Opioid Pharmacology and Dosing Management

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[1]These individuals were involved in the planning of the original 2017 content
[2] These individuals were involved in the 2021 review, update, and approved rerelease of this activity

Educational Objectives

At the conclusion of this activity participants should be able to:

- Describe opioid pharmacology, efficacy, and safety
- Explain how to start, continue, modify, and discontinue or taper opioid therapy

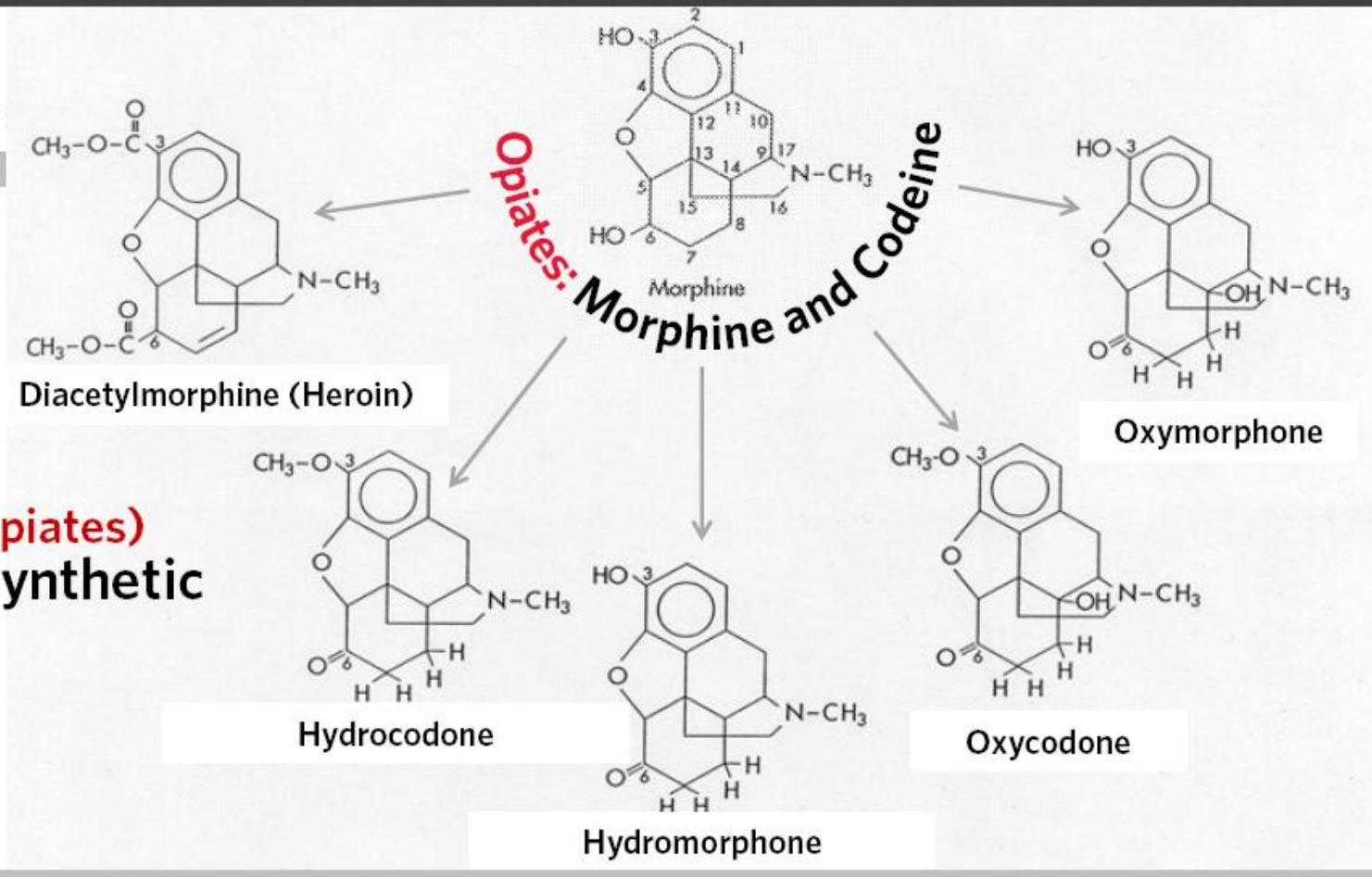
Case 1

- 52 yo man with chronic cervical radiculopathy, cervicalgia and HTN. He has been taking naproxen 500mg BID for 10 years since undergoing spinal surgery that was not effective.
- He does not have depression or history of substance use disorder.
- He has tried multiple medications including TCAs, gabapentin, pregabalin, lidocaine patches, acetaminophen, and duloxetine.
- He has tried steroid injections and botox with little improvement.
- He works full time and exercises 3 days a week. He stretches 5 times a week.
- He requests an opioid to help with pain that is not relieved by his NSAID. He is not currently taking an opioid.

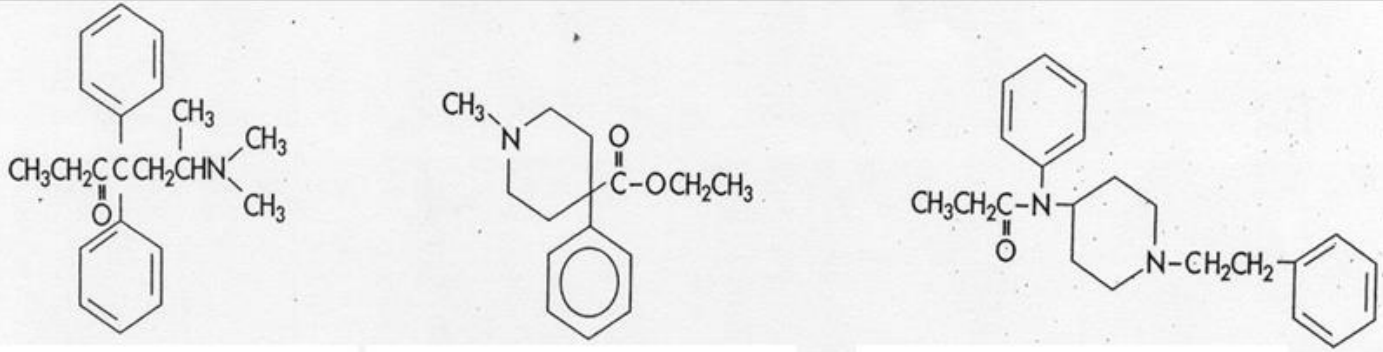
OPIOID PHARMACOLOGY

Opioids

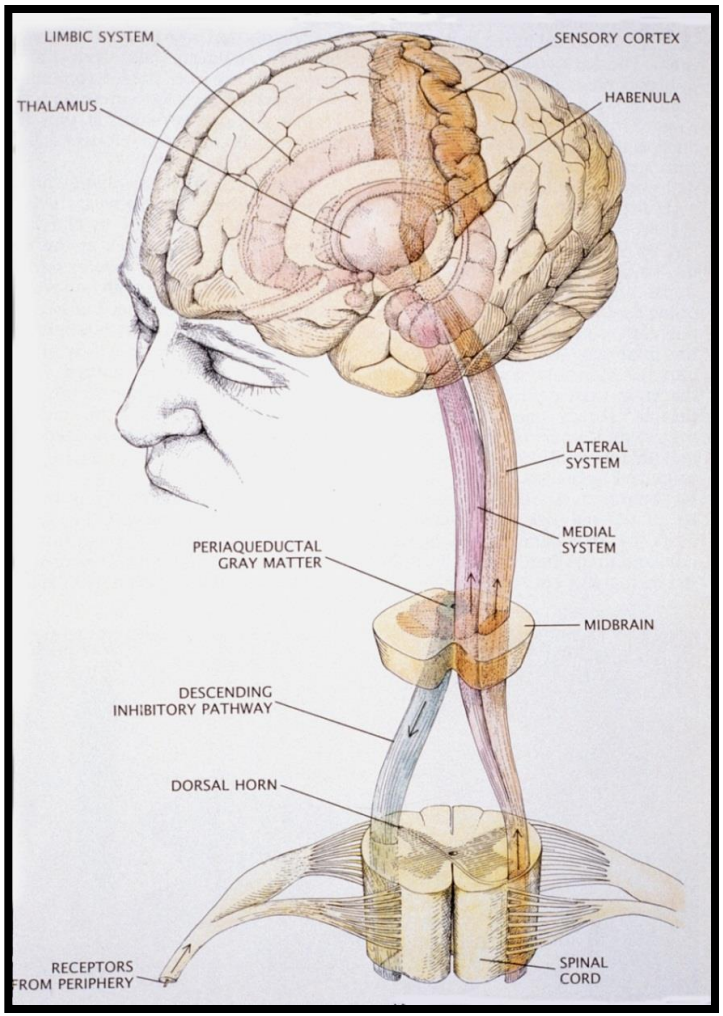
Natural (Opiates) and Semisynthetic



Synthetic



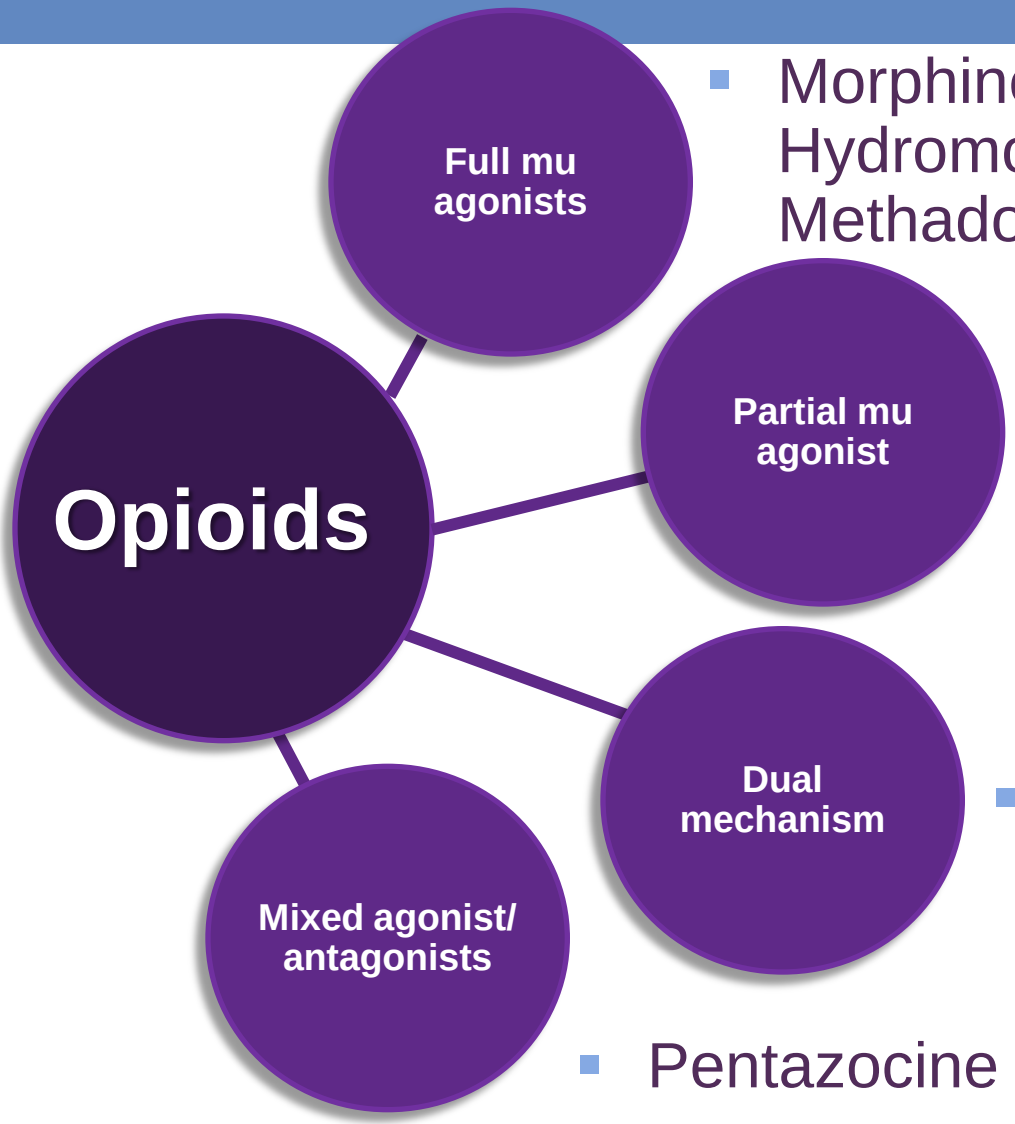
Activation of μ-Opioid Receptors



- Turn on descending inhibitory systems
- Prevent ascending transmission of pain signal
- Inhibit terminals of C-fibers in the spinal cord
- Inhibit activation of peripheral nociceptors
- **Activate opioid receptors in midbrain ("reward pathway")**

McCleane G, Smith HS. Med Clin N Am 2007

Opioid Choices with Examples



- Morphine, Oxycodone, Hydrocodone, Hydromorphone, Fentanyl, Methadone, Oxymorphone
- Buprenorphine
- Tramadol, Tapentadol
- Pentazocine

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Opioid Choice*

Immediate Release/ Short-acting (IR/SA)

- Morphine
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Tramadol
- Tapentadol

- Codeine

Extended Release/ Long-acting (ER/LA)

- Morphine
- Hydrocodone
- Hydromorphone
- Oxycodone
- Oxymorphone
- Tramadol
- Tapentadol

- Methadone
- Fentanyl transdermal
- Buprenorphine transdermal

*Product-specific information at:

- http://dailymed.nlm.nih.gov/dailymed;
- pharmacy medication guide;
- https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm

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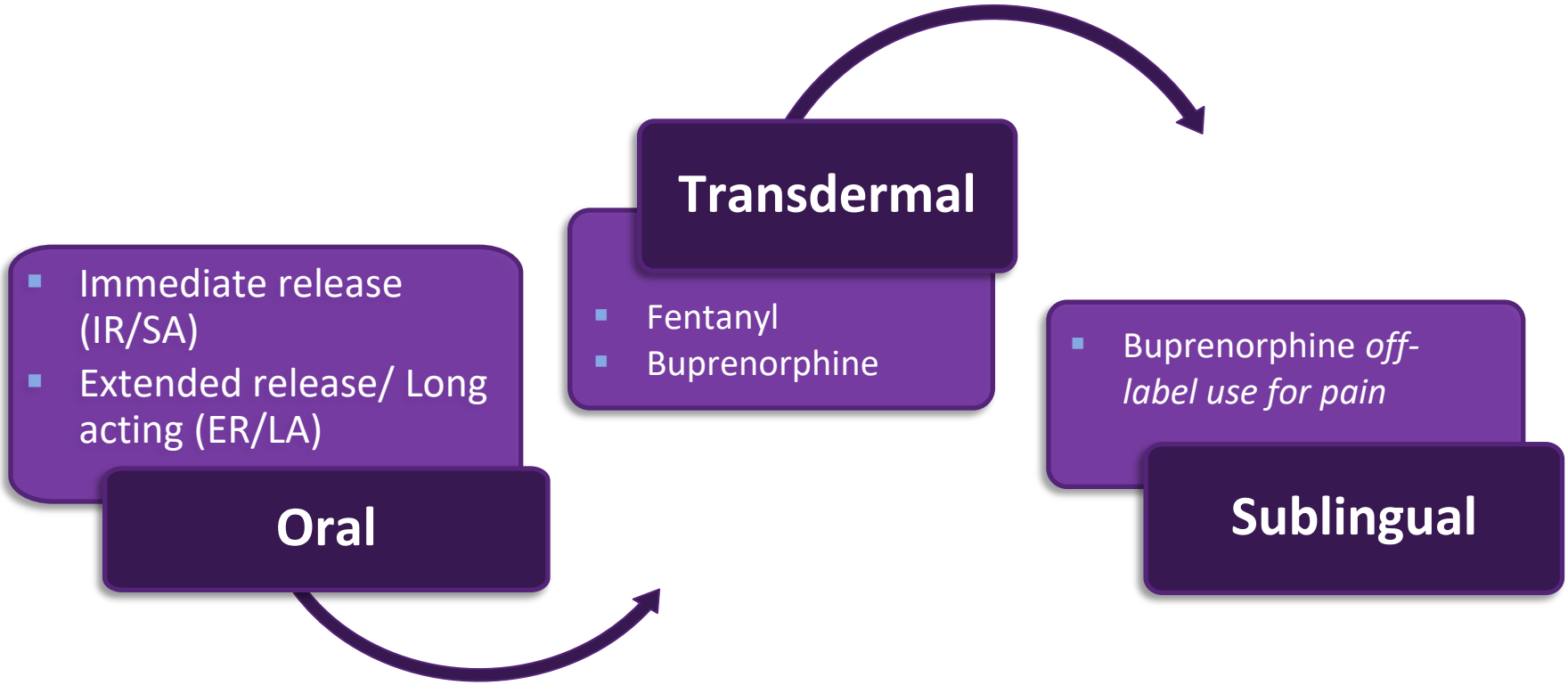
Opioid Formulations and Routes



Opioid Choice

- Duration and onset of action
  - Short-acting opioids increase risk of opioid-withdrawal mediated pain
- Patient's prior experience
  - μ-opioid receptor polymorphisms
  - Individual differences in pharmacokinetics & pharmacodynamics

Currently there are NO <u>proven</u> abuse resistant opioids or formulations

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Stanos SP et al. Mayo Clin Proc. 2012;87(7):683-694.

Opioid Choice

IR/SA Opioids
- No opioid tolerance/opioid naïve
- Intermittent or occasional pain
- Incident or breakthrough pain with ER/LA opioids

ER/LA Opioids
- Not for acute pain treatment
- Opioid tolerance exists
- Constant, severe, around-the-clock pain
- To stabilize pain relief when patient using multiple doses of IR/SA opioids
- MUST NOT be broken, chewed or crushed

Always start low and go slow

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IR/SA vs. ER/LA Uncertainties

- Insufficient evidence to determine whether ER/LA opioids are more effective or safer than IR/SA opioids
- Debate whether bolus dosing (IR/SA) or continuous exposure (ER/LA) is more likely to result in tolerance, hyperalgesia or addiction

Choose options that best meet patient needs

Individualize Treatment

Chou R, Clark E, Helfand M. *J Pain Symptom Manage*. 2003;26(5):1026-48.
Argoff CE, Silvershein DI. *Mayo Clin Proc*. 2009;84(7):602-12.

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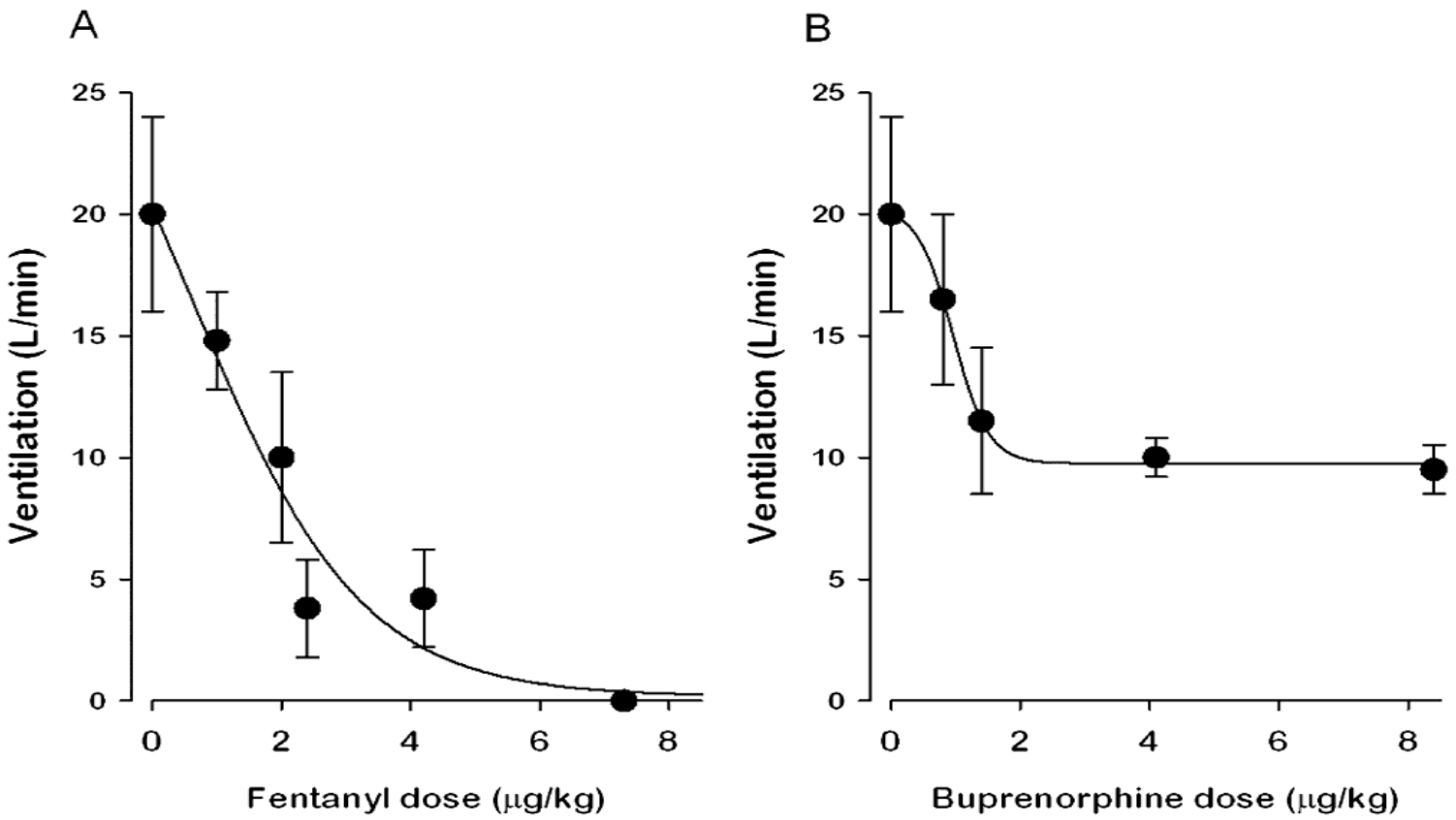
Opioid Pharmacology

- Ongoing exposure causes tolerance
  - Larger dose required to maintain original effects (analgesic and AE's)
  - Inter-individual variability in development of tolerance
  - "There appears to be no limit to the development of tolerance, and with appropriate dose adjustments, patients can continue to obtain pain relief."— Inturrisi C. Clin J Pain 2002;18:S3-13
  - **No theoretical dose ceiling**

Dose-response Relationship for Respiratory Depression



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Dahan A. Br J Anaesth 2005;94:825-34

SELECTED OPIOIDS WITH UNIQUE PROPERTIES

Transdermal Preparations

- Convenient dosing
- Slow peak onset (>24-72h)
- Delayed offset (serum t½ life >17-26h)
- Sustained release requires predictable blood flow and adequate subcutaneous fat
- Absorption increased with fever or broken skin
- Absorption decreased with edema
- Some with metal foil backing not compatible with MRI

Fentanyl

- Every 72 hours
- Dosages (mcg/hr): 12, 25, 37.5, 50, 62.5, 75, 87.5, 100

Buprenorphine

- Every 7 days
- Dosages (mcg/hr): 5, 7.5, 10, 15, 20 (max)
- Taper prior opioid to ≤30 MME before starting buprenorphine

Methadone is Different

The problem…

- Long, variable, unpredictable half-life
  - Analgesia 6-8 hours
  - Serum t½ 20-120 hours
- QTc prolongation, risk of torsades de pointes

Some possible advantages…

- NMDA receptor antagonist
  - Potentially less tolerance, better efficacy in neuropathic pain
- No active metabolites
- Inexpensive, small dosage units (5mg tablets)

Fredheim OM, et al. *Acta Anaesthesiol Scand*. 2008;52(7):879-89
Chou R et al. *J Pain*. 2014;15(4): 321-337

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Dual Mechanism Opioids

Tramadol

- Weak mu-opioid agonist and NE and serotonin reuptake inhibitor
- Seizure risk
- Physical dependence
- Not scheduled as controlled substance BUT has addiction potential
- Has a maximum therapeutic dose of 400mg per day

Tapentadol

- Stronger mu-opioid agonist and NE reuptake inhibitor
- Seizure risk
- Physical dependence
- Schedule II controlled substance with addiction potential

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Medical Letter April 2010

Opioid Safety and Risks

Allergies: Rare

Immunosuppression

- Animal models, opioid induced immuno-suppression
- Humans increased risk invasive pneumococcal disease[1], community acquired pneumonia[2]

Organ Toxicities

- Suppression of hypothalamic-pituitary-gonadal axis
- >50 MME associated with 2 fold increase fracture risk[3]

Adverse Effects

- Nausea, sedation, constipation, urinary retention, sweating
- Pruritus (histamine release)
- **Respiratory depression**

Report AE to FDA
1-800-FDA-1088
www.fda.gov

Benyamin R, et al. *Pain Phys*. 2008

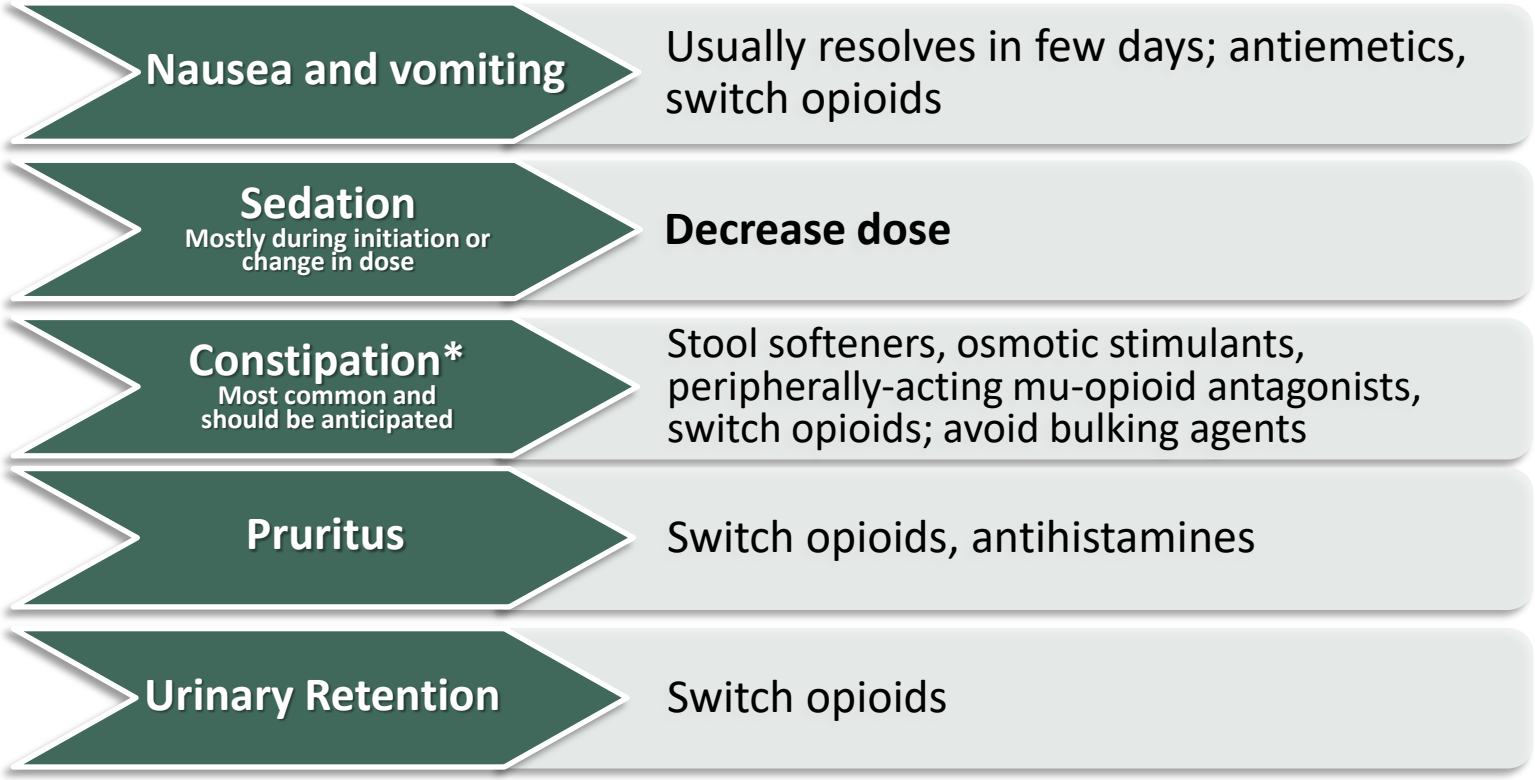
1. Wiese AD, et al. *Ann Intern Med.* 2018
2. Edelman EJ, et al. *JAMA Intern Med.* 2019
3. Saunders KW, et al. *J Gen Intern Med*. 2010

Respiratory Depression

- Depression of the medullary respiratory center
- Decreased tidal volume and minute ventilation
- Right-shifted CO_2 response
- Hypercapnea, hypoxia and decreased oxygen saturation
- Immediately life threatening
- Sedation occurs before significant respiratory depression and therefore is a warning sign

Dahan A, et al. *Anesthesiology*. 2010;112(1):226-38.

Managing Opioid Adverse Effects



Benyamin R, et al. *Pain Physician*. 2008

*Hanson B et al. *Gastroenterology.* 2019

Medication-related Risk Factors

Medication Factors	Risk	
Daily dose >100 MME	Overdose	Addiction
Long-term opioid use (>3 months)	Overdose	Addiction
ER/LA opioid formulation	Overdose	
Initial 2 weeks after starting ER/LA opioid	Overdose	
Combination opioids and benzodiazepines	Overdose	

CDC Recommendation 11:

Avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

Dowell D, et al. *MMWR.* 2016.

Volkow ND, et al. *N Engl J Med.* 2016

Patient-related Risk Factors

Patient Factors	Risk	
Mental health disorder (e.g. depression, anxiety)	Overdose	Addiction
Substance use disorder (e.g., alcohol, tobacco, illicit and prescription drug)	Overdose	Addiction
Family history of substance use disorder		Misuse
Adolescent		Addiction
Age >65	Overdose	
Sleep-disordered breathing	Overdose	
Legal history (e.g., DUI, incarceration)		Misuse
History of sexual abuse		Misuse
History of overdose	Overdose	

Akbik H, et al. *J Pain Symptom Manage*. 2006
Ives J, et al. *BMC Health Serv Res*. 2006
Liebschutz JM, et al. *J Pain*. 2010
Michna E, et al. *J Pain Symptom Manage*. 2004
Reid MC, et al. *J Gen Intern Med*. 2002
Volkow ND, et al. *N Engl J Med.* 2016

High Dose Opioids

>90*mg morphine equivalents

Considered higher dose opioid therapy by different authors[1,2,3]

Higher doses indicated in some patients

- Manage as higher risk
- Increase monitoring and support

Higher doses more likely associated with:

- Tolerance[4]
- Hyperalgesia[5,6]
- Reduced function[7,8]
- Overdose[9-13]

*Sample morphine equivalents:

90mg morphine = **60mg oxycodone**, **22mg hydromorphone**, **90mg hydrocodone**

1. Chou R, et al. *J Pain*. 2009;10(2):147-59.
2. Ballantyne JC, Mao J. *N Engl J Med*. 2003;349(20):1943-53.
3. Kobus AM, et al. *J Pain*. 2012;13(11):1131-8.
4. Huxtable CA, et al. *Anaesth Intensive Care*. 2011;39(5):804-23.
5. Brush DE. *J Med Toxicol*. 2012;8(4):387-92.
6. Lee M, et al. *Pain Physician*. 2011;14(2):145-61.
7. Braden JB. *Arch Intern Med*. 2010;170(16):1425-32.
8. Bohnert AS, et al. *JAMA*. 2011;305(13):1315-21.
9. Gomes T, et al. *Open Med*. 2011;5(1):e13-22.
10. Paulozzi LJ. *Pain Med*. 2012;13(1):87-95.

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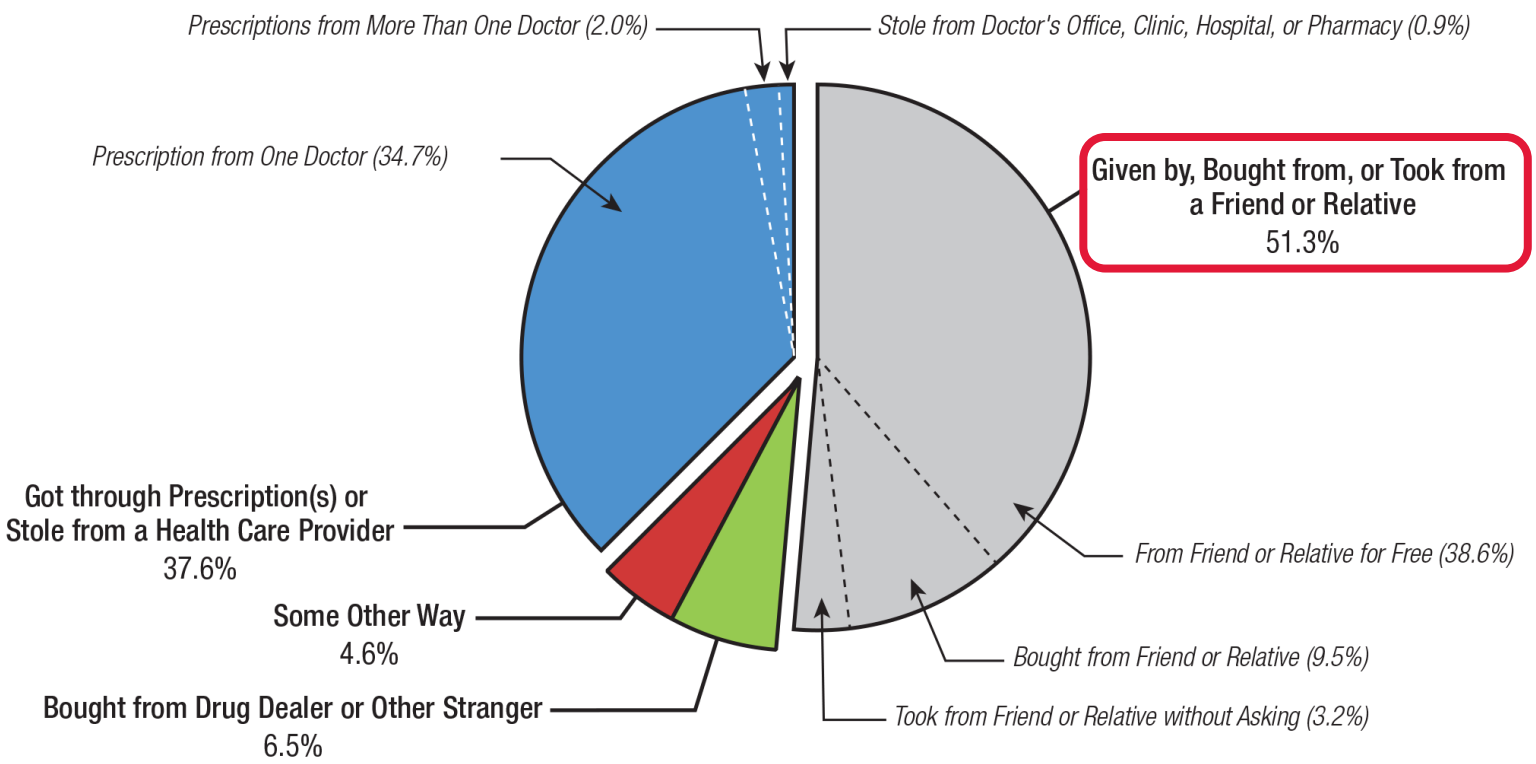
Source of Prescription Opioids Misused



SAMHSA 2019. *Results from the 2018 National Survey on Drug Use and Health*

Collateral Opioid Risk

- **Risks**
  - Young children's ingestion and overdose
  - Adolescent experimentation leading to overdose and addiction

- **Mitigating risk**
  - Safe storage and disposal (i.e., lock box)
  - Educate family members
  - Have poison control number handy
  - Naloxone distribution (if available)*

* Beletsky L, Rich JD, Walley AY. *JAMA* 2012; 308(18):1863-4
•SAMHSA Overdose Toolkit (http://store.samhsa.gov/shin/content/SMA13-4742/Toolkit_Patients.pdf)
•www.prescribetoprevent.org

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INITIATION OF OPIOIDS

General Principles

- Initial course of treatment should be viewed as a short-term (<60 days), therapeutic trial
- Start low and titrate cautiously
- Avoid doses >90 mg morphine equivalent dose (MED)
- Opioid selection and initial dosing should be individualized based on
  - Patient's health status (age, comorbid conditions)
  - Previous exposure to opioids (i.e. opioid tolerance)
- Do not start ER/LA formulations in opioid naïve patients

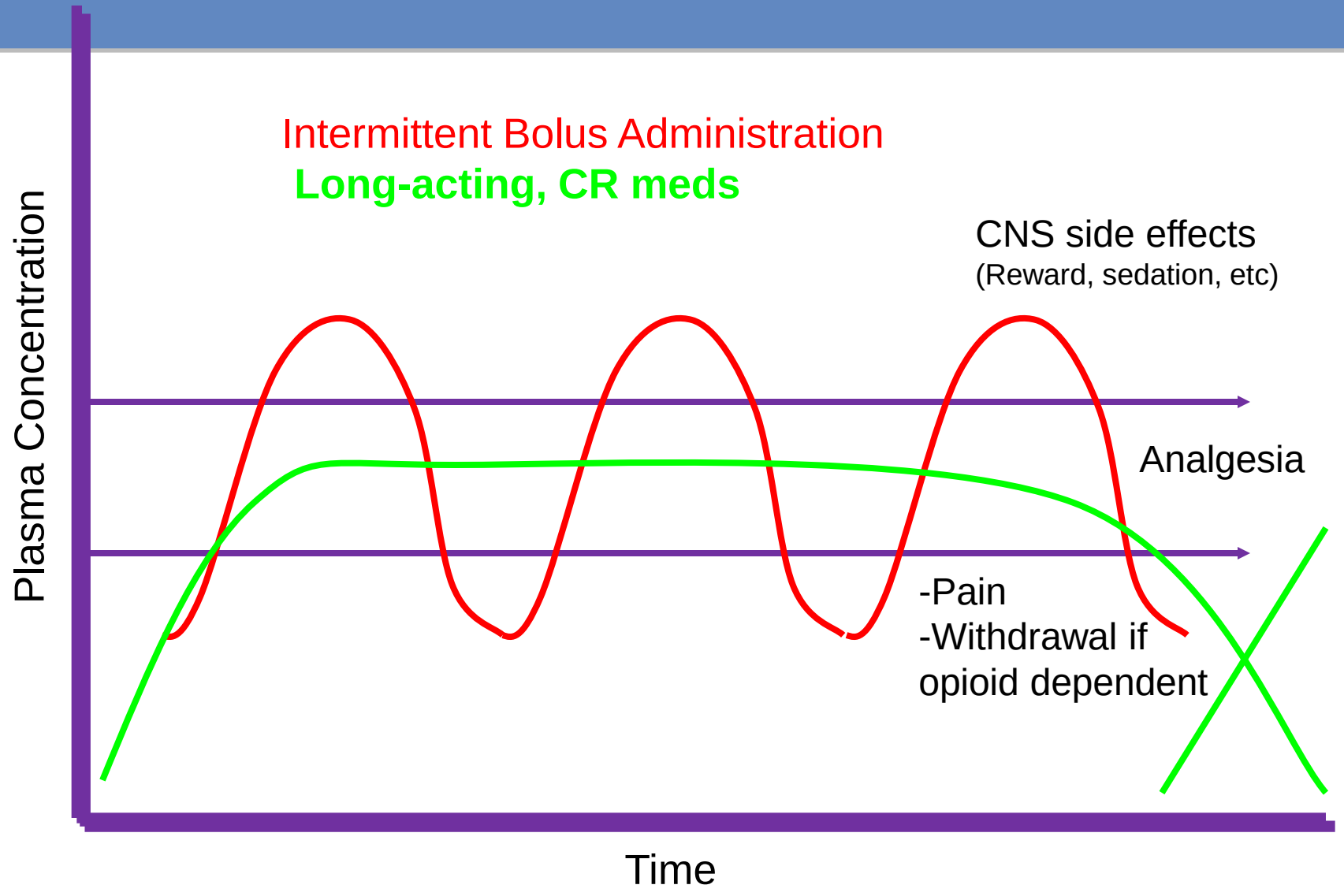
General Principles, continued

- Immediate release opioids provide pain relief between 3-6 hours
- ER/LA opioids provide analgesia between 6-24 hours depending on the formulation

General Criteria for Opioid Tolerance

- Based on daily use for more than 7 days
  - 60mg oral morphine per day
  - 30mg oral oxycodone per day
  - 25mcg transdermal fentanyl per 72 hours
  - 8mg oral hydromorphone per day
  - 25mg oral oxymorphone per day

Opioid Characteristics
Schedules of Administration



Initiation of Opioids: IR Formulation Key Principles

Immediate Release Opioid	Typical Starting Dose*	Considerations
Codeine (oral)	30mg every 4-6 hours	-Typically a combination product -Low potency opioid -Avoid concurrent use of OTC products
Hydrocodone/acetaminophen (oral)	5mg of hydrocodone every 4-6 hours	-Efficacy >40mg in question -Moderate potency opioid -Avoid concurrent use of OTC products
Hydromorphone (oral)	2mg every 4-6 hours	-High potency opioid -Should not be your first choice in IR opioids
Morphine IR (oral)	10mg every 4-6 hours	-Moderate potency opioid -Do not use in patient with CKD stage 4-5
Oxycodone (oral)	5mg every 4-6 hours	-Moderate potency opioid
Oxymorphone (oral)	5mg every 4-6 hours	-High potency opioid
Tapentadol	50mg every 12 hours	-Low potency opioid -Avoid concomitant serotonin products
Tramadol	25mg oral once daily	-Poor efficacy at doses >400mg -Low potency opioid -Avoid concomitant serotonin products

**May be lower in patients with renal failure, hepatic failure, or age >65*

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Initiation of ER/LA Opioids: Key Principles
**not for initiation in opioid naïve patients*

ER/LA Opioid	Typical Starting Dose*	Considerations
Buprenorphine (Transdermal)	5mcg/hr patch every 7 days	-Should be off of other opioids for at least 5-7 days and not taking >30mg MED
Fentanyl (Transdermal)	12mcg/hr patch every 72 hours	-High potency opioid -Use only in opioid-tolerant patients taking >60mg MED for a week or longer
Hydrocodone ER	10mg every 12 hours	
Hydromorphone ER		
Methadone	2.5mg TID	See next slide
Morphine ER/LA	15mg every 12 hours	-Moderate potency opioid
Oxycodone ER/LA (oral)	10mg every 12 hours	-Moderate potency opioid
Oxymorphone ER/LA (oral)	10mg every 12 hours	-High potency opioid
Tapendatol ER	50mg every 12 hours	-Avoid concomitant serotonin products
Tramadol ER	100mg once daily	-Poor efficacy at doses >400mg -Low potency opioid -Avoid concomitant serotonin products

**May be lower in patients with renal failure, hepatic failure, or age >65*

Initiation of Methadone

- Start at low doses, individualized based on prior opioid exposure. Obtain baseline ECG due to QTc prolongation risk.
  - Chronic pain in opioid-naïve adults

    (or <40-60mg MED)
    - starting dose 2.5mg TID
    - Dose increases no more than 5mg/day every 5-7 days
  - Should not be started for opioid use disorder outside of an opioid treatment program

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Chou, et al. J Pain, 2014

Resources on Specific Opioids

Providers

e.g., dosing, specific product risks, limitations for use in patients with gastrointestinal problems such as inability to swallow, feeding tubes or malabsorption issues

- **dailymed.nlm.nih.gov/dailymed**
- **https://www.accessdata.fda.gov/scripts/cder/daf/**
- **Package inserts on ER/LA website**
- **Adverse events to be reported to FDA https://www.fda.gov/Drugs/InformationOnDrugs/ucm135151.htm**

Patients

e.g., side effects, drug-drug interactions including CNS depressants, safe disposal

- **Materials: er-la-opioidrems.com/IwgUI/rems/products.action**
- **Medication guide given at the pharmacy**

Calculating Morphine Equivalent Dose
DO NOT USE FOR OPIOID ROTATION

TABLE 2. Morphine milligram equivalent (MME) doses for commonly prescribed opioids

Opioid	Conversion factor*
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	
1–20 mg/day	4
21–40 mg/day	8
41–60 mg/day	10
≥61–80 mg/day	12
Morphine	1
Oxycodone	1.5
Oxymorphone	3
Tapentadol†	0.4

Source: Adapted from Von Korff M, Saunders K, Ray GT, et al. Clin J Pain 2008;24:521–7 and Washington State Interagency Guideline on Prescribing Opioids for Pain (http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf).

CDC Mobile App:
https://www.cdc.gov/drugoverdose/prescribing/app.html

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Calculating Morphine Equivalent Dose

- Fentanyl 25mcg/hr patch
  - 25 x 2.4 conversion factor (CF) = **60mg MED**
- Hydromorphone 2mg every 4 hours + Oxycodone 60mg BID
  - 2mg x 6 = 12mg x 4 CF = 48mg MED
  - 60mg x 2 = 120mg x 1.5 CF = 180mg MED
  - **TOTAL 228mg MED**
- Methadone 20mg TID
  - 20mg x 3 = 60mg x 10.0* CF = **600mg MED**

CDC Mobile App:
https://www.cdc.gov/drugoverdose/prescribing/app.html

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www.agencymedicaldirectors.wa.gov/Files/DosingCalc.xls

Overdose Risk Increases with Dose

	VA patients (fatal overdose)	HMO patients (any overdose)
Dose (mg/day)	Hazard ratio (95% CI)	
<20	1.0	1.0
20-49	1.9 (1.3, 2.7)	1.4 (0.6, 3.6)
50-99	4.6 (3.2, 6.7)	3.7 (1.5, 9.5)
≥ 100	7.2 (4.9, 10.7)	8.9 (4.0, 19.7)

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Dunn KM et al, Ann Intern Med 2010;152:85-92; Bohnert AS et al, JAMA 2011;305:1315-21

Case 1

- Patient has constant pain, but he self-manages
- He is not opioid tolerant
- He is asking for an opioid for activity PRN
- Best initial choice = IR formulation of tramadol, oxycodone, or hydrocodone dosed once-twice daily PRN activity
- Prescribe #28 per month to determine his response to treatment and opioid usage

Case 1

- If his pain were to progress and he started to need IR formulations of opioids around the clock, when would you transition to ER/LA formulation?
  - When he is having worsening pain on a consistent basis when the opioid dose wears off
  - When he develops opioid tolerance
  - If his pain progresses

Case 1

- You decide to switch him from IR oxycodone 10mg every 6 hours PRN to ER/LA oxycodone 20mg BID
- He will utilize self-management techniques for break through pain

OPIOID ROTATION

***If you are not experienced in switching opioids in patients on long-term opioid therapy, seek expert consultation.**

Opioid Rotation

Definition and Purpose

- Defined *switching from one opioid to another to improve therapeutic outcome and/or to avoid adverse events due to the current drug*
- Theory
  - Variations in activity at mu opioid receptors may lead to improved benefit vs development of AE

Considerations

- Patient wishes/therapy adherence
- Cost/insurance concerns
- Titration leading to AE/poor analgesia
- Drug-drug interactions

Fine PG, et al. *J Pain Symptom Manage*. 2009;38:418-25.
Knotkova H, et al. *J Pain Symptom Manage.* 2009;38:426-39.
Pasternak GW. *Neuropharmacol*. 2004;47(suppl 1):312-23.

Consider Opioid Rotation

- Switch to another opioid to:
  - Restore analgesic efficacy
  - Limit adverse effects
  - Decreasing overall MME
- Based on large intra-individual variation in response to different opioids
- Different variants of mu-opioid receptors
- Based on surveys and anecdotal evidence
- Promising but needs validation

Inturrisi CE. *Clin J Pain*. 2002
Fine PG , Portenoy RK. *J Pain Symptom Manage*. 2009
Smith HS, Peppin JF. *J Pain Res*. 2014

Opioid Conversion Tables

- Derived from relative potency ratios using single-dose analgesic studies in opioid-naïve patients
- Based on limited doses or range of doses
- Does not reflect clinical realities of chronic opioid administration
- Are not reliable due to individual pharmacogenetic differences
- Most tables do NOT adjust for incomplete cross-tolerance

Treillet E, et al. *J Pain Res.* 2018
Webster LR, Fine PG. *Pain Med*. 2012
Pereira J, et al. *J Pain Symptom Manage*. 2001

Variable Response to Opioids

Mu-opioid Receptor

- >100 polymorphisms in the human MOR gene
- Mu-opioid receptor subtypes

Opioid Pharmacokinetics

- Opioid metabolism differs by individual opioid and by individual patient

Not all patients respond to the same opioid in the same way

Trial of several opioids may be needed to find acceptable balance between analgesia and tolerability

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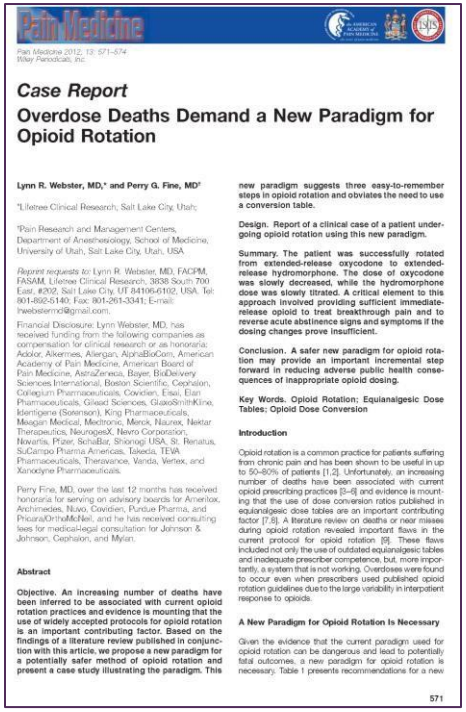
Smith HS. *Pain Physician*. 2008;11(2):237-48.

WARNING!

Equianalgesic ≠ **Conversion** Tables



Pain Medicine

Pain Medicine 2012; 13: 571–574
Wiley Periodicals, Inc.

Case Report

Overdose Deaths Demand a New Paradigm for Opioid Rotation

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Perry Fine, MD, over the last 12 months has received honoraria for serving on advisory boards for Ameritox, Archimedes, Nuvo, Covidien, Purdue Pharma, and Pricara/OrthoMcNeil, and he has received consulting fees for medical-legal consultation for Johnson & Johnson, Cephalon, and Mylan.

Abstract

Objective. An increasing number of deaths have been inferred to be associated with current opioid rotation practices and evidence is mounting that the use of widely accepted protocols for opioid rotation is an important contributing factor. Based on the findings of a literature review published in conjunction with this article, we propose a new paradigm for a potentially safer method of opioid rotation and present a case study illustrating the paradigm. This new paradigm suggests three easy-to-remember steps in opioid rotation and obviates the need to use a conversion table.

Design. Report of a clinical case of a patient undergoing opioid rotation using this new paradigm.

Summary. The patient was successfully rotated from extended-release oxycodone to extended-release hydromorphone. The dose of oxycodone was slowly decreased, while the hydromorphone dose was slowly titrated. A critical element to this approach involved providing sufficient immediate-release opioid to treat breakthrough pain and to reverse acute abstinence signs and symptoms if the dosing changes prove insufficient.

Conclusion. A safer new paradigm for opioid rotation may provide an important incremental step forward in reducing adverse public health consequences of inappropriate opioid dosing.

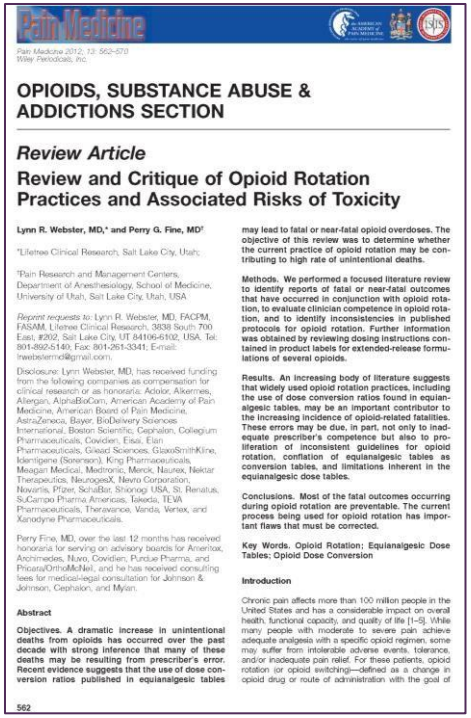
Key Words. Opioid Rotation; Equianalgesic Dose Tables; Opioid Dose Conversion

Introduction

Opioid rotation is a common practice for patients suffering from chronic pain and has been shown to be useful in up to 50–80% of patients [1,2]. Unfortunately, an increasing number of deaths have been associated with current opioid prescribing practices [3–6] and evidence is mounting that the use of dose conversion ratios published in equianalgesic dose tables are an important contributing factor [7,8]. A literature review on deaths or near misses during opioid rotation revealed important flaws in the current protocol for opioid rotation [9]. These flaws included not only the use of outdated equianalgesic tables and inadequate prescriber competence, but, more importantly, a system that is not working. Overdoses were found to occur even when prescribers used published opioid rotation guidelines due to the large variability in interpatient response to opioids.

A New Paradigm for Opioid Rotation Is Necessary

Given the evidence that the current paradigm used for opioid rotation can be dangerous and lead to potentially fatal outcomes, a new paradigm for opioid rotation is necessary. Table 1 presents recommendations for a new



Pain Medicine

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OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Review Article

Review and Critique of Opioid Rotation Practices and Associated Risks of Toxicity

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Abstract

Objectives. A dramatic increase in unintentional deaths from opioids has occurred over the past decade with strong inference that many of these deaths may be resulting from prescriber's error. Recent evidence suggests that the use of dose conversion ratios published in equianalgesic tables may lead to fatal or near-fatal opioid overdoses. The objective of this review was to determine whether the current practice of opioid rotation may be contributing to high rate of unintentional deaths.

Methods. We performed a focused literature review to identify reports of fatal or near-fatal outcomes that have occurred in conjunction with opioid rotation, to evaluate clinician competence in opioid rotation, and to identify inconsistencies in published protocols for opioid rotation. Further information was obtained by reviewing dosing instructions contained in product labels for extended-release formulations of several opioids.

Results. An increasing body of literature suggests that widely used opioid rotation practices, including the use of dose conversion ratios found in equianalgesic tables, may be an important contributor to the increasing incidence of opioid-related fatalities. These errors may be due, in part, not only to inadequate prescriber's competence but also to proliferation of inconsistent guidelines for opioid rotation, conflation of equianalgesic tables as conversion tables, and limitations inherent in the equianalgesic dose tables.

Conclusions. Most of the fatal outcomes occurring during opioid rotation are preventable. The current process being used for opioid rotation has important flaws that must be corrected.

Key Words. Opioid Rotation; Equianalgesic Dose Tables; Opioid Dose Conversion

Introduction

Chronic pain affects more than 100 million people in the United States and has a considerable impact on overall health, functional capacity, and quality of life [1–5]. While many people with moderate to severe pain achieve adequate analgesia with a specific opioid regimen, some may suffer from intolerable adverse events, tolerance, and/or inadequate pain relief. For these patients, opioid rotation (or opioid switching)—defined as a change in opioid drug or route of administration with the goal of

- Equianalgesic tables provide insufficient guidance to determine the equivalent doses of different opioids
  - Individual consideration is necessary for every patient

Webster LR. *Pain Med*. 2013;14:959-61. Knotkova H, et al. *J Pain Symptom Manage*. 2009; 38:426-39. Webster LR, Fine PG. *Pain Med*. 2012;13:562-70. Webster LR, Fine PG. *Pain Med*. 2012;13:571-4.

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Opioid Rotation

- Seek expert advice if you are not experienced switching opioids in patients prescribed long-term opioid therapy.
- Calculate current Morphine Equivalents per day using an opioid conversion calculator
  - One example here
- For all opioids other than fentanyl or methadone, apply an “automatic dose reduction window” of 25-50% lower than the calculated equianalgesic dose
- Stop previous opioid and start new opioid (do not overlap doses)
- Reassess the patient frequently

Fine PG , Portenoy RK. *J Pain Symptom Manage*. 2009;38(3):418-25.
Smith HS. *Pain Physician*. 2008;11(2):237-48.

Methadone Rotation

- Opioid rotation from <40-60mg MED
  - Start methadone at 2.5mg TID
  - Initial dose increases no more than 5 mg/day every 5-7 days

Chou R, et al. (2014) J Pain;15(4):321-37

Methadone Rotation

- Opioid rotation from >60mg MED
  - Start methadone at a dose 75-90% less than the calculated equianalgesic dose, but no higher than 30-40mg/day
  - Initial dose increases no more than 5-10mg/day every 5-7 days
  - Much lower doses are prescribed when switching to methadone due to incomplete cross tolerance and the long half-life of methadone

Chou R, et al. (2014) J Pain;15(4):321-37

Case 1: Rotation Option 1

- After 1 year, the patient's analgesic response to oxycodone ER 20mg BID wanes
- You decide to switch him to Morphine ER 15mg BID – a dose that is corrected by 50% for incomplete tolerance
  - https://www.cdc.gov/drugoverdose/prescribing/app.htm
- Patient Instructions:
  - Stop Oxycodone ER 20mg BID and wait 12 hours
  - Start Morphine ER 15mg BID

DISCONTINUING OR TAPERING OPIOIDS

Step 1: Evaluate Risks and Benefits, Establish an Indication for Opioid Tapering

- Substance Use Disorder
  - including opioids, alcohol, etc.
- Diversion
- At risk for immediate harms
  - Aspiration, hypoxia, bowel obstruction, overdose, etc.
  - Refusing monitoring (urine drug testing, abstain from marijuana or alcohol, etc.)
- Therapeutic Failure of opioids
- At risk for future harms (>90 MED, benzos)
  - High dose chronic use without misuse
  - Concomitant benzos

Use a Risk-Benefit Framework

NOT…

- Is the patient good or bad?
- Does the patient deserve opioids?
- Should this patient be punished or rewarded?
- Should I trust the patient?

RATHER…

Do the benefits of opioid treatment outweigh the untoward effects and risks for this patient (or society)?

Nicolaidis C. Pain Med. 2011 Jun;12(6):890-7.

Discontinuing Opioids

- Do not have to prove addiction or diversion - only assess and reassess the risk-benefit ratio
- If patient is unable to take opioids safely or is nonadherent with monitoring then discontinuing opioids is appropriate even in setting of benefits
- Need to determine how urgent the discontinuation should be based on the severity of the risks and harms
- Document rationale for discontinuing opioids
- Determine if the opioid needs to be tapered due to physical dependence

You are abandoning the opioid therapy NOT the patient

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Step 2: Taper Plan and Start Taper

- Discuss goals of taper —how and when will we know if it is successful?
  - Establish dose target and timeframe
  - Maintain current level of analgesia *(may not be possible in short term)*

- Discuss potential withdrawal symptoms
  - Temporary increase in pain
  - Discuss how to contact
  - Schedule follow-up or nurse check ins

- Identify at least one self-management goal

How to Approach an Opioid Taper/Cessation

Indication	Recommended Length of Taper	Intervention/Setting
Substance Use Disorder	Recommend immediate referral and initiation of treatment	**Intervention**: *Transition* to medication assisted treatment (buprenorphine or methadone) maintenance therapy, Naloxone rescue kit **Setting**: Inpatient or Outpatient Buprenorphine (OBOT) or methadone
Diversion	No taper*	Determine need based on actual use of opioids, if any
At risk for immediate severe harms	Weeks to months	**Intervention**: Supportive care Naloxone rescue kit **Setting**: Outpatient opioid taper
Therapeutic failure	Months	**Intervention**: Supportive care Naloxone rescue kit **Setting**: Outpatient opioid taper **Option**: Buprenorphine (OBOT)
At risk for smaller harms	Months to Years	**Intervention**: Supportive care Naloxone rescue kit **Setting**: Outpatient opioid taper **Option**: Buprenorphine (OBOT)


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Instructions for use found inside on device
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You can save a life!
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Shout their name
2 Call 911 if unresponsive
3 Naloxone
Inject 1 ampule (1cc) of Naloxone
Leg muscle
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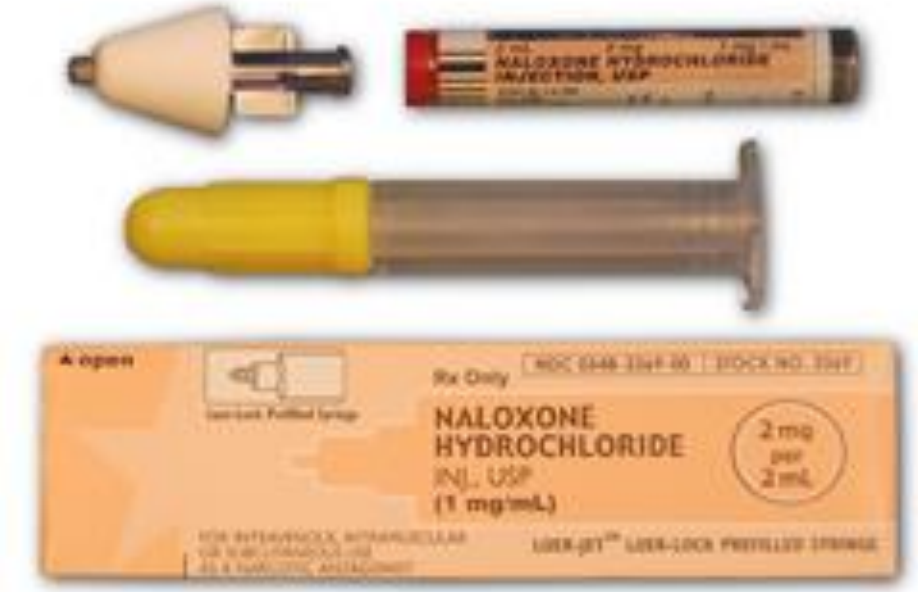
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Outpatient Tapering Options

- Gradual taper:
  - 5-10% decreases of the original dose every 5-28 days until 30% of the original dose is reached, then weekly decreases by 10% of the remaining dose
  - You may elect to taper Extended release (ER) or Immediate release (IR) first, though I generally taper ER first and use IR for breakthrough pain
  - Provide the patient a copy of the taper plan for reference and to help keep patient moving forward

Outpatient Tapering Options

- Rapid taper:
  - Daily to every other day reductions over 1-2 weeks as appropriate

- Initiation of Medication for Opioid Use Disorder
  - Adjuvant opioid withdrawal medications only
  - Office based buprenorphine treatment transition
  - Methadone treatment, refer to opioid treatment program

Adjuvant Opioid Withdrawal Medications	Geriatric (>65 years) Considerations
For sweating, anxiety, agitation Clonidine 0.1mg by mouth three times daily PRN anxiety Hold for sedation or dizziness	Do not use if baseline SBP < 110 Caution with patients who are at risk for falls (On Beers list*)
For anxiety Hydroxyzine 25-50 mg by mouth every 4-6 hours PRN anxiety	Hydroxyzine 12.5-25 mg by mouth every 8 hours PRN anxiety Increased potential for anti-cholinergic side effects (on Beers list)
For nausea or vomiting Phenergan 12.5-25 mg by mouth every 4-6 hours PRN nausea/vomiting OR Zofran 4mg every 12 hours PRN nausea/vomiting	Alternative: Zofran 4 mg by mouth every 12 hours PRN for nausea or vomiting Phenergan associated with anticholinergic side effects and somnolence in older adults (on Beers list) Caution with patients who are at risk for falls
For abdominal cramping/diarrhea Hyocosamine 0.125mg by mouth every 4-6 hours PRN abdominal cramping	Avoid use in this age group due to potent anticholinergic side effects and uncertain effectiveness (on Beers list).
For increased pain with taper and from opioid withdrawal Ibuprofen 400-600 mg by mouth three times daily PRN with food and water for pain OR Tylenol 500mg by mouth every 4-6 hours PRN pain (Maximum dose 3,250mg in 24 hours)	Alternative: Acetaminophen 1000 mg by mouth three times daily if not contraindicated Ibuprofen contraindicated in chronic kidney disease, history of GI bleed, chronic warfarin use, etc. (on Beers list)

*The AGS 2012 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (AGS 2012 Beers Criteria) J Am Geriatr Soc. 2012 Apr;60(4):616-31

**It is not legal or safe to prescribe Methadone for opioid withdrawal in the outpatient setting.

**It is not advised to prescribe benzodiazepines for opioid withdrawal.

Weimer, M, et al. 2013. Oregon Health & Science University Guidelines for Safe Chronic Opioid Therapy Prescribing for Patients with Chronic Non-cancer pain

Step 3: Provider Self-Care

- Check in with a colleague
- Process what went well and what was hard
- Develop an “opioid committee” to support you and the clinic

You are abandoning the opioid therapy NOT the patient

Step 4: Medication for Opioid Use Disorder

- Some patients will struggle with an opioid taper. Continually evaluate the risks and benefits.
  - Methadone >30mg
  - MED >200mg
  - Long term use > 5 years
  - Mental illness, distress intolerant, history of adverse childhood experiences, history of substance use disorder, weak social supports
- Buprenorphine/naloxone is an important resource for these patients
- Also consider interdisciplinary pain programs

Case 2: Immediate Risks

50 yo man on opioids for LBP x 5 years develops severe constipation that is not amendable to treatments. You decide the risks outweigh the benefit of him remaining on morphine ER 15mg BID.

- Taper Plan:
  - Step 1: convert his morphine to IR and reduce it to morphine IR 7.5mg Q8H for 2 weeks
  - Step 2: Reduce morphine IR 7.5mg BID for 2 weeks
  - Step 3: Morphine IR 7.5mg daily for 2 weeks
  - Step 4: stop morphine

Case 3: Immediate Risks

- What if that same 50 yo man on opioids for LBP x 5 years is prescribed fentanyl 75mcg/72 hours.
- Taper Plan:
  - Step 1: convert his fentanyl to a different opioid that is easier to taper like morphine ER or oxycodone ER. Ex. Morphine ER 45mg/30mg/30mg.
  - Step 2: Morphine ER 30/30/30mg TID x 2 weeks – 1 mo
  - Step 3: Continue in 10-20% reductions until done

Case 4: Substance Use Disorder

50 yo male prescribed hydromorphone 4mg every 3 hours and fentanyl 50mcg patch for chronic pancreatitis. You detect alcohol on a routine urine drug screening, and he admits that he has had a recurrence of his alcohol use disorder.

- What do you do?
  - Decide that the risks greatly outweigh the benefit
  - Refer to detoxification from alcohol and opioids
  - Evaluate opioid dose for safety and taper accordingly

Case 5

28 yo female prescribed opioids for chronic abdominal pain. She states she has lost her opioid prescription for the third time. She has had two negative urine drug tests for the opioid that is prescribed and refuses to come in for a pill count.

- You suspect diversion.
- Taper Plan: None. You stop prescribing opioids immediately.

Case 6: Long term opioid therapy with therapeutic alliance

68 yo female with rheumatoid arthritis pain. She is prescribed a total of 350mg MED for the last 5 years with no adverse events. She is moderately functional. Your clinic has developed a new opioid policy stating that patients prescribed doses >120mg MED need to attempt an opioid taper. She is concerned that she might develop serious harms from her opioids.

- Taper plan: Slow taper by 10% per month over a year. May elect to slow down the taper if she experiences periods of worsening pain and/or opioid withdrawal.
- Provide education about opioid overdose and naloxone rescue kit.

Case 7: Long term opioid therapy with difficult therapeutic engagement

63 yo man with history of low back pain and severe depression after a work injury in 1982. He has not worked since and spends most of his day being sedentary. He has been unwilling to engage in additional pain modalities despite multiple offers. He is prescribed oxycodone IR 30mg every 4 hours. You have tried other opioids but he has not had improvements. He refuses an opioid taper and states he will seek another provider if you start to taper his opioids.

- Taper Plan: Offer buprenorphine OR a 1 month rapid taper
- Provide education about opioid overdose and naloxone rescue kit.

Risk Benefit Framework

Useful in Decision to Continue or Discontinue Opioids

Benefits	Risks/Harm
Pain	Misuse
Function	Addiction, Overdose
Quality of Life	Adverse Effects

Useful to Avoid Pitfalls

- "But I really, really need opioids."
- "Don't you trust me?"
- "I thought we had a good relationship/I thought you cared about me."
- "If you don't give them to me, I will drink/use drugs/hurt myself."
- "Can you just give me enough to find a new doc?"

RESPONSE: "I cannot continue to prescribe a medication that is not helping you (or is hurting you or both)."

Summary

- Several different formulations and routes of opioids are available. It is important to understand these differences in order to safely prescribe the medications.
- Patients can benefit from opioid rotation to achieve better pain control and less side effects, but clinical experience is needed to ensure a safe opioid transition.
- Tapering opioids can be a challenging process, but general principles can help promote success.
- In the right situation, allowing a patient to share some decision making about the opioid taper can help a taper's success.
- There will be several occasions where shared decision making about the opioid taper is not possible.
- See also Scope of Pain

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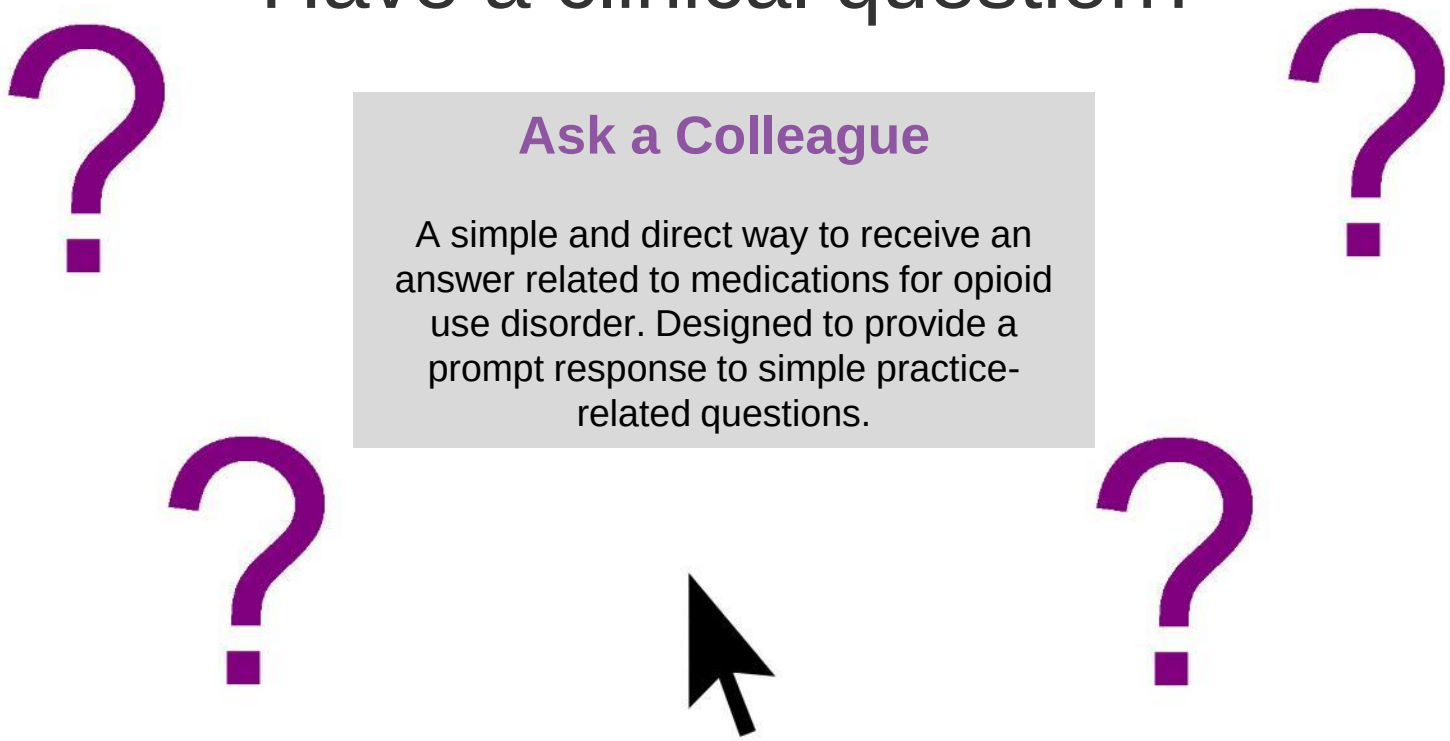

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