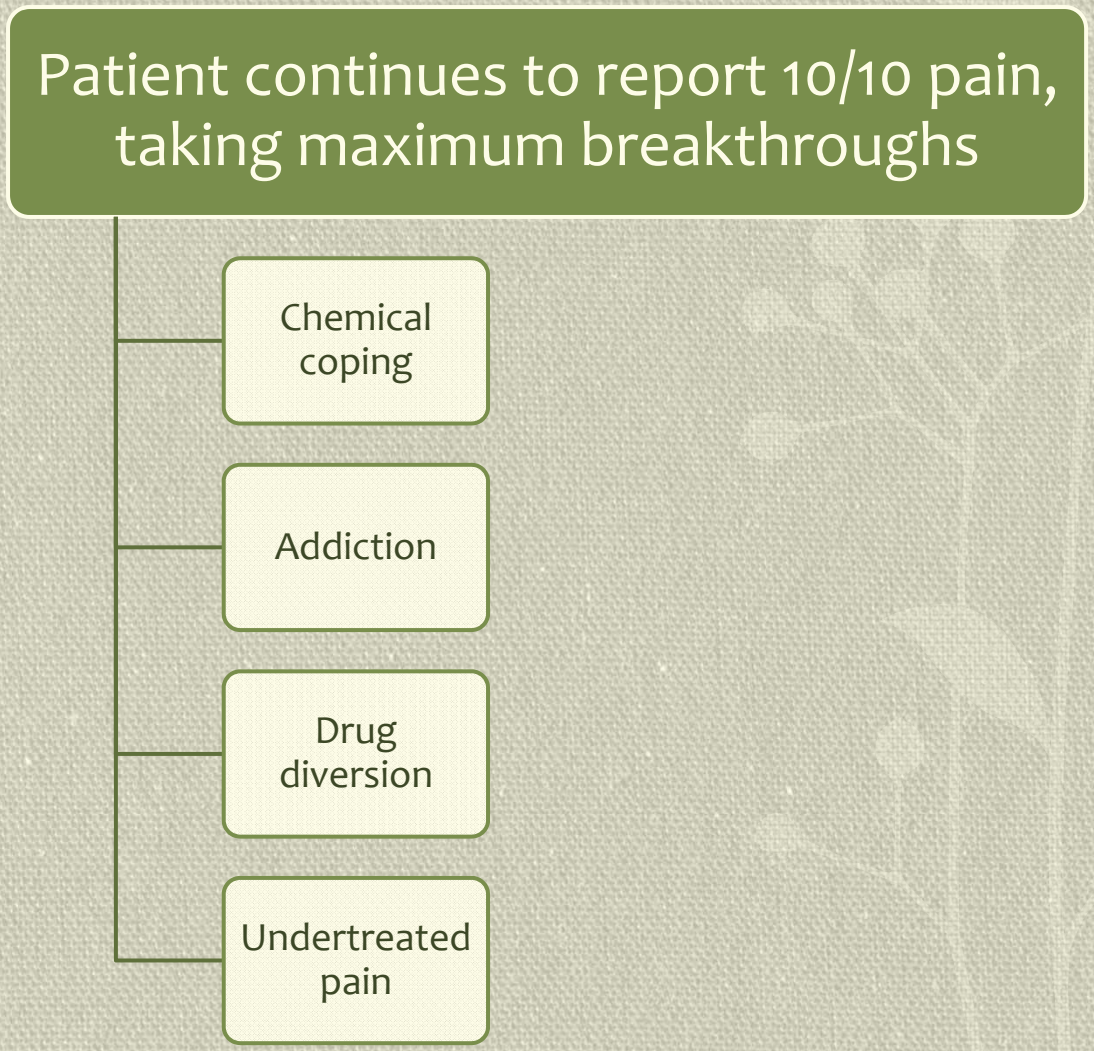
Onset of withdrawal:

- Range: 6-12h with short-acting opioids to 36-48h with methadone

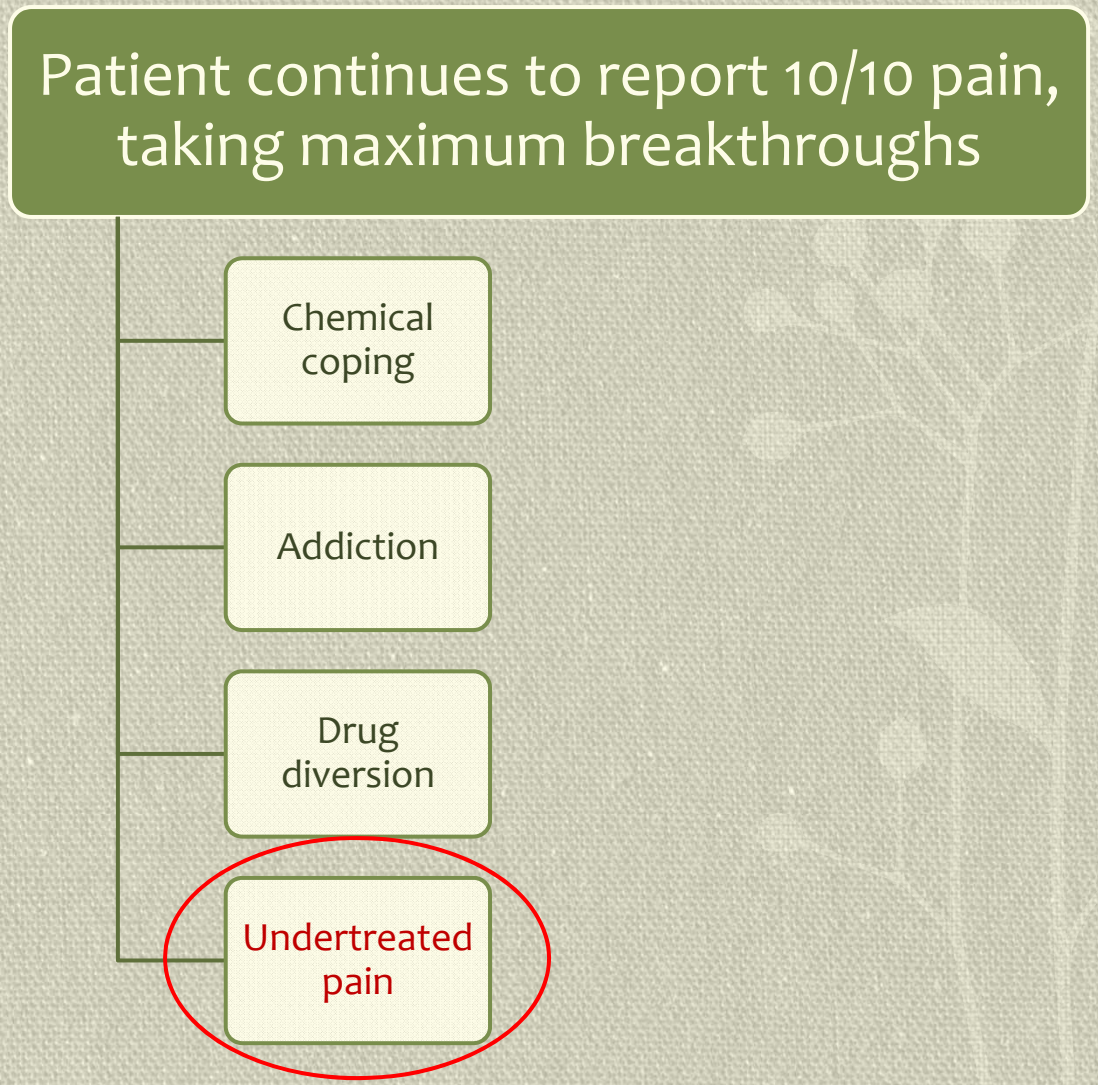
Duration of withdrawal:

- Few days with short-acting opioids but can last weeks with methadone

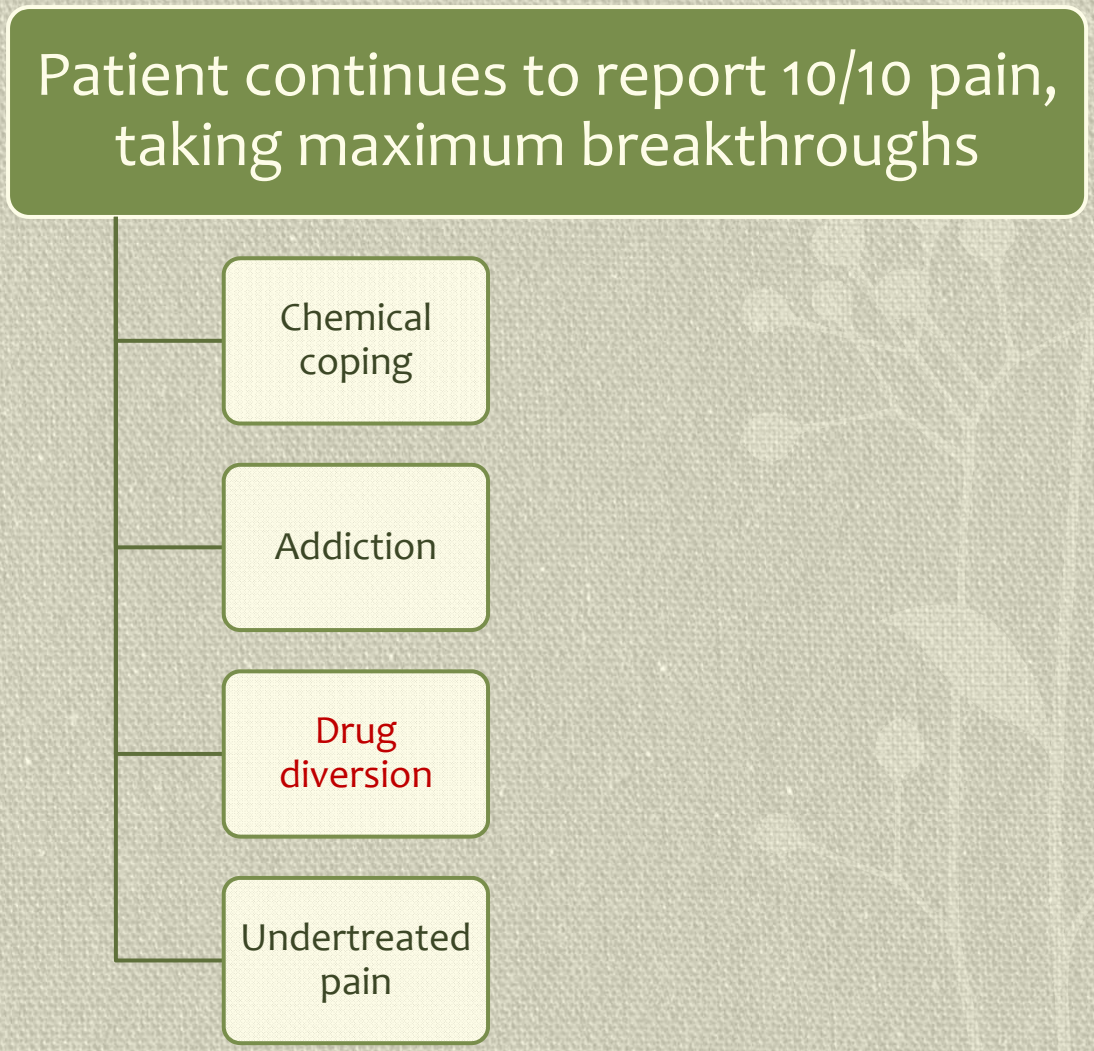
Opioid titration: scenario



Opioid titration: scenario



Opioid titration: scenario



Drug diversion

Prescription opioids can be more potent than illegal opioids (heroin)

Prescription opioids have government oversight and are manufactured with quality control by pharmaceutical companies → perceived as safer than illegal opioids

DEA: 6 million Americans abuse prescription drugs; 70% of them obtain the drug from friends and family (2011 Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health (NSDUH))

Disposal: many narcotics can be flushed down the toilet

- list at DEA website
- Other medication disposal instructions: DailyMed (http://dailymed.nlm.nih.gov)

Drug diversion: "street pharmacists"

Caveat: this information is gleaned from Google.

Drug	Price per mg ($)	Potential value for 30 tabs ($)
morphine	0.1 - 0.5	45 – 225 (15 mg tabs)
oxycodone	0.5 - 1	75 – 150 (5 mg tabs)
hydrocodone	0.3 - 1	45 – 150 (5/325 mg tabs)
hydromorphone	1 - 5	60 – 300 (2 mg tabs)
Fentanyl patch	30 – 50 (per patch)	300 – 500 (for 10 patches)

BOARD QUESTION

- A 45-year-old man with newly diagnosed prostate cancer develops left leg pain and is found to have a proximal femur bone metastasis. Prior to this he has never had significant problems with pain other than tension headaches, which he manages with intermittent use of ibuprofen. He has never used opioids. His oncologist tells him to take ibuprofen around-the-clock, and although his pain is improved, it remains quite bothersome. He then starts oxycodone 5 mg PO every 4 hours as needed for pain. His pain is well controlled with this regimen, but he becomes nauseous 30 to 60 minutes after each oxycodone dose. The patient is referred to the palliative care clinic, but the nausea persists after 2 weeks despite around-the-clock metoclopramide and trials of haloperidol and ondansetron. The patient has regular bowel movements.
- Which of the following should be considered next in the management of this patient?

  a. Add around-the-clock prochlorperazine.

  b. Discontinue oxycodone and manage pain with ibuprofen alone.

  c. Arrange for a trial of intrathecal opioids due to dose-limiting nausea.

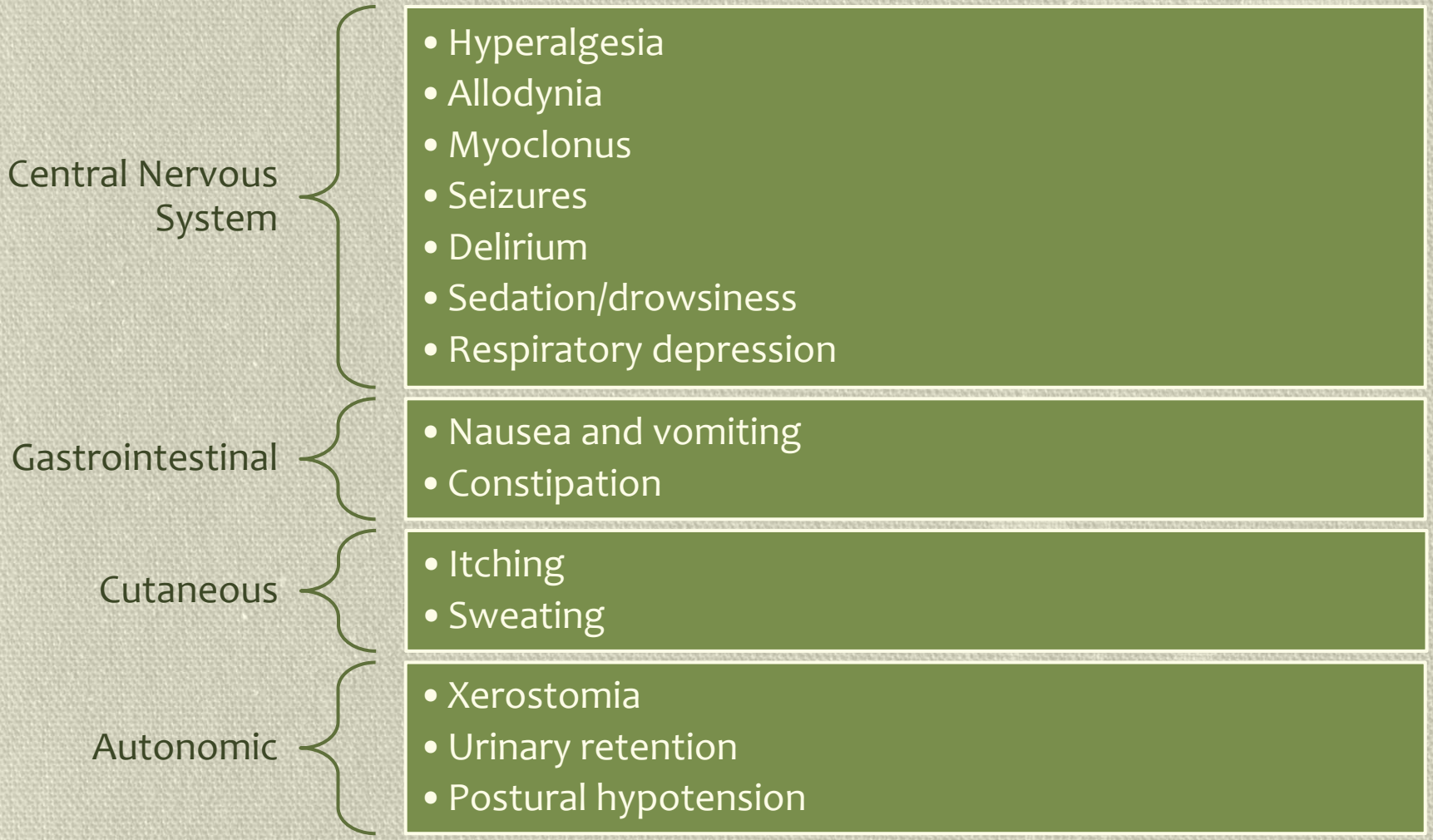
  d. Switch the patient to an equianalgesic dose of morphine.

  e. Initiate a trial of subcutaneous octreotide for refractory nausea.

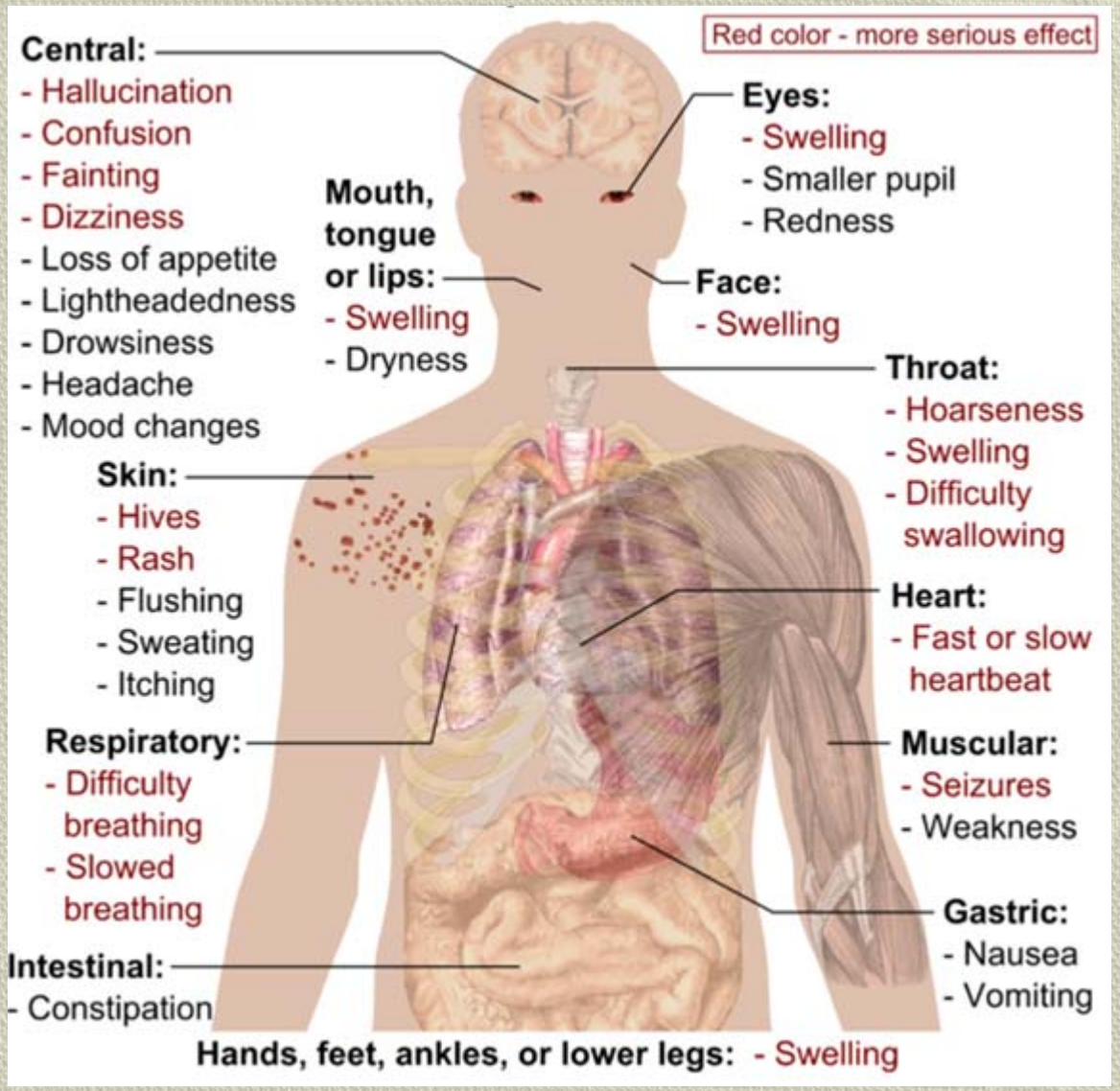
Changing therapy:

OPIOID ROTATION

Opioid adverse effects

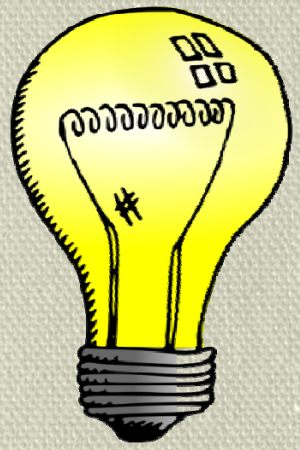


Opioid adverse effects



Use of naloxone: respiratory depression

Reverses respiratory depression, sedation, and ANALGESIA



Respiratory Rate < 8

OR

Respiratory insufficiency

Opioid rotation

When to rotate

- Opioid toxicity
  - Hyperalgesia/allodynia
  - Delirium due to opioids
  - Severe myoclonus/seizures due to opioids
- MEDD escalation above 300-500 (risk of hyperalgesia causing the escalation)
- High dosages burdensome (e.g. too many pills per breakthrough dose)

Incomplete cross-tolerance

- Opioids bind to different mu subtypes; tolerance to one opioid only confers partial tolerance to another opioid
- Must reduce MEDD by 30-50% when rotating opioids to prevent toxicity
  - Generally, reduce by 50%
  - Use 30% if pain uncontrolled at time of rotation

QUESTION

- An 82-year-old woman with moderate cognitive impairment was admitted 5 days ago for end-stage heart failure. The palliative medicine consult team met with the family and determined that the family wants to focus on making the patient comfortable. Accordingly, all her cardiac medications were stopped, including the diuretics, because she was no longer responding to the diuretic medications. The patient had been on long-acting morphine sulfate, 15 mg every 12 hours, as an outpatient. Because she is unable to swallow, she was started on a morphine drip at 1 mg/hour.
- Two days later, the primary team calls you (palliative care physician) for help with agitation. They report that she was initially very comfortable and pain free but then slowly became progressively agitated.

QUESTION, cont…

- At the bedside you notice that the patient is now confused, agitated, thrashing in her bed, and moaning, without a furrowed brow. Her respiratory rate varies from 10 to 14, her heart rate is 90, and her blood pressure is 98/70. She is receiving 2 L of oxygen per minute via nasal cannula. There is frequent twitching of her eyebrows and arms. Extremities reveal slowed capillary refill but no cyanosis or mottling. The morphine infusion is now at 4 mg/hour. The nurses confirm that she has had 20 cc of urine output in the last 24 hours. The patient's daughter is in the room and, clearly distressed, shares with you that this is not what her mother was ever like before. She asks you whether you can increase the morphine to better manage her mother's suffering.

BOARD QUESTION, cont…

What is the most appropriate next step in management?

a. Stop the morphine and administer midazolam.

b. Increase the morphine infusion to 6 mg/hour.

c. Stop the morphine infusion and start ketorolac administration.

d. Maintain the morphine drip and start a midazolam infusion after obtaining consent for palliative sedation.

e. Change the morphine infusion to a fentanyl infusion and add lorazepam.

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BOARD QUESTION CALCULATION

- On morphine drip 4mg/h

MEDD: 4mg/h IV x 24 hours in a day
=96 mg IV over one day

Conversion: morphine IV (mg) x 10 = fentanyl IV (mcg)

96 mg IV morphine x 10
= 960 mcg IV fentanyl over one day

Dose reduce!!! 50%

960 mcg IV fentanyl ÷ 2
=480 mcg IV fentanyl per day

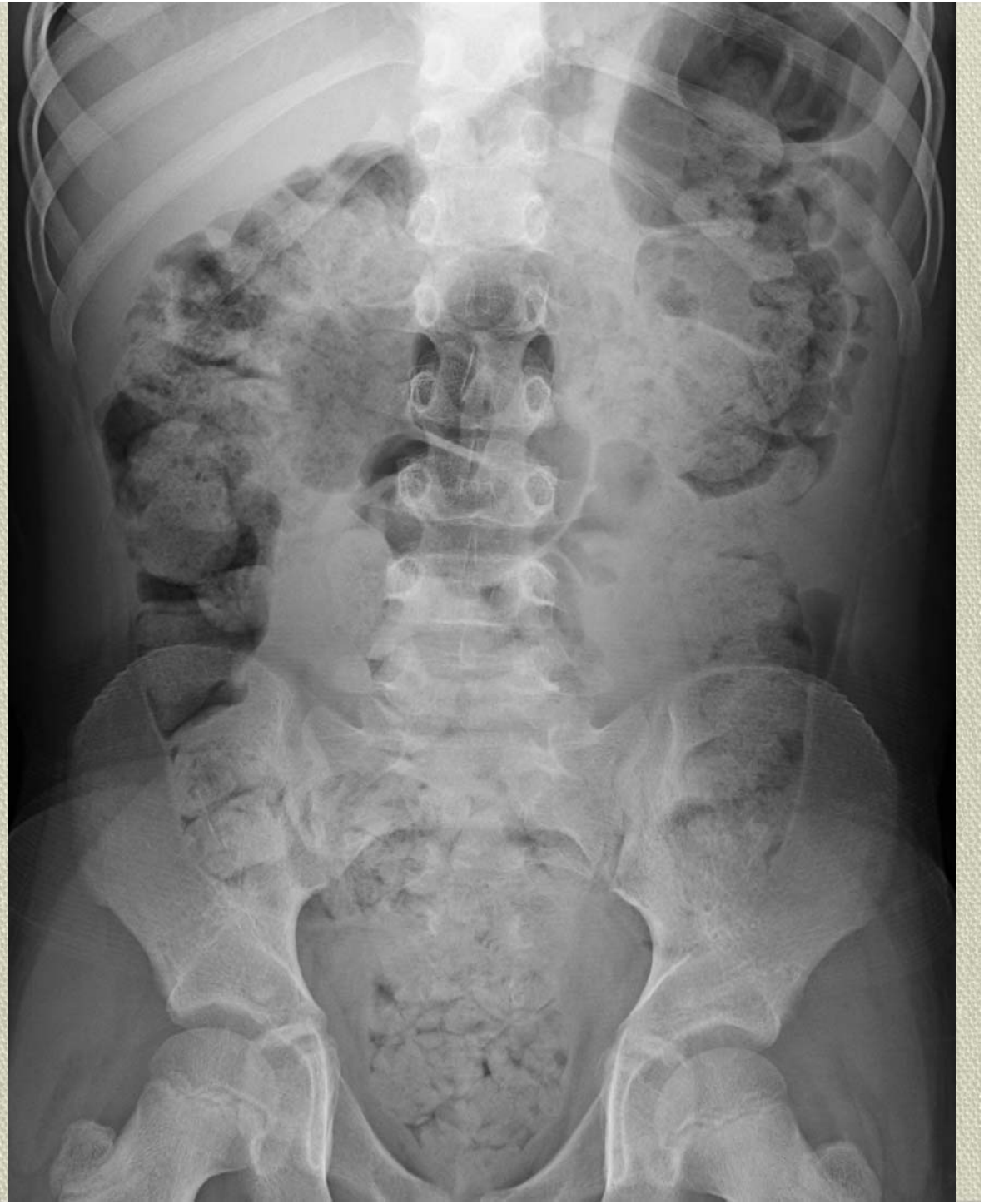
480 mcg IV fentanyl ÷ 24 hours
=20 mcg IV fentanyl/h

Breakthrough:
10-15% of "long-acting" dose

480 x 0.1 = 48 mcg IV fentanyl Q1h PRN

Prescribing opioids?

Rx: LAXATIVES



Xray by James Heilman, MD

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