Safe Opioid Prescribing

A Patient-Centered Approach to the FDA Blueprint

Escape, by Amanda Arbaugh
Watercolor with computer edits; Fisherville, Virginia

Part 2:
Initiation and Management of Opioid Therapy

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Saturday November 13, 2011
11 AM – 1:00 PM

Introduction

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Program and presenters

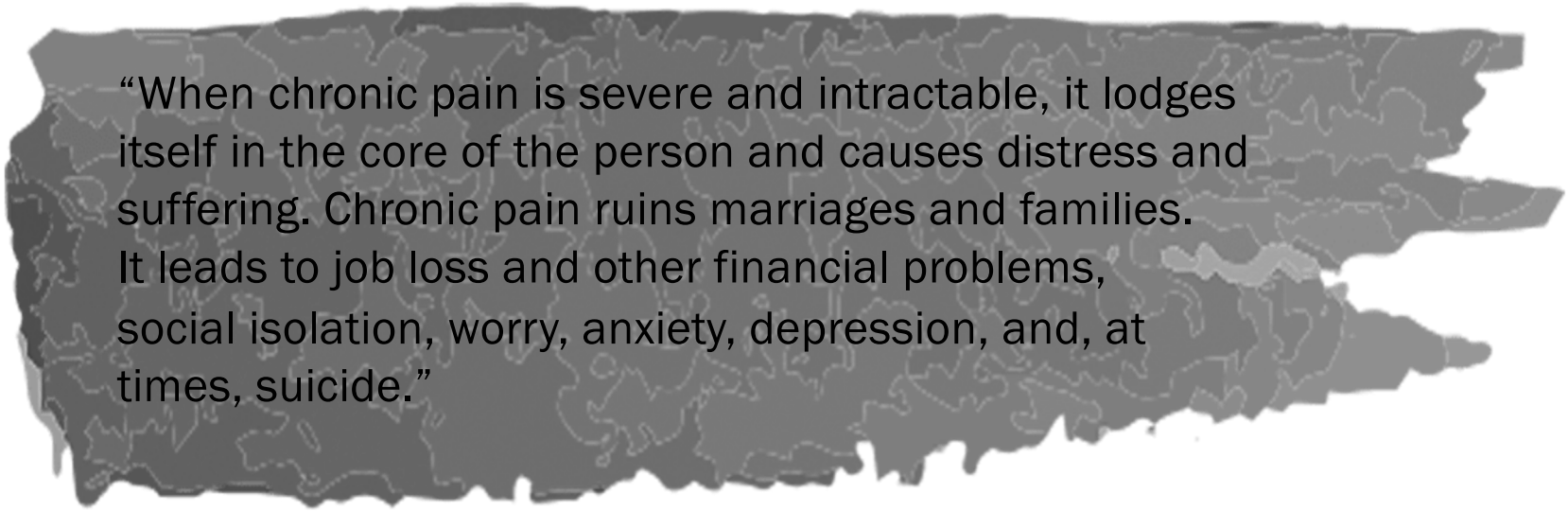
Topic	Presenter	Time
Introduction	Dr. Argoff	5 minutes
	Dr. Kominek	20 minutes
	Dr. Argoff	20 minutes
Conclusion	Dr. Argoff	5 minutes
Live Q&A	Panel	10 minutes

- **Learning objectives**
  - Explain how to integrate opioid analgesics into a pain treatment plan individualized to the needs of the patient
  - Review how to safely and effectively manage patients on opioid analgesics in the acute and chronic pain settings, including initiation and titration
  - Discuss how to counsel patients and caregivers about the safe use of opioid analgesics, including storage and disposal and use in special populations
  - Describe the use of naloxone for opioid overdose

Disclosures

- Charles E. Argoff, MD: Consulting fees (eg, advisory boards): Amgen, BDSI, Collegium, Gruenenthal, Lilly, Lundbeck, Neumentum, Redhill Pharma, Teva, Vertex; Contracted research (principal investigators must provide information, even if received by the institution): AbbVie, Amgen, Lilly, Teva; Speakers' bureaus: AbbVie, Amgen, Biohaven, Gruenenthal, Lilly, Lundbeck, Red Hill Pharma, Teva
- Courtney M. Kominek, PharmD: Honoraria: Quest Diagnostics

Why are we here?



Katz J, et al. *Can J Psychiatry*. 2015;60(4):160-167.

Part 1 of this activity described the fundamentals of pain management and opioid risk

- Effective treatment for pain is an active, ongoing process requiring multiple skill sets and a good therapeutic relationship
- Poorly managed acute pain can transform into chronic pain
- Comprehensive assessment of patients in pain is multifactorial and includes identification of risk factors for opioid abuse and addiction
- Functional goals should be set, documented, and revisited

- Therapeutic options for managing pain are numerous and diverse
  - Nonpharmacologic approaches
  - Non-opioid analgesics
  - Adjuvants across a variety of classes
  - All treatments carry risk
- Opioid analgesics
  - MOA produces analgesia and AEs
  - Even at prescribed doses, these agents carry risk for misuse, abuse, OUD, overdose, and death

AE, adverse event; **MOA,** mechanism of action; **OUD,** opioid use disorder.

When are opioids appropriate?

- Mainstay for cancer pain, palliative care
  - Very few opioid-associated deaths among cancer patients, relative to general population[1]
- Other cases
  - Post-surgical pain
  - Moderate to severe pain affecting function or QoL
  - Documented failure of alternative therapies
  - Benefits > risks

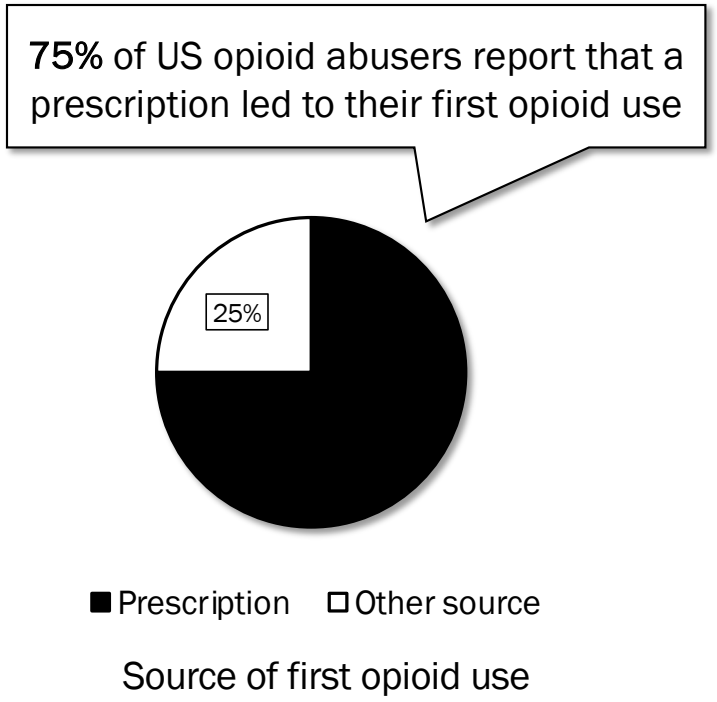
- Factors to consider
  - Source or type of pain
  - Pain intensity
  - Goals of therapy based on functional outcomes - social, occupational, family, recreational
  - Existence of risk factors for opioid abuse or misuse
  - Comorbidities that make opioid use complicated or dangerous - respiratory, renal, and hepatic

QoL, quality of life.

1. Wong SS, Cheung CW. *Ann Palliat Med*. 2020;9(2):558-570. **2.** Brooks A, et al. *Med Clin N Am*. 2016;100(1):81-102.
3. Stein C. *Expert Opin Investig Drugs*. 2018;27(10):765-775. **4.** O'Brien T, et al. *Eur J Pain*. 2017;21(1):3-19.

Opioid prescribing presents specific challenges

- Wide variety of products
  - Classes: full vs partial agonist
  - Formulations: IR vs ER/CR/LA
  - Modes of administration: pill/capsule, transdermal patch, orally disintegrating tablet, lozenge, injection
- Differences in approach to opioid use among health plans and clinicians
  - Dosing and titration, sequence
- Lack of definitive evidence that opioids are beneficial beyond 12 weeks
- Individual differences in patient response
- Risks for misuse, abuse, diversion

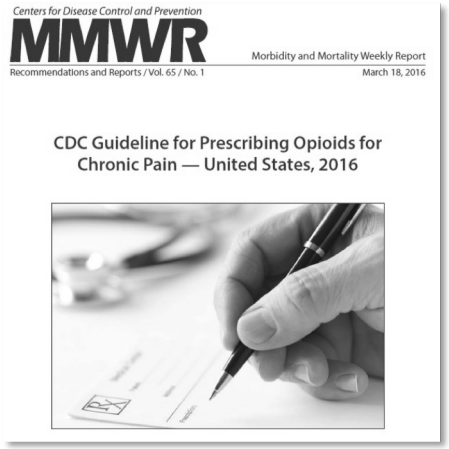


CR, controlled-release; **ER,** extended-release; **IR,** immediate-release; **LA,** long-acting.

O'Brien T, et al. *Eur J Pain*. 2017;21(1):3-19. Busse JW, et al. *JAMA*. 2018;320(23):2448-2460.

The evidence for initiating opioid therapy in chronic pain is complex

- Evidence of long-term benefit is complicated to assess
  - CDC found no RCTs showing benefit in chronic pain at ≥1 year[1]
    - Few studies of that duration
    - Ethical issues with placebo arm of such a trial
  - Positive results in several other studies
    - 12-wk double-blind RCT (oxymorphone ER)[2]
    - 12-mo open-label study (hydrocodone ER)[3]
- Possible harms: OUD, OD, motor vehicle injury[1]
- Known AEs: constipation, sedation/dizziness, nausea/vomiting, respiratory depression[1]



CDC, Centers for Disease Control and Prevention; **RCT,** randomized clinical trial; **OD,** overdose.

1. Dowell D, et al. *MMWR Morb Mortal Wkly Rep*. 2016;65(1):1-49; **2.** Hale ME, et al. *J Pain*. 2007;8(2):175-184; **3.** Hale ME, et al. *J Opioid Manag*. 2015;11(5):425-434.

A recent meta-analysis illustrates evidence gaps in the use of opioids for chronic noncancer pain

- Meta-analysis
  - 96 RCTs including >26,000 patients
  - Median pain score 6.54/10.0 on VAS
  - Follow-up at ≥4 weeks

In contrast to the clear value of opioids in cancer and post-surgical pain, benefits in chronic noncancer pain were small

- Key results
  - Relative to placebo, opioid treatment was associated with small improvements in pain, physical functioning, and sleep quality; with increased vomiting and nausea
  - Opioids were equally efficacious for nociceptive, neuropathic, and central sensitization conditions
  - Efficacy of opioids was similar to that of NSAIDS, TCAs, and synthetic cannabinoids for pain and physical functioning; slightly superior to anticonvulsants for pain relief
  - No trial lasted >6 months
  - No trial reported rates of OUD

Busse JW, et al. *JAMA*. 2018;320(23):2448-2460.

NSAID, nonsteroidal anti-inflammatory drug; **TCA,** tricyclic antidepressant; **VAS,** visual analog scale.

All About Opioids

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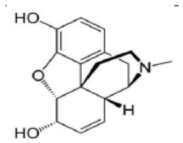
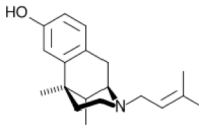
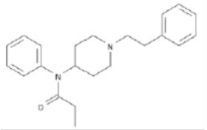
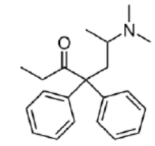
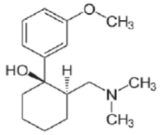
Opioids represent several chemical classes

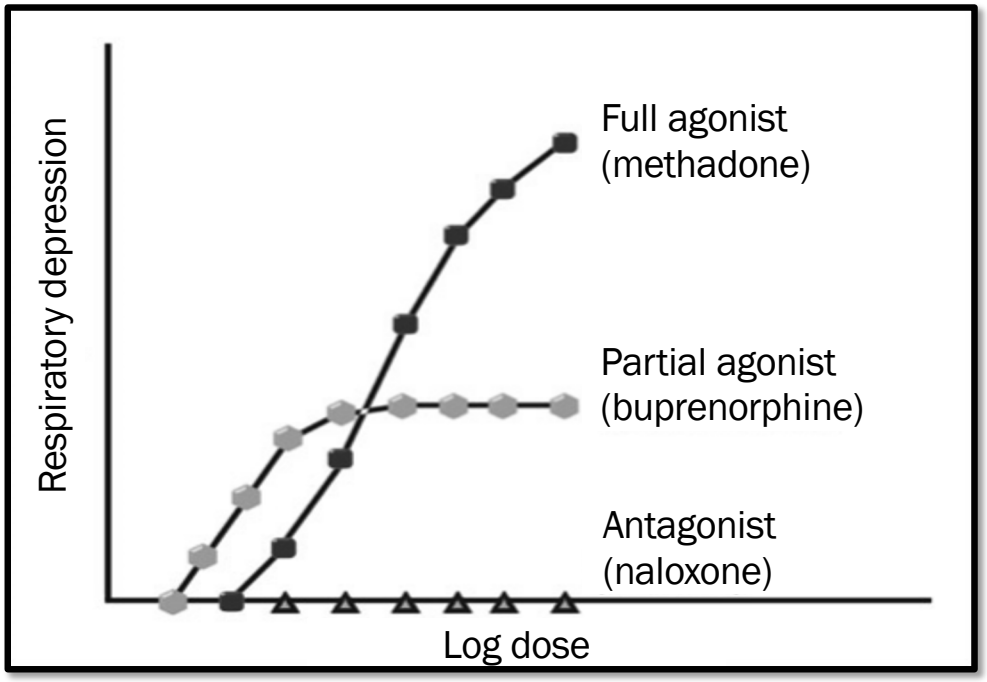
Phenanthrenes	Benzomorphans	Phenylpiperidines	Diphenylheptanes	Phenylpropyl amines
				
Morphine	Pentazocine	Fentanyl	Methadone	Tramadol
Buprenorphine,[a] butorphanol,[a] codeine, dextromethorphan,[a] dihydrocodeine, heroin, hydrocodone,[a] hydromorphone,[a] levorphanol,[a] methylnaltrexone,[b] morphine (opium), nalbuphine,[a] naloxone,[a] naloxegol,[a] naltrexone,[b] oxycodone,[a] oxymorphone[a]	Diphenoxylate	Alfentanil, fentanyl, meperidine, remifentanil, sufentanil	Methadone, propoxyphene	Tapentadol, tramadol
		Illicit fentanyl		
		Furanyl fentanyl, acetyl fentanyl, fluoro-fentanyl, carfentanil		
		Others		
		Pentazocine		
Cross-sensitivity risk				
Probable	Possible	Low risk	Low risk	Low risk

[a]Agents lacking the 6-OH group of morphine; possibly decreases cross-tolerability within the phenanthrene group.
[b]6-position is substituted with a ketone group; tolerability is similar to hydroxylation.

Fudin J. https://paindr.com/wp-content/uploads/2018/10/Opioid-Structural-Classes-Figure_-updated-2018Oct.pdf.

Conceptual dose–response curves for 3 opioids

- Unique pharmacology of buprenorphine
  - Partial opioid agonist with high affinity for mu receptor
  - Significant analgesic activity within spinal cord c/t brain
  - Stimulates sufficient G-protein signaling while limiting beta-arrestin recruitment to the receptor



Adapted from: McNicholas L. www.naabt.org/documents/TIP40.pdf and Webster L, et al. *Pain Med*. 2020;21(4):714-723.

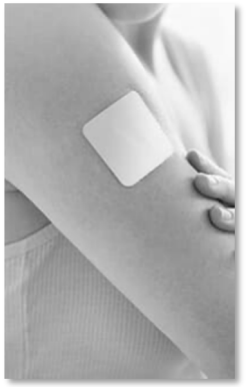
Opioids can be administered via many routes

Route	Comments
Oral	Inexpensive, simple, noninvasive; consider before all other routes; extensive hepatic metabolism (slow onset)
Transmucosal	Lipophilic drugs absorbed well; bypasses hepatic metabolism; helpful for breakthrough pain in opioid-tolerant patients
Buccal	Effective and convenient for fentanyl; helpful for breakthrough pain in opioid-tolerant patients
Sublingual	Buprenorphine, fentanyl, and methadone absorbed well (only buprenorphine available in US)
Transdermal	Available for fentanyl; can provide analgesia for 48-72 hours by continuous drug release; slow onset, gradual decline; difficult to titrate; not suitable for acute pain
Intranasal	Butorphanol available but not recommended for persistent pain; main drawback is burning/stinging on inhalation
Subcutaneous	Morphine and hydromorphone most common; alternative for patients unable to take medication PO or with limited venous access; requires skill and expertise
Intravenous	Indicated when rapid titration required; provides steady blood levels; opioids with short half-lives recommended
Epidural	Indicated for major abdominal, thoracic, and joint surgeries; may be alternative for patients with dose-limiting AEs from systemic opioids
Intrathecal	Indicated for some acute pain (single bolus); may be alternative for patients with dose-limiting AEs from systemic opioids; usually administered via implanted infusion pump
Intra-articular	Produces analgesia for joint surgeries; further study needed to establish other uses
Rectal	Alternative for patients unable to take medication PO; considerable variation in dose and time to effect; any opioid can be compounded for rectal administration

PO, by mouth.

Opioids can be classified as short- or long-acting

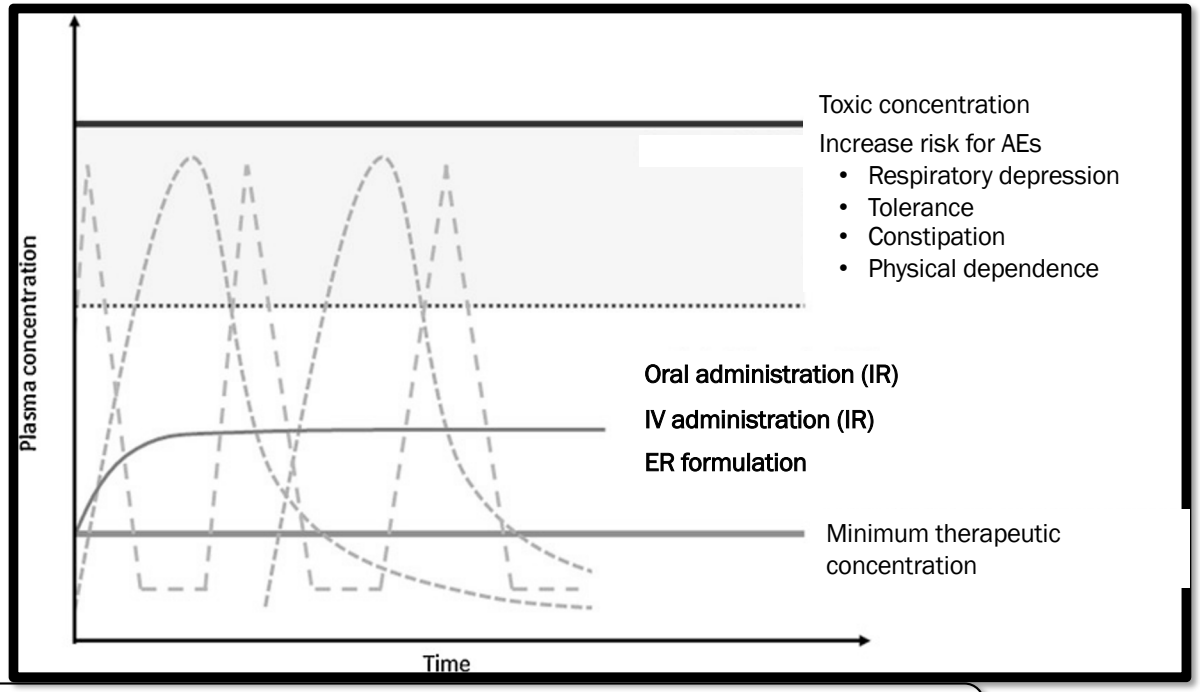
Short-acting opioids	Long-acting opioids
• Active in blood for 2-6 hours • Use for initiation of opioid therapy • Indicated for moderate to severely moderate pain for which alternative treatments are inadequate	• Active in blood for 12-24 hours • Some are safe only for opioid-tolerant patients: LA fentanyl, LA hydromorphone • Indicated for pain severe enough to require daily, ATC, long-term opioid treatment and for which alternative treatments are inadequate
○ Codeine ± acetaminophen ○ Hydrocodone ○ Hydrocodone + acetaminophen ○ Hydromorphone ○ Morphine ○ Oxycodone ○ Oxycodone + acetaminophen ○ Tramadol ± acetaminophen ○ Tapentadol	○ Buprenorphine buccal film, patch ○ Fentanyl transdermal patch ○ Hydrocodone ER ○ Hydromorphone ER ○ Morphine ER/CR ○ Oxycodone CR ○ Methadone ○ Tramadol ER ○ Tapentadol ER



ATC, around-the-clock.

Release characteristics: IR vs ER

- IR drugs
  - Dose adjustments can be made more easily
  - Less expensive; preferentially covered by formularies
  - Greater risk for immediate intoxication
- ER/LA drugs
  - May improve sleep, adherence
  - Less clock-watching, short-term euphoria
  - Do not allow rapid dose adjustments, if needed.
  - Higher risk for OD



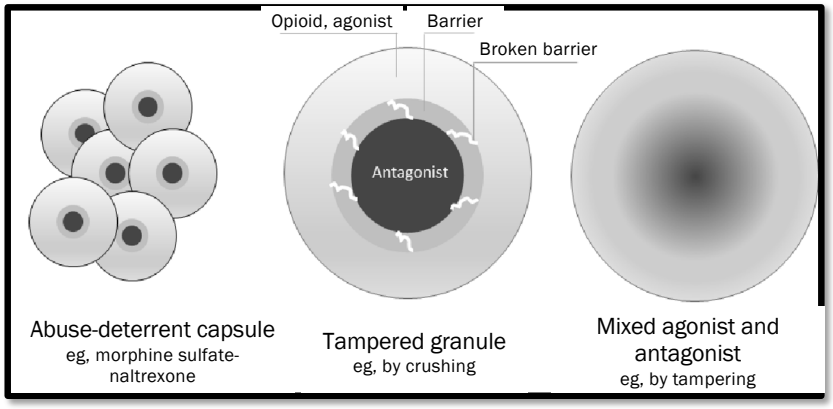
No evidence available regarding improved efficacy or safety with long-acting compared to short-acting

Ali HS, et al. *Int J Pharmaceut Clin Res*. 2019;11(1):30-33. Martin C, et al. *Materials Today*. 2016;19(9):491-502.

Abuse-deterrent formulations are available

- Designed to make opioid abuse more difficult or less rewarding
- Target known routes of manipulation used to defeat ER properties
  - Crushing
  - Dissolving
- Still have potential for abuse and overdose via oral administration
- FDA labeling is based on:
  - Laboratory-based in vitro manipulation and extraction studies
  - Pharmacokinetic studies
  - Clinical abuse potential studies
  - Postmarketing studies

- Several approaches
  - Physical/chemical barriers
  - Agonist/antagonist combinations
  - Aversion
  - Delivery system (depot injectable/implant)
  - New molecular entities/prodrugs



US Department of Health and Human Services. www.fda.gov/media/84819/download.

Abuse-deterrent technologies vary

Physical/chemical barrier

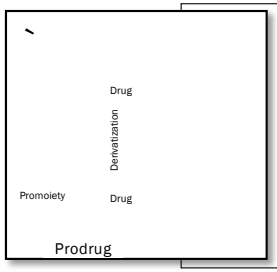
- Can prevent manipulation of product, including chewing, crushing, cutting, grinding, or extraction via use of solvents
- Examples: OxyContin, Exalgo, Oxecta, Hysingla ER, Zohydro ER

Agonist-antagonist combo

- Antagonist is sequestered and not active when swallowed but is released if product is manipulated (ie, crushed)
- Examples: Suboxone, Embeda, Targiniq ER, Troxyca ER

Aversion

- Inclusion of substances that produce unpleasant effects if dosage form is manipulated or drug is taken at higher doses than prescribed



New molecular entity/ prodrug

- Could include need for enzymatic activation, different receptor-binding properties, slower CNS penetration, etc

Delivery system

- Drug-release design or method of delivery can offer resistance to abuse
- Examples: SR IM depot injection, SC implant

CNS, central nervous system; **IM,** intramuscular; **SC,** subcutaneous.

https://rxinformer.healthesystems.com/article.php?id=74.

Opioids have many warnings and contraindications

Boxed Warnings

- Addiction, abuse, misuse
- Life-threatening respiratory depression
- Accidental ingestion
- Neonatal opioid withdrawal syndrome
- Cytochrome p450 3a4 interaction
- Risks from concomitant use with benzodiazepines and other CNS depressants
- Interaction with alcohol
- CYP2D6 and pharmacogenomics

Contraindications

- Respiratory instability
- Acute psychiatric instability
- History of substance abuse
- Life-limiting drug–drug interactions
- Prolonged QTC interval (heart arrhythmia) with methadone
- Active diversion of prescription opioids to street sales

Common opioid AEs and how to manage them

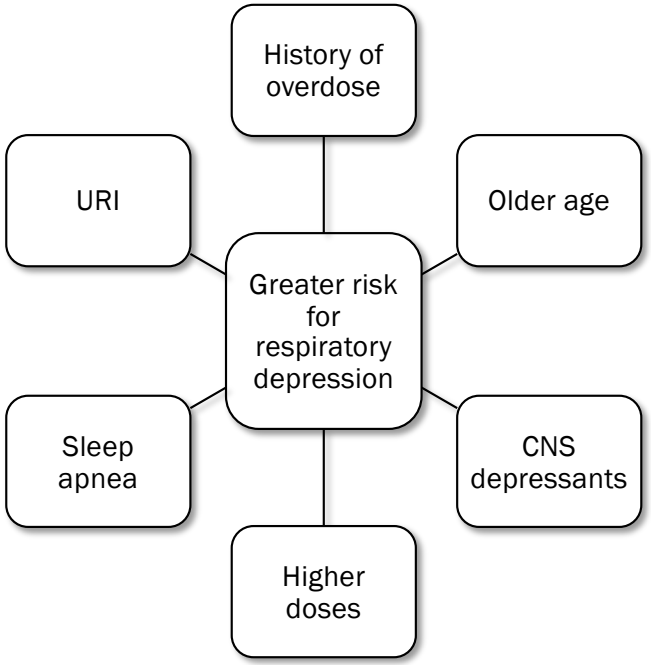
Adverse events	Details/recommended management strategy[1]
Sedation, respiratory depression	• May contribute to overdose and death • Dose-related; risk increases when given with CNS depressants (eg, alcohol, benzodiazepines, sedative-hypnotics); reduce dose and terminate drugs that elevate risk; lower risk with partial agonist buprenorphine • Risk mitigation option: naloxone
Nausea, vomiting	• Prevalence of 40% and 15%-25%, respectively • Switch opioid, use antiemetics, or change route of administration[2]
Constipation	Prophylactic stool softener and laxatives, opioid dose reduction or rotation
Cardiovascular effects	Risk for qtc interval prolongation and myocardial infarction/ECG monitoring and opioid rotation or dose reduction
Sexual dysfunction, infertility	Opioids may decrease testosterone/androgen replacement therapy or opioid rotation, dose reduction
Rash/pruritis	Antihistamine therapy

ECG, electrocardiogram.

Brooks A, et al. *Med Clin North Am*. 2016;100(1):81-102. Sande T, et al. *J Palliat Med*. 2019;22(1):90-97.

Respiratory depression is a key concern

- May occur at any time; increased risk during:
  - Treatment initiation
  - Dose increases
- Monitor patients closely, especially during first 24 to 72 hours
- Increased risk with concurrent use of benzodiazepines
- Reduce risk via proper dosing and titration
- Lower risk with buprenorphine (partial agonist)
- Consider using the **RIOSORD**: Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression
- Initiate therapy with IR opioids



URI, upper respiratory infection.

Zedler B, et al. *Pain Med*. 2015;16(8):1566-1579.

The post-operative period may be critical for opioid-naïve patients

- **22% to 28%** of post-surgical patients filled opioid prescriptions ≥1 month post-surgery in a retrospective survey[1]
- **>5%** of opioid-naïve patients became chronic users in a study of elective orthopedic surgery[2]

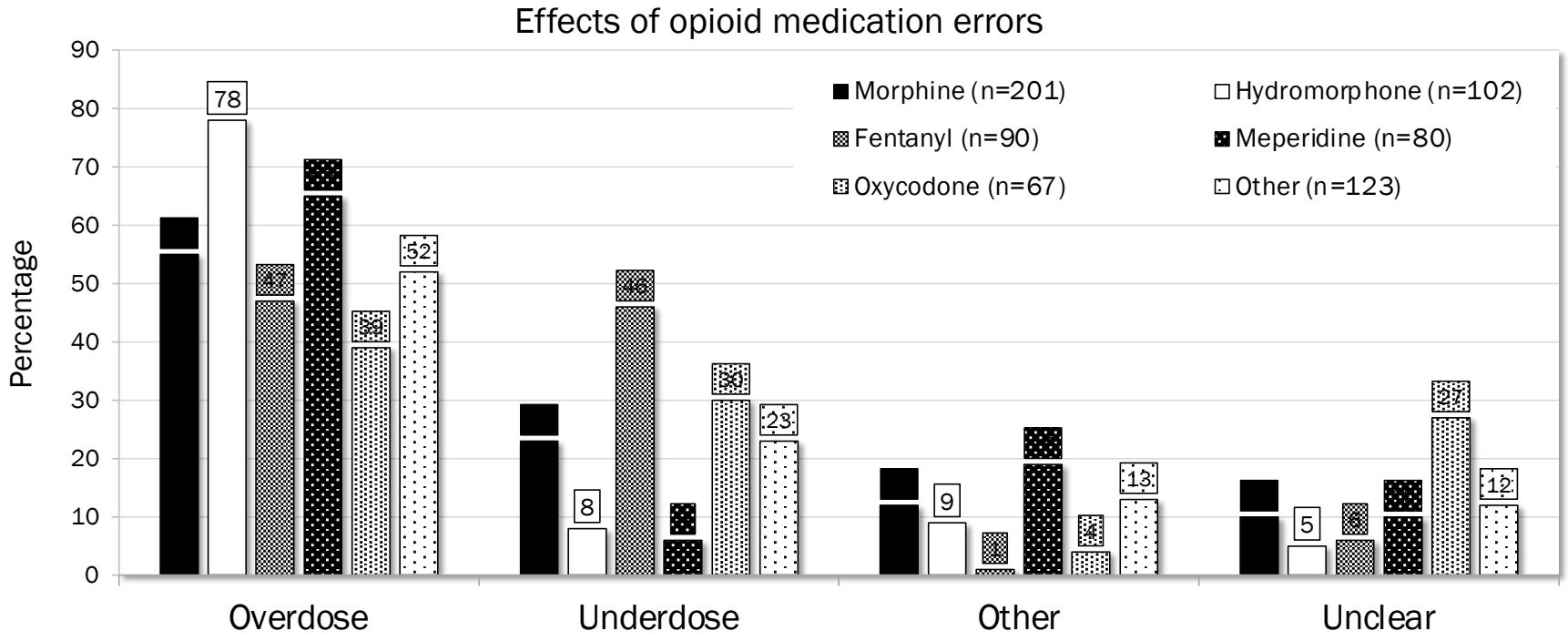
Given that most post-operative healing should be complete by 30 days, any prescriptions after that time should trigger HCPs to evaluate the reason for continued opioid use and consider alternatives

Risk factors for opioid use ≥1 year after sugery[3]	Odds ratio	*P* value
Male	1.34	<0.001
Age	1.74	<0.001
Preoperative use of antidepressants	1.65	<0.001
Preoperative use of benzodiazepines	1.82	<0.001
Comorbid depression	1.15	<0.03
Comorbid alcohol abuse	1.83	<0.001
Comorbid drug abuse	3.15	<0.001

HCP, health care provider.

1. Bartels K, et al. *Drug Alcohol Depend*. 2018;187:61-65. **2.** Cunningham DJ, et al. *Mayo Clin Proc Innov Qual Out*. 2021;5(1):23-34.
4. Sun EC, et al. *JAMA Intern Med*. 2016;176(9):1286-1293.

Opioid-related medication errors lead to over- and under-dosing

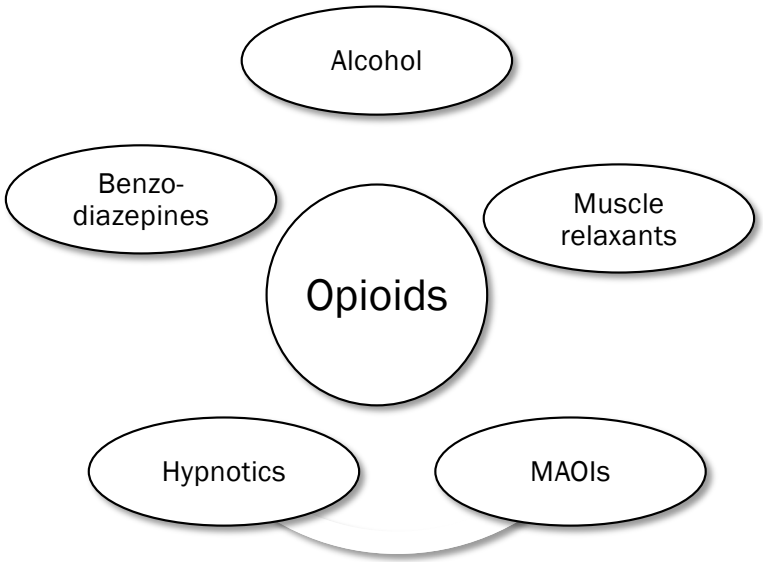


Dy SM, et al. *J Opioid Manag*. 2007;3(4):189-194.

Potential drug interactions are numerous

- Obtain complete history of all prescription, OTC, and natural products
- Determine sources of metabolic drug–drug interactions
- Recommend changes when appropriate
- Discuss PK/PD interactions with alcohol

The number of patients prescribed both opioid analgesics and benzodiazepines increased **41%** from 2002 to 2014



MAO, monoamine oxidase inhibitor; **OTC,** over-the-counter; **PD,** pharmacodynamic; **PK,** pharmacokinetic.

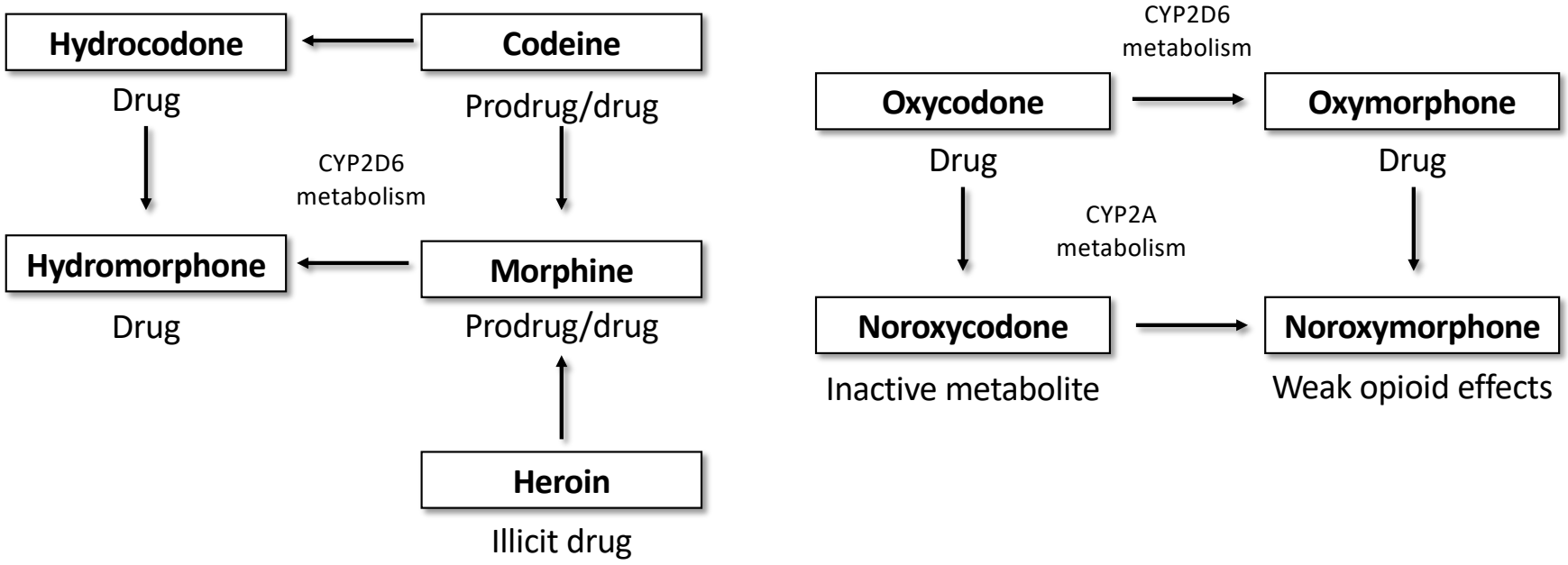
US FDA. www.fda.gov/news-events/press-announcements/fda-requires-strong-warnings-opioid-analgesics-prescription-opioid-cough-products-and-benzodiazepine; CDC. www.cdc.gov/drugoverdose/pdf/aha-patient-opioid-factsheet-a.pdf; Gillman PK. *Br J Anaesth*. 2005;95(4):434-441. Pergolizzi JV, et al. *Pract Pain Manag*. 2017;12(7).

Opioid metabolism involves several key enzymes

Phase	Key enzymes involved	Opioid medication metabolized
Phase I	• Cytochrome P450 (CYP450) • Examples: CYP2D6, CYP2C19, CYP2B6, CYP2C9, CYP3A4, CYP3A5	Codeine, hydrocodone, oxycodone, tramadol, fentanyl, methadone, buprenorphine
Phase II	• Uridine 5'-diphospho-glucuronosyl-transferase • Examples: UGT2B7, 2B15	Morphine, oxymorphone, hydromorphone, tapentadol, levorphanol

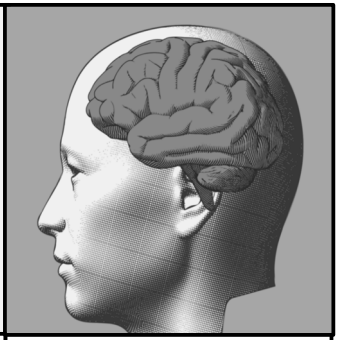
Smith HS. *Mayo Clin Proc*. 2009;84(7):613-624.

Interrelations among opioid molecules: prodrugs, drugs, and inactive metabolites



Overholser BR, Foster DR. *Am J Manag Care*. 2011;17(suppl 11):S276-S287.

Certain comorbidities increase opioid risk

				
COPD[1] • Averse respiratory outcomes and mortality can occur with new use of short- or long-acting opioids	Renal insufficiency[2] • Metabolism of opioids excreted through the kidney can be impaired, causing over-or under-dosing • Avoid morphine and tramadol • Preferred: buprenorphine, fentanyl, methadone	Hepatic impairment[2] • Opioid metabolism can be impaired • Avoid codeine • Reduce doses or use ER for morphine, oxycodone, or tramadol • Reduce doses of hydromorphone • Avoid LA opioids	Sleep disorders[3] • Increased risk for respiratory depression • Chronic opioid use associated with sleep-disordered breathing	Mental health disorders[4,5] • High prevalence in patients with chronic pain • Benzodiazepines should not be combined with opioid therapy without specialist consult

COPD, chronic obstructive pulmonary disease.

1. Vozoris NT, et al. *Eur Respir J*. 2016;48(6):1818. **2.** O'Brien T, et al. *Eur J Pain*. 2017;12(1):3-19. **3.** American Academy of Sleep Medicine. https://aasm.org/chronic-opioid-therapy-position-statement-jcsm/. **4.** Gebhardt S, et al. *J Clin Psychopharmacol.* 2016;36(6):658-668. **5.** [no author listed] *Pract Pain Manage*. www.practicalpainmanagement.com/treatments/pharmacological/opioids/use-opioids-pain-patients-psychiatric-disorders.

Special populations: children and adolescents

- Chronic pain estimated to affect 5%-38% of this population
- Etiology
  - Congenital/ noncongenital diseases
  - Primary chronic pain conditions
  - Cancer
- Poor acute pain management increases risk for persistent pain and increased impairment

- Guidelines do not address best practices for pediatric opioid prescribing
- Few FDA-approved therapies for this use
- Opioids rarely used
- Traditional analgesics routinely used in adults may be trialed in younger patients
- Specialty training or consultation with expert before treating this population
- Black box warning with codeine

Baumbauer KM, et al. *Med Clin N Am*. 2016;100(1):183-197. US Department of Veteran Affairs. www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf.

Special populations: older patients

- Chronic pain is common in older patients
- Age-related physiologic changes
  - May increase risk for pharmacotherapy-related AEs
- Comorbidities
- Polypharmacy
- Respiratory depression risk with opioids

Baumbauer KM, et al. *Med Clin N Am*. 2016;100(1):183-197. US Department of Veteran Affairs. www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf.

Special populations: women

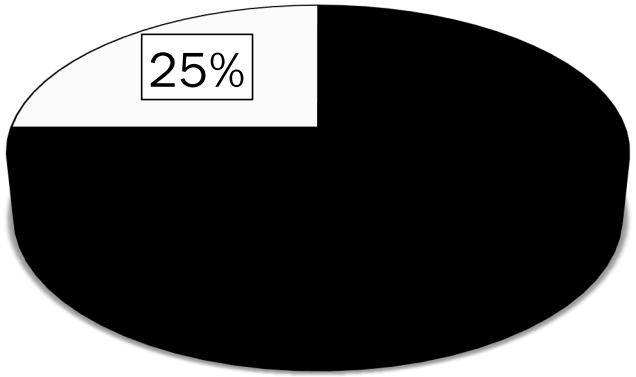
- Unique challenges, differences
  - Pain sensitivity
  - Response to pain medications
  - Predisposition to clinical pain conditions
- Pregnancy
  - Screening for substance use
  - Avoid or minimize opioid use
  - Administer alternative pain therapies
  - Discuss risk and benefits of opioids
- Breastfeeding
  - Encourage in women stable on opioids
- Neonatal opioid withdrawal syndrome
  - Monitor infants born to women who used opioids during pregnancy

US Department of Veteran Affairs. www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf.
ACOG Committee. *Obstet Gynecol*. 2017;130(2):e81-e94.

Special populations: pharmacogenomic variability

- Affects drug metabolism, response to pain, and risk for addiction
- General population has 40%-60% phenotype variability
- CYP450 enzymes most frequently involved

Genetic differences affect 25% of all drugs



Cavallari LH, et al. *Curr Opin Mol Ther*. 2009;11(3):243-251. Lynch T, Price A. *Am Fam Physician*. 2007;76(3):391-396.
Ma JD, et al. *Pharm Pract*. 2012;25(4):417-427.

Initiation of Opioid Therapy

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Initiating opioid therapy: patient selection

- Numerous risk assessment tools available
  - Opioid Risk Took (ORT)[1]
  - Screener and Opioid Assessment for Patients with Pain - Revised (SOAPP-R)[2]
  - Addiction Behaviors Checklist (ABC)[3]
  - Diagnosis, Intractability, Risk and Efficacy (DIRE)[4]
- Factors surveyed include:
  - Disability
  - Chaotic personal life
  - Underemployment
  - History of serious mental illness
  - History of substance abuse
  - History or current use of CNS depressants and benzodiazepines

1. Cheatle MD, et al. *J Pain*. 2019;20(7):842-851. **2.** Chou R, et al. *J Pain*. 2009;10(2):131-146.
3. Wu SM, et al. *J Pain Symptom Manage*. 2006;32(4):342-351. **4.** Belgrade MJ, et al. *J Pain*. 2006;7(9):671-681.

Patient–provider agreements can be helpful

- Formal written agreements designed to support appropriate and safe use of opioids
- Create open conversation between patient and provider about benefits, risks, and limitations of opioid therapy
- Clarify situations that will result in opioid discontinuation, among other consequences
- Health care systems may ask patients to sign an informed consent as well

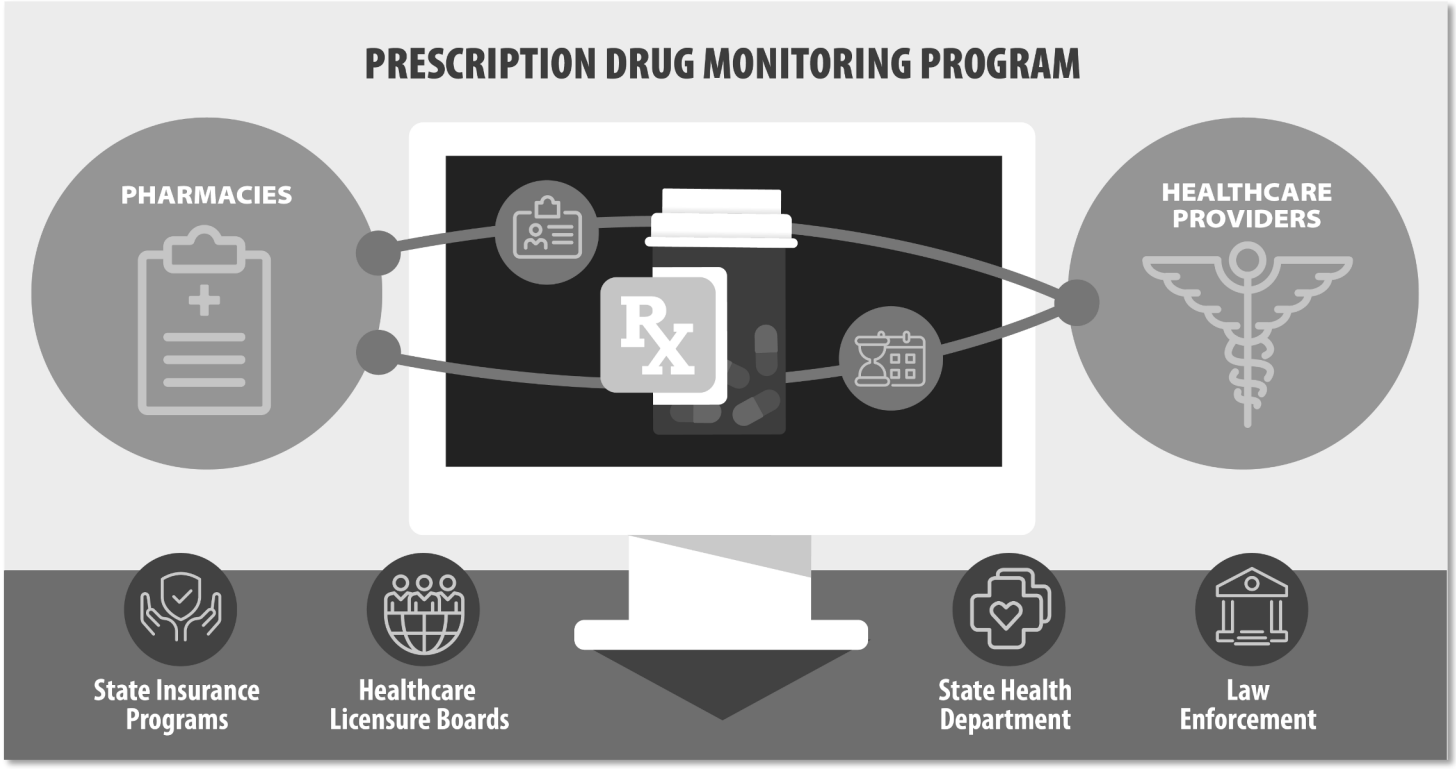
FDA. www.fda.gov/media/114694/download. Institute for Clinical Systems Improvement. www.icsi.org/wp-content/uploads/2019/01/Pain.pdf.

Patient–provider agreements have advantages and disadvantages

Advantages	Disadvantages
• Educate patients and caregivers about treatment plans • Inform treatment risks and benefits • Clarify treatment goals • Promote treatment adherence • Enhance therapeutic relationship • Facilitate active patient role in treatment • Lay out patient and provider responsibilities	• Efficacy not well established and may be limited by patients' misunderstanding • No evidence-based guidelines for development or revision • Increased stigmatization risk • May suggest patient/provider distrust • May be applied or interpreted with discriminatory intent • Often contain punitive language

Chapman L, et al. *Am J Psych Res J*. 2016;11(9):14-16.

How does the PDMP work?

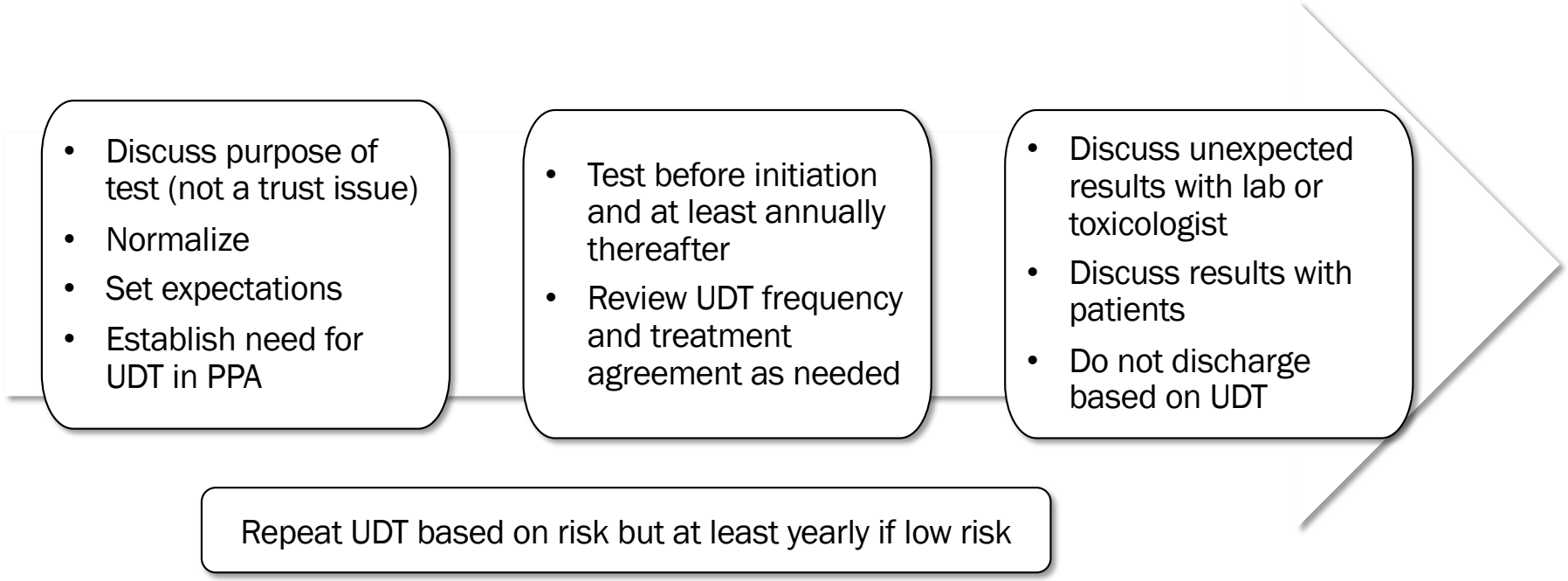


PDMP, prescription drug monitoring program.

Your state's PDMP is a useful tool

- Statewide database that monitors prescribing of controlled substances
- Data submitted by pharmacies and dispensing practitioners
- PDMP InterConnect facilitates interstate data sharing
- CDC recommends clinicians check the PDMP before every opioid prescription and at least every 3 months for ongoing prescribing
  - Can be delegated to office staff
- Uses
  - Identify patients who obtain controlled substances from multiple providers
  - Calculate total amount of opioids prescribed per day
  - Identify patients who have been prescribed drugs that increase opioid risk (eg, benzodiazepines)
  - Support research, education, abuse prevention, and enforcement

UDT is recommended before starting opioid therapy and annually thereafter



PPA, patient-provider agreement; **UDT,** urine drug testing.

Argoff CE, et al. *Pain Medicine*. 2018;19(1)97-117. Centers for Disease Control and Prevention. www.cdc.gov/drugoverdose/pdf/prescribing/CDC-DUIP-UrineDrugTesting_FactSheet-508.pdf. Accessed October 27, 2021.

Urine drug testing

Immunoassay	GC/MS
Less expensive, fast, easy to use; most often used	More expensive, labor-intensive, requires advanced laboratory services
Commonly used for screening	Primarily confirms positive immunoassay results
Engineered antibodies bind to drug metabolites	Measures drugs and metabolites directly
Qualitative; positive or negative	Quantitative
Screens for presence of drugs or drug panel	Identifies specific drugs and metabolites
Does not differentiate natural opiates	Differentiates all opioids
Usually misses semisynthetic and synthetic opioids	More accurate for semisynthetic and synthetic opioids
High cutoff levels, leading to false-negative results	Very sensitive, detects low levels, fewer false negatives
Will show false positives	Very specific, less cross-reactivity, fewer false positives

GS/MS, gas chromatography/mass spectrometry.

Centers for Disease Control and Prevention. www.cdc.gov/drugoverdose/pdf/prescribing/CDC-DUIP-UrineDrugTesting_FactSheet-508.pdf.

Initiating opioid therapy for acute pain opioid-naïve patients

- Abbreviated risk assessment
- Moderate to severe pain
- Lowest practical dose
- Shortest practical duration
  - Outpatients: ≤3 d; occasionally >7 d
  - Supervised inpatients or very closely monitored outpatients
    - IR morphine 10-30 mg q4h PO PRN
    - IV morphine 1-4 mg q1-4h as needed; increase for uncontrolled severe pain by ≤10 mg q4h PRN in patients at low risk for respiratory depression

Start low

Go slow

PRN, as needed.

Dowell D, et al. *MMWR Morb Mortal Wkly Rep*. 2016;65(1):1-49. National Comprehensive Cancer Network. www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Pharmacist's Letter. https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2015/Jul/Equianalgesic-Dosing-of-Opioids-for-Pain-Management-8635. Scully RE, et al. *JAMA Surg*. 2018;153(1):37-43.

Initiating opioid therapy for acute pain: opioid-tolerant patients

- PO opioid therapy equivalent to 10%-20% of total opioid dose from prior 24 h
- Reassess every hour
- Increase dosage PRN for uncontrolled pain
  - 50% higher for moderate pain
  - 100% higher for severe pain

Opioid tolerance

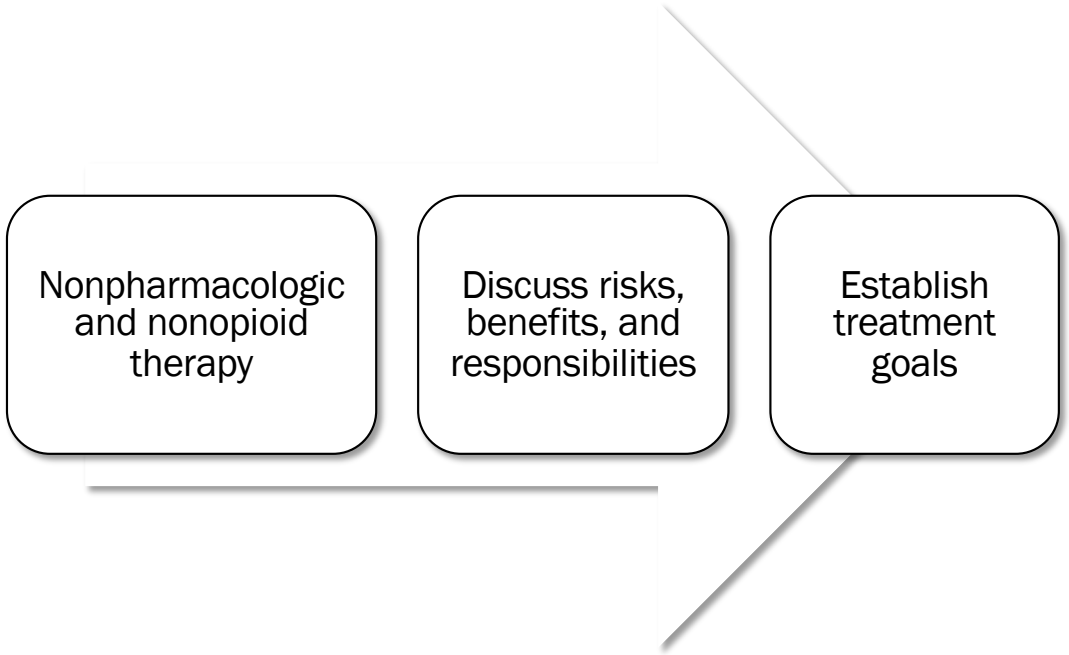
Daily use, for ≥7 of prior 14 days, of:

- ≥60 mg PO morphine
- ≥30 mg PO oxycodone
- ≥8 mg PO hydromorphone
- ≥60 mg PO hydrocodone
- Equianalgesic dose of another opioid

McPherson ML. Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. Bethesda, MD: American Society of Health-System Pharmacists; 2018. FDA Briefing Document. www.fda.gov/media/127780/download.

Initiating opioid therapy for chronic pain: first steps

- Comprehensive assessment
  - Establish diagnosis
    - History
    - Physical exam
    - Treat underlying medical conditions
  - Family history
  - Psychosocial history
- Review PDMP data
- UDT
  - PDMP and UDT may not be essential if first exposure to opioids and low risk



Dowell D, et al. *MMWR Morb Mortal Wkly Rep*. 2016;65(1):1-49. Munzing T. *Perm J.* 2017;21:16-169.

Initiating opioid therapy for chronic pain: risk factors

Risks for Misuse, Abuse, and Overdose at Opioid Initiation	
• Age ≤35 • Current or prior use of alcohol or illicit drugs • Use of drug culture language • Prior OD • Family members taking similar controlled substances • Tobacco smoking • Male gender	• Depression • Sleep-disordered breathing • Renal or hepatic impairment • No education past high school • Medicaid/self pay • >2 psychological diseases • Single marital status • Caucasian

Gostine ML, et al. *Practical Pain Management*. 2014;14(4); Munzing T. *Perm J*. 2017;21:16-169; Volkow ND, et al. *NEJM*. 2016.

Initiating opioid therapy for chronic pain: dosing, formulations

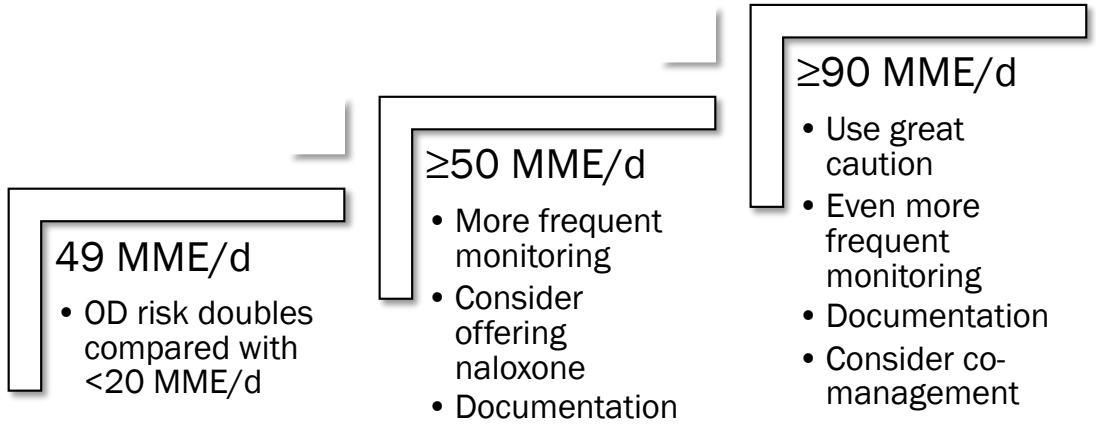
- PRN vs ATC
- IR preferable to ER/LA opioids
- Provider comfort is most important
  - Hydrocodone
  - Tramadol
  - Codeine
  - Oxycodone
- Use lowest effective dosage
- Opioid-related OD risk is dose-dependent
- Use caution when prescribing opioids at any dosage

- ER/LA opioids
  - **Indication:** pain severe enough to require daily, ATC, long-term opioid therapy when other options are ineffective, not tolerated, or otherwise inadequate
  - Associated with substantially higher average daily opioid dosage vs PRN use
  - Higher risk for OD vs IR formulas
- No true ceiling dose for pain relief
- Co-prescribe naloxone

Dowell D, et al. *MMWR Morb Mortal Wkly Rep*. 2016;65(1):1-49. Stachnik JM. *Pract Pain Manag*. 2011;11(4). Zedler BK, et al. *Pain Med*. 2018;19(1):68-78.

Dose matters

- The higher the dose of opioid, the greater the risk for AEs
- All guidelines support appropriate monitoring to reduce risk
  - CDC is one example
  - MME is controversial

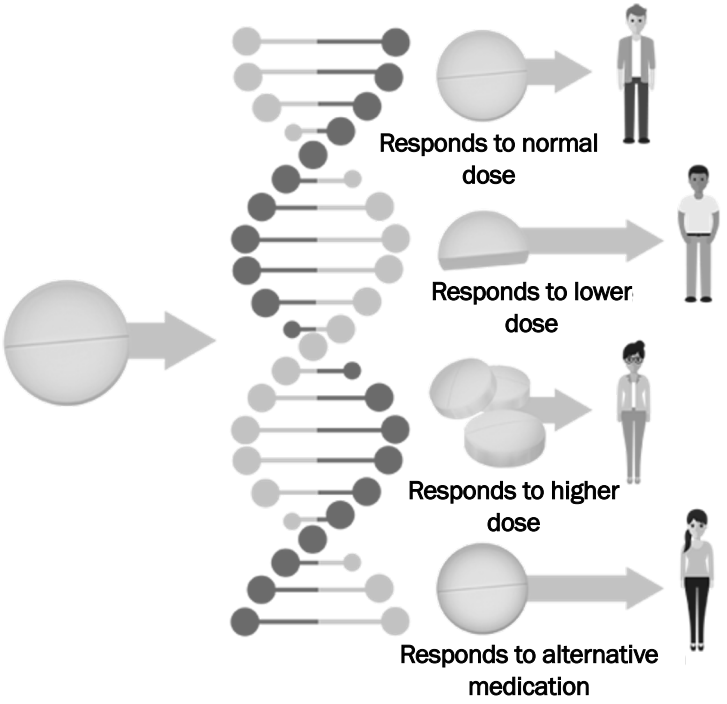


CDC, Centers for Disease Control and Prevention; **MME,** morphine milligram equivalent.

Centers for Disease Control and Prevention. www.cdc.gov/drugoverdose/pdf/prescribing/CDC-DUIP-QualityImprovementAndCareCoordination-508.pdf.

Issues with MEDD and opioid conversion

- Pharmacogenetic variability
- Drug interactions
- Lack of universal MEDD
- Specific opioids that should never have an MEDD
  - Methadone, buprenorphine, tapentadol, tramadol



MEDD, morphine equivalent daily dose.

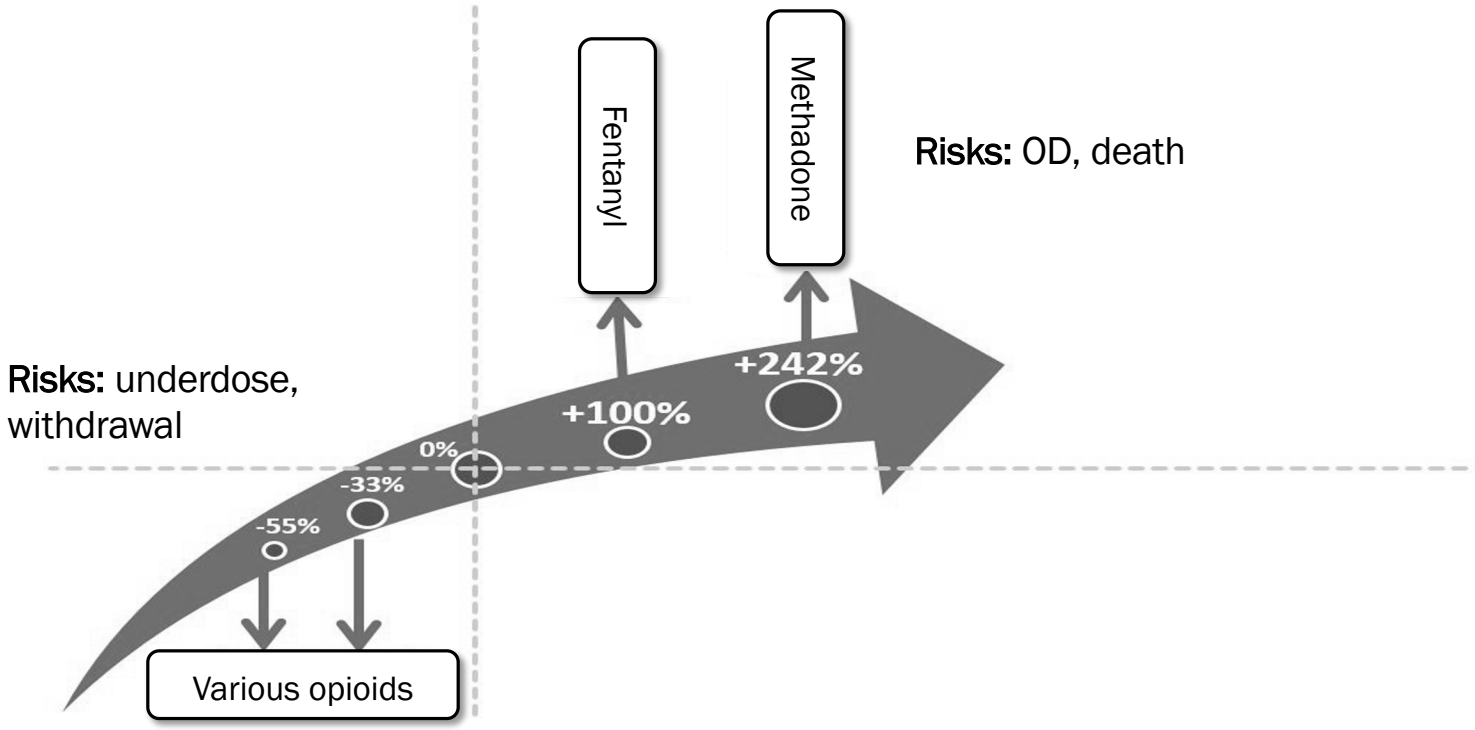
Fudin J, et al. *Pract Pain Manag*. 2012;12(8):46-51. Donner B, et al. *Pain*. 1996;64:527-534. Breitbart W, et al. *Oncology*. 2000;14:695-705. Shaw K, Fudin J. *Pract Pain Manag.* 2013;13(7):61-66. Fudin J, et al. *J Pain Res*. 2016;9:153-156.

Variability in opioid equivalence survey

Specialty	Fentanyl 75 mcg/h	Hydrocodone 80 mg	Hydromorphone 48 mg	Methadone 40 mg	Oxycodone 120 mg
Pain management (n=39)	166 ± **115** (150)	85 ± 43 (80)	191 ± 68 (192)	192 ± **111** (120)	167 ± 45 (180)
Palliative care (n=35)	168 ± 57 (150)	84 ± 17 (80)	188 ± 67 (192)	251 ± **166** (240)	154 ± 68 (180)
None of the above (n=247)	177 ± **124** (150)	88 ± 43 (80)	191 ± 50 (192)	169 ± **115** (160)	177 ± 37 (180)

Rennick A, et al. *Pain Med*. 2016;17:5:892-898.

Available online opioid conversion calculators (±) % variation (vs manual calculation)



Shaw K, Fudin J. *Pract Pain Manag*. 2013;13(7):61-66.

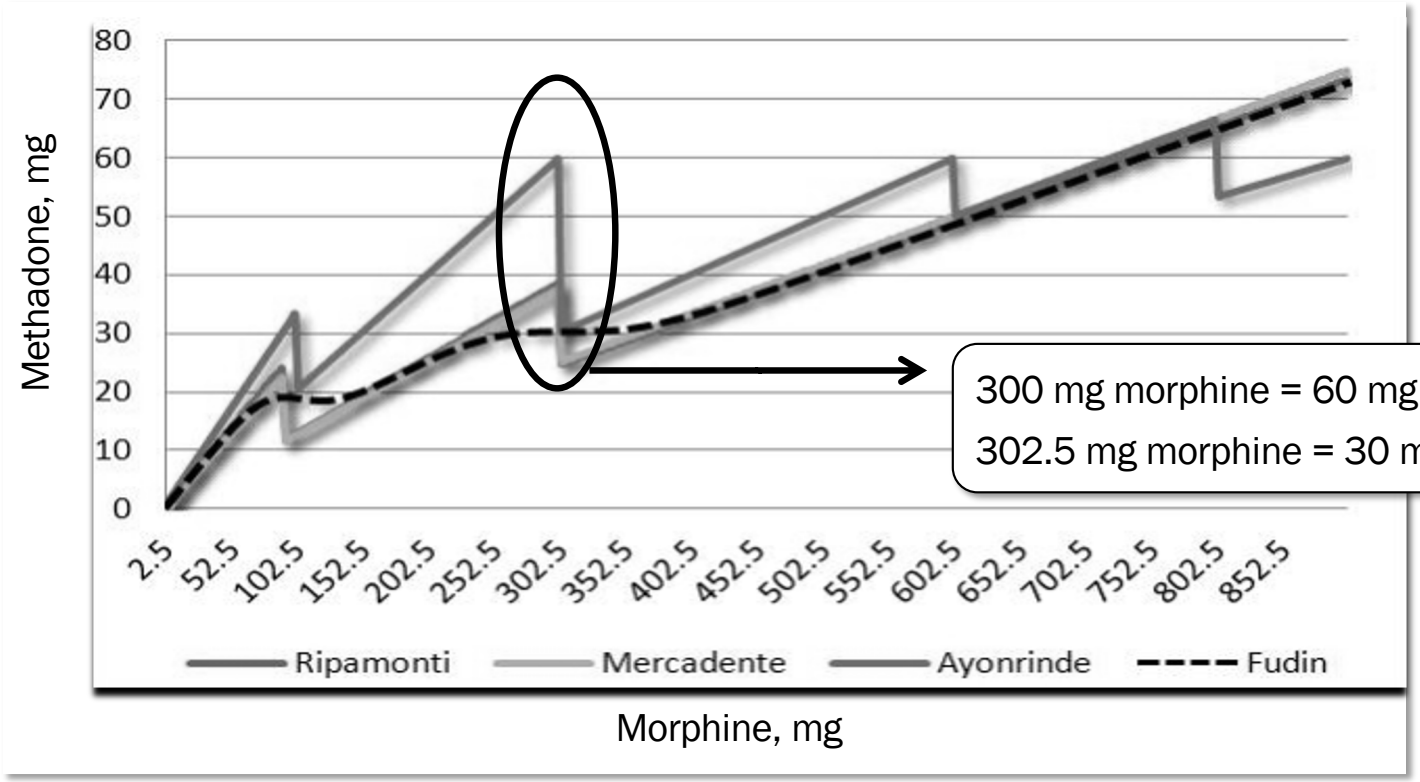
Comparison of proposed morphine-to-methadone equivalents

Ripamonti et al, 1998	Morphine dose (mg/d)	30-90		91-300		301+	
	Morphine:methadone	3.70:1		7.75:1		12.25:1	
Ayonrinde et al, 2000	Morphine dose (mg/d)	<100	101-300	301-600	601-800	801-1.000	>1.001
	Morphine:methadone	3:1	5:1	10:1	12:1	15:1	20:1
Mercadante et al, 2001	Morphine dose (mg/d)	30-90		91-300		301+	
	Morphine:methadone	4:1		8:1		12:1	
Fudin et al, 2012	$\text{Methadone (mg)} = \frac{X}{21}\left\{5.7 - 3\sin\left[\frac{90}{\left(\frac{110}{X}\right)^5 + 1}\right] - \sin\left[\frac{90}{\left(\frac{320}{X}\right)^7 + 1}\right]\right\}$ Let X = Morphine (mg)						

X, morphine (mg); **EDR,** equianalgesic dose ratio.

Fudin J, et al. *Pract Pain Manag*. 2012;12(8):46-51.

Equianalgesic doses: morphine to methadone



Special considerations for fentanyl and methadone

TD fentanyl

- Prolonged onset and steady-state achievement
- No dose increase in first 3 days after initial patch
- Titrate no more frequently than q6d
- CDC guidelines suggest limiting use of fentanyl to experts

IR fentanyl

- Should only be used for cancer-related breakthrough pain

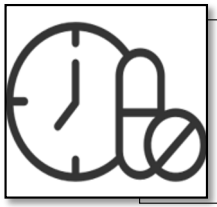
Methadone

- Titrate in doses ≤10 mg no more frequently than q3-5d
- Some patients may require longer intervals due to prolonged, variable half-life
- Prescriber must have considerable experience
- Special considerations: OD risk, interpatient variability, QT prolongation, numerous drug–drug interactions, hepatic dysfunction

TD, transdermal.

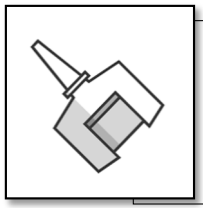
Duragesic (fentanyl transdermal system) [prescribing information]; Titusville, NJ: Janssen Pharmaceuticals Inc; 2019. Dolophine (methadone hydrochloride) [prescribing information]. Columbus, OH: Roxane Laboratories Inc; 2014. Chou R, et al. *J Pain*. 2014;15(4):321-337. Dowell D, et al. *MMWR Morb Moral Weekly Rep*. 2016;65(1):1-49. Heung Y, Reddy A. *Curr Treat Options Oncol*. 2020;21(4):30. McPherson ML. *Demystifying Opioid Conversion Calculations: A Guide For Effective Dosing*. Bethesda, MD: American Society of Health-System Pharmacists; 2018.

Key safety messages for opioid medications



Dosing instructions including daily maximum

Safe storage to reduce risk for accidental exposure by household contacts or theft

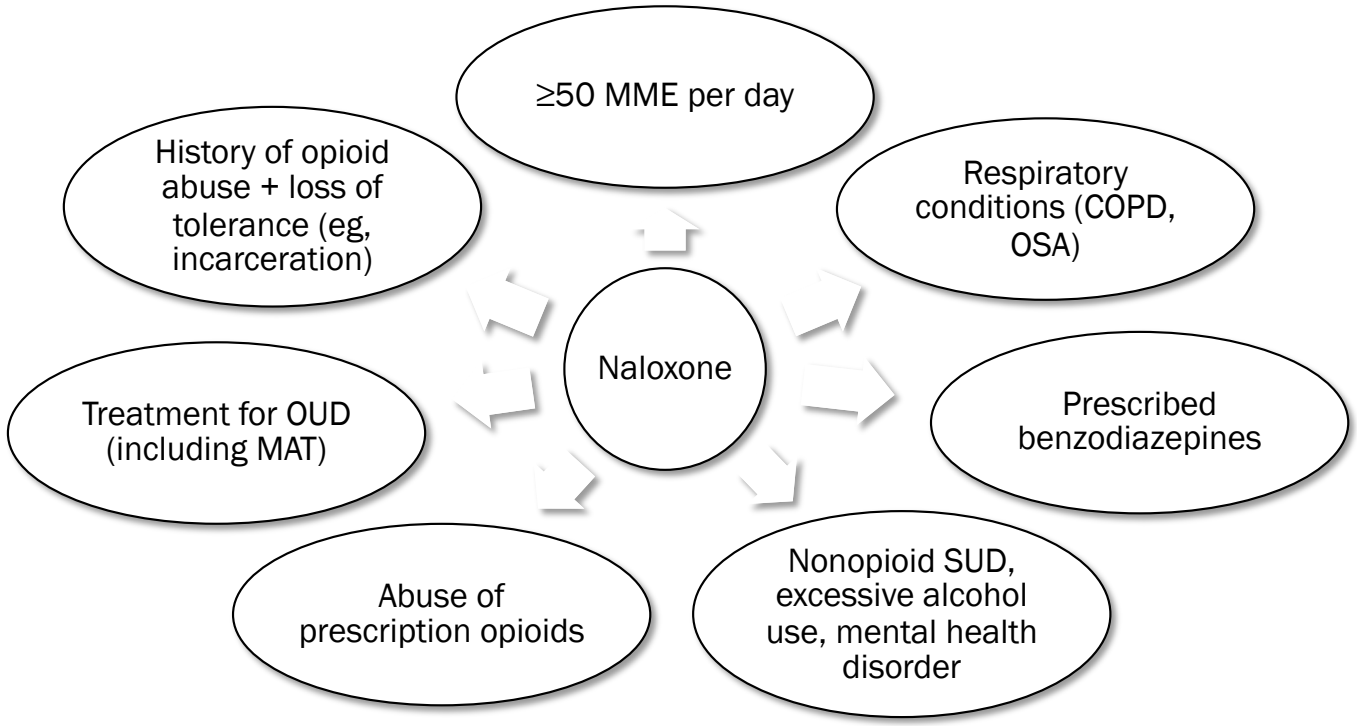


Naloxone products to reduce risk for OD deaths in patients and household contacts

Proper disposal of used (eg, TD systems) and unused opioids

Driving and work safety

Consider co-prescribing naloxone in certain clinical scenarios



MAT, medically assisted treatment; OSA, obstructive sleep apnea; SUD, substance use disorder.

US Department of Health and Human Services. www.hhs.gov/opioids/sites/default/files/2018-12/naloxone-coprescribing-guidance.pdf.

Instructions for the use of naloxone

	Nasal spray[1,2]	Prefilled syringe[3]
Concentration	4 mg/0.1 mL, 8 mg/0.1 mL	5 mg/0.5 mL
Administration	Lay the patient on their back	
	• Support back of neck to allow head to tilt up • Administer single spray into 1 nostril • Turn patient on his/her side	• Remove cap to expose needle • Hold by finger grips and insert needle slowly into thigh • For children <1 year of age, pinch thigh muscle while administering • Push plunger until click and hold 2 seconds
	Call 911	
Additional doses	If the patient does not respond or responds and then relapses into respiratory depression, may give additional doses q2-3 minutes until EMS arrives	
	Use a new device for each dose; not reusable	

EMS, emergency medical services.

1. Narcan prescribing information. Radnor, PA: Adapt Pharm, Inc; 2019; **2.** Kloxxado prescribing information. Columbus, OH: Hikma Pharmaceuticals. **3.** Zimho prescribing information. San Diego, CA: Adamis Pharmaceuticals; 2021.

Conclusion

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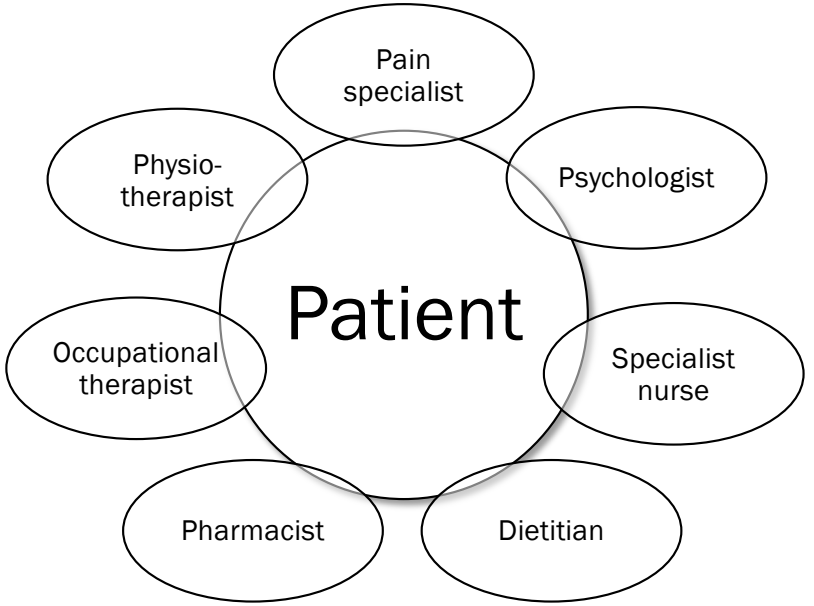
Conclusion

- Chronic pain is optimally treated in a multidisciplinary fashion
  - Patient-focused
  - Evidence-based
  - Art and science
- Opioid medications can play a role in this care in appropriately selected patients
  - Agent selection
  - Dosing, titration, conversion
  - Warnings and precautions, AEs
  - Special populations
- Risk risk mitigation is an important element
  - Multi-step process
  - Ongoing



Q&A

Thank you