Pain Management and Opioids:

Balancing Risks and Benefits

PRESENTED BY

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UPDATED JANUARY 2023

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FACULTY INFORMATION

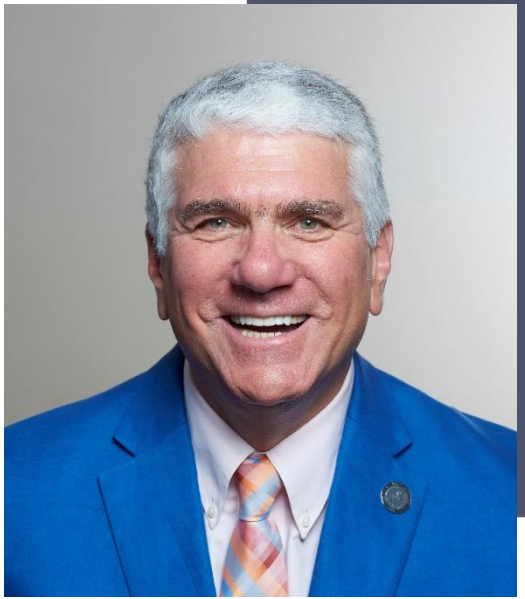
BIO: Anita Karnik, MD

Anita Karnik MD is the program director for University of Arizona College of Medicine Phoenix Addiction Medicine Fellowship. She is an addiction psychiatrist at the Phoenix VA Health Care System and practices in an integrated pain and addiction chronic pain and wellness center. She received her M.D. at Texas A&M College of Medicine and completed her general and child and adolescent psychiatry training though the Baylor Scott and White Psychiatry Residency Program. Dr. Karnik went on to further specialize in addiction psychiatry at the University of Cincinnati Addiction Psychiatry Fellowship.

DISCLOSURE:

Nothing to disclose

FACULTY INFORMATION



BIO: Edwin Salsitz, MD, DFASAM

Dr. Edwin A. Salsitz has been an attending physician in the Mount Sinai Beth Israel, Division of Chemical Dependency, New York City, since 1983, and is an Associate Clinical Professor of Psychiatry at the Mount Sinai School of Medicine. He is the principal investigator of the Methadone Medical Maintenance (office-based methadone maintenance) research project. Dr. Salsitz is certified in Addiction Medicine by the American Board of Preventive Medicine, as well as by the Board of Internal Medicine and Pulmonary Disease. He has published and lectures frequently on addiction medicine topics.

DISCLOSURE:

Nothing to disclose

ACKNOWLEDGMENTS

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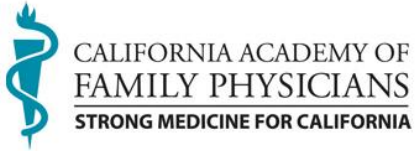
This activity is supported by an independent educational grant from the Opioid Analgesics REMS Program Companies (RPC).

Please see https://www.opioidanalgesicrems.com/Resources/Docs/List_of_RPC_Companies.pdf for a listing of REMS Program Companies. This activity is intended to be fully compliant with the Opioid Analgesic REMS education requirements issued by the U.S. Food and Drug Administration.

For more information about the Opioid Analgesics REMS visit https://opioidanalgesicrems.com/RpcUI/products.u.

THE CO*RE COLLABORATIVE



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None of the Faculty Advisors, Reviewers or Planners for this educational activity have relevant financial relationships with ineligible companies to disclose.

BY THE END OF THIS SESSION YOU WILL BE ABLE TO:

- Describe the pathophysiology of pain as it relates to the concepts of pain management.
- Accurately assess patients in pain.
- Develop a safe and effective pain treatment plan.
- Identify evidence-based non-opioid options for the treatment of pain.
- Identify the risks and benefits of opioid therapy.
- Manage ongoing opioid therapy.
- Recognize behaviors that may be associated with opioid use disorder.

WHY ARE WE HERE?

CO*RE STATEMENT

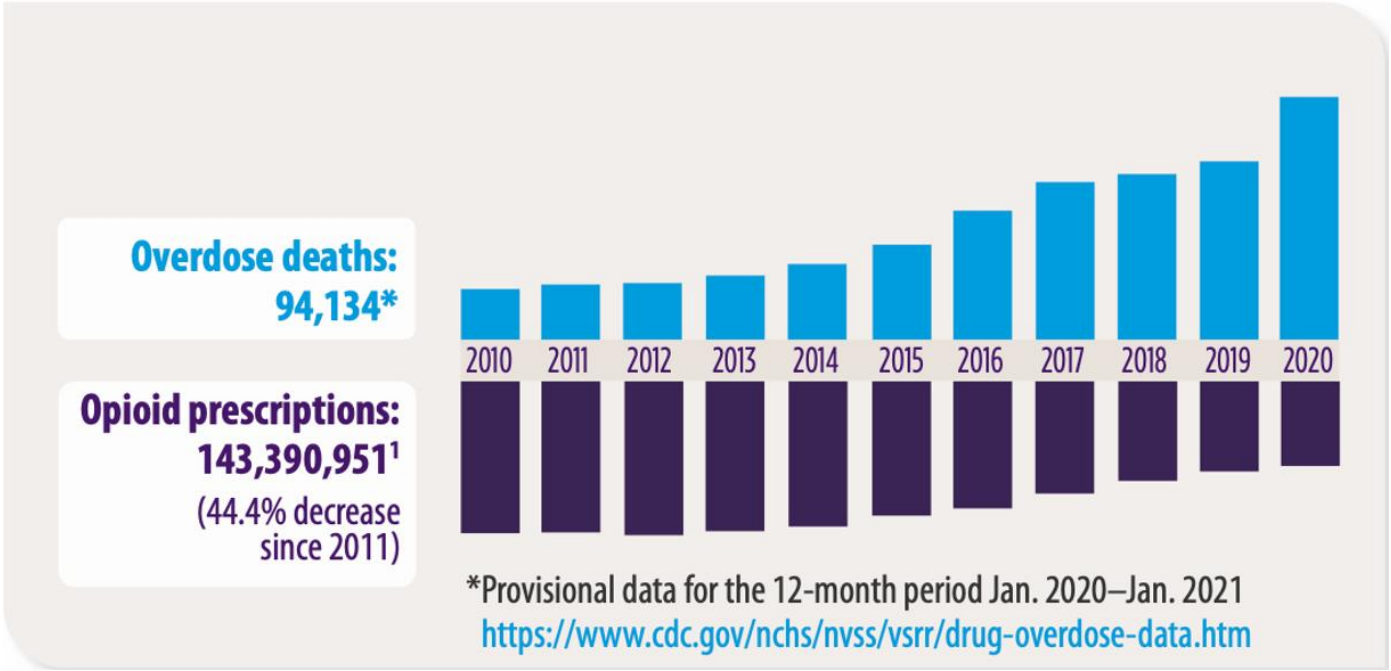
Historical over-prescribing, a massive and sustained exposure to opioids, and a gap in treatment availability have fueled the opioid overdose epidemic in the United States.

When prescribed well, and used as prescribed, opioids can be valuable tools for effective pain management.

Unintended consequences may occur from both under-prescribing (unmanaged pain) and over-prescribing (injudicious use of opioids).

This course does not advocate for or against the use of opioids. We intend to help health-care providers manage pain without putting vulnerable patients at risk for misuse or opioid use disorder. The goal
is to keep our patients, our communities, and ourselves SAFE.

REDUCTIONS IN OPIOID PRESCRIBING HAVE NOT LED TO REDUCTIONS IN OVERDOSE DEATHS



SOURCE: https://www.ama-assn.org/delivering-care/overdose-epidemic/physicians-progress-toward-ending-nation-s-drug-overdose-epidemic

TYPES OF OPIOIDS

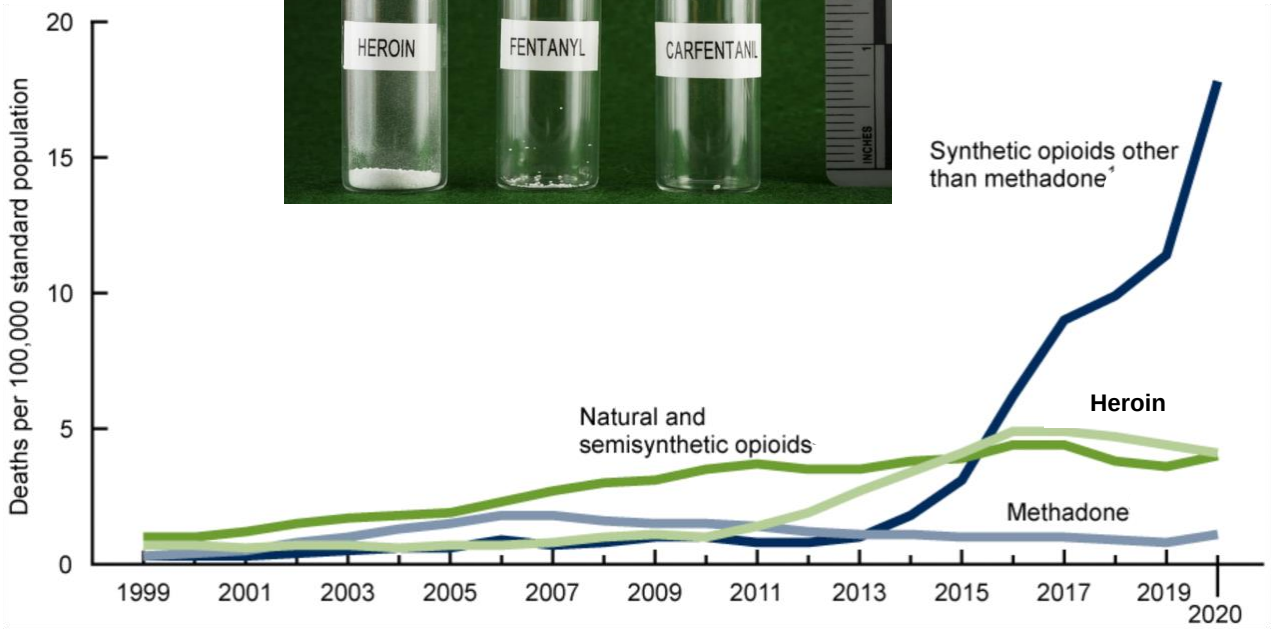
NATURALLY OCCURRING OPIATES	SEMI-SYNTHETIC OPIOIDS	SYNTHETIC OPIOIDS
Codeine Morphine	Buprenorphine Hydrocodone Hydromorphone Oxycodone Oxymorphone	Alfentanil Fentanyl Methadone Remifentanil Tapentadol
AGONISTS	**PARTIAL AGONISTS**	**ANTAGONISTS**
Codeine Methadone Morphine Oxycodone	Buprenorphine Nalbuphine	Naloxone Naltrexone

DEA SCHEDULED DRUGS

SCHEDULE	DESCRIPTION	EXAMPLES
I	High potential for abuse; no currently accepted medical use	Cannabis, ecstasy, heroin, LSD, peyote
II	High potential for abuse, which may lead to severe psychological or physical dependence	Codeine, fentanyl, hydrocodone combination products, hydromorphone, meperidine, methadone, morphine, opium, oxycodone,
III	Potential for abuse, which may lead to moderate or low physical dependence or high psychological dependence	Products containing ≤ 90 mg codeine per dose, buprenorphine, benzphetamine, phendimetrazine, ketamine, anabolic steroids
IV	“Low potential” for abuse*	Alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, tramadol
V	Low potential for abuse	Cough preparations containing ≤ 200 mg codeine/100 ml

Complete list of products covered under the Opioid Analgesic REMS available at: https://www.opioidanalgesicrems.com/products.html

OPIOID OVERDOSE DEATHS BY TYPE OF OPIOID



SOURCE: https://www.cdc.gov/nchs/images/databriefs/401-450/db428-fig4.png, https://www.cdc.gov/nchs/products/databriefs/db428.htm

PHOTO SOURCE: New Hampshire State Police Forensic Lab

FENTANYL AND FENTANYL ANALOGUES

ON THE PLUS SIDE:

- Short-acting and easily metabolized
- Useful for controlling acute pain

ON THE MINUS SIDE:

- Cheap and easy to manufacture
- Easy to store, easy to smoke, easy to conceal
- Unpredictable dosing with non-prescribed fentanyl
- Two causes of fentanyl OD death: opioid-induced respiratory depression and rigid chest wall syndrome; higher or repeated doses of naloxone are required to reverse a fentanyl overdose.

RISKS VERSUS BENEFITS OF PRESCRIBED OPIOIDS

POTENTIAL RISKS

- Life-threatening respiratory depression/overdose
- Development of SUD/OUD
- Diversion
- Inadvertent exposure to family and pets
- Interactions with other meds and substances
- Neonatal abstinence syndrome
- Physiologic dependence and withdrawal

POTENTIAL BENEFITS

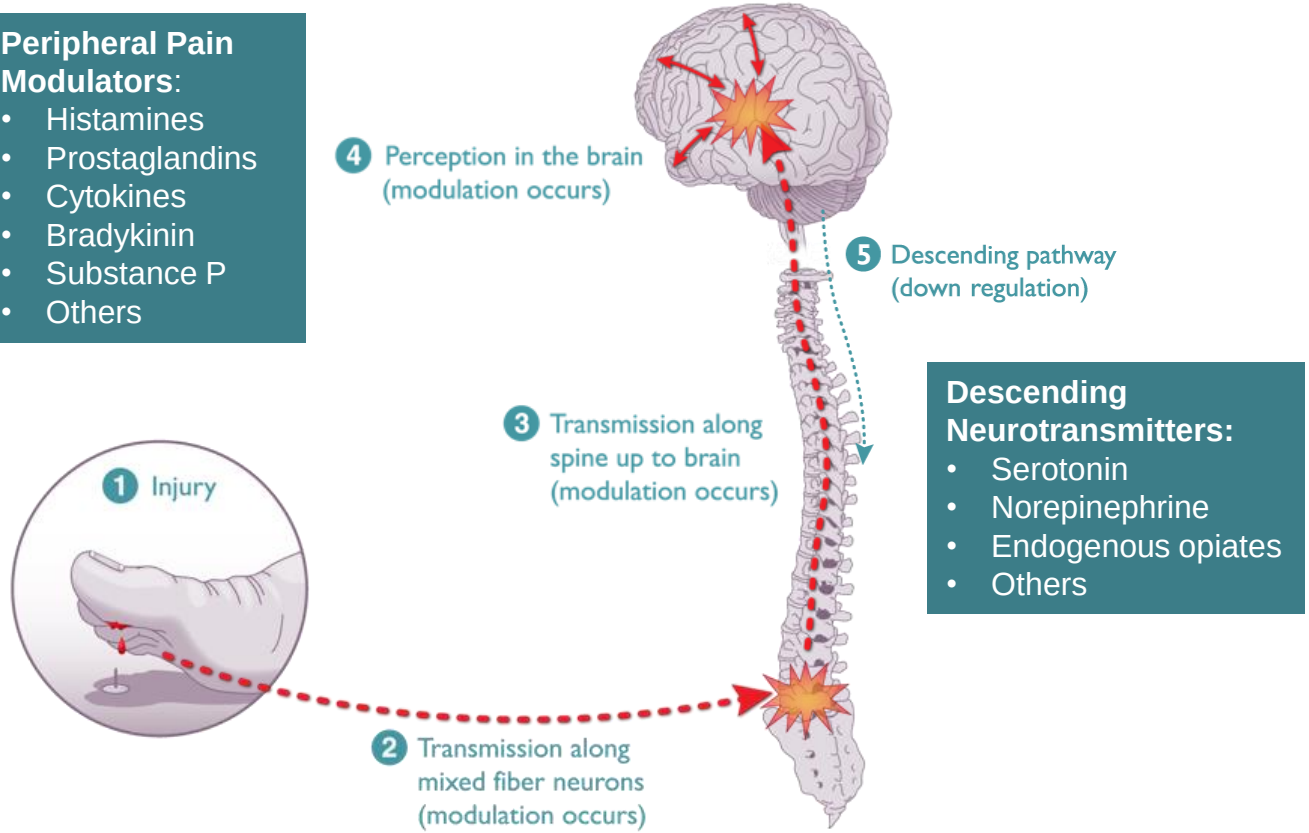
- Analgesia
- Option for patients with contraindications for non-opioid analgesics
- Relieves suffering
- May improve function and quality of life

CHAPTER 1
PAIN

Color of Pain by Dr. Kathleen A. Sluka
www.kathleenslukaart.com

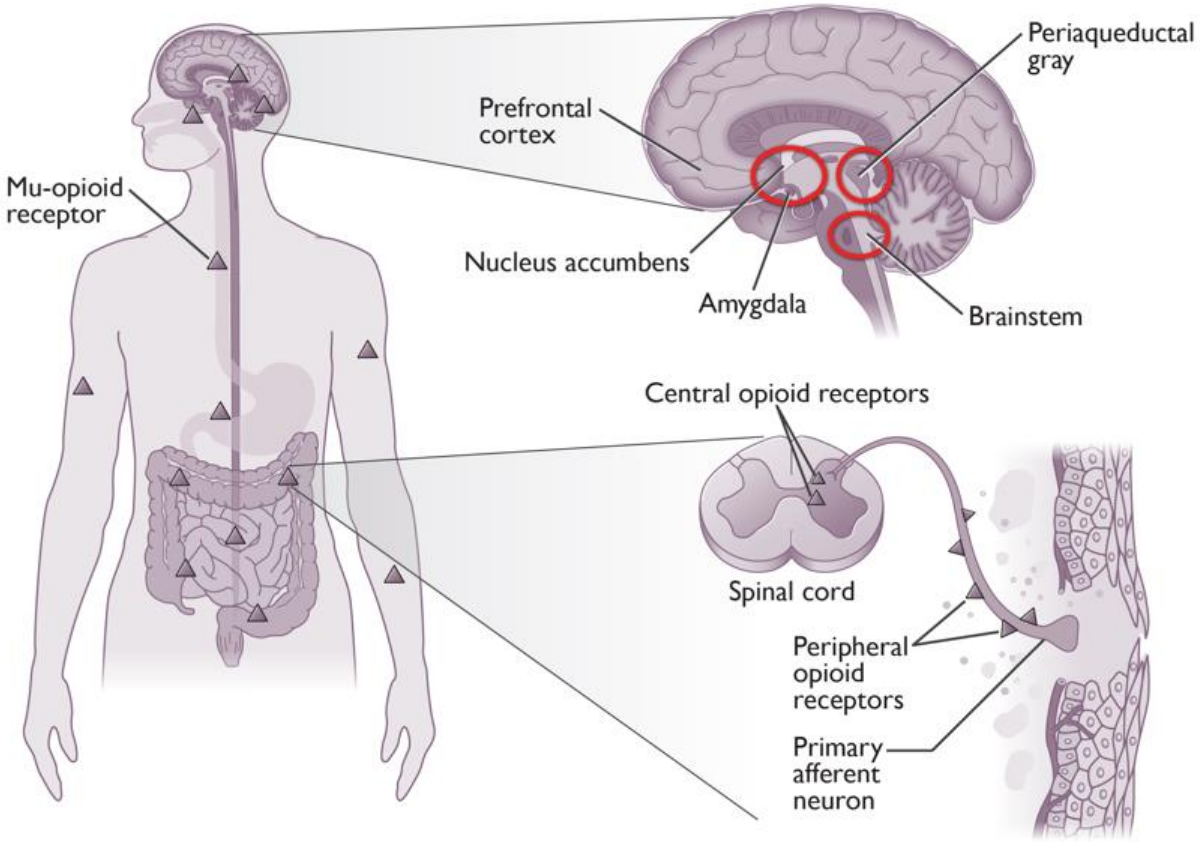
THE NEUROMECHANISMS OF PAIN

Peripheral Pain Modulators:
- Histamines
- Prostaglandins
- Cytokines
- Bradykinin
- Substance P
- Others



Descending Neurotransmitters:
- Serotonin
- Norepinephrine
- Endogenous opiates
- Others

OPIOID RECEPTOR LOCATIONS



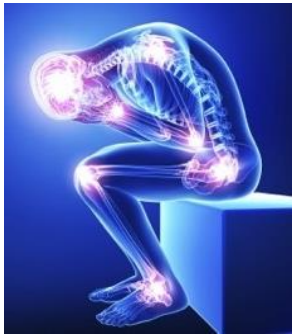
PAIN

"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage."

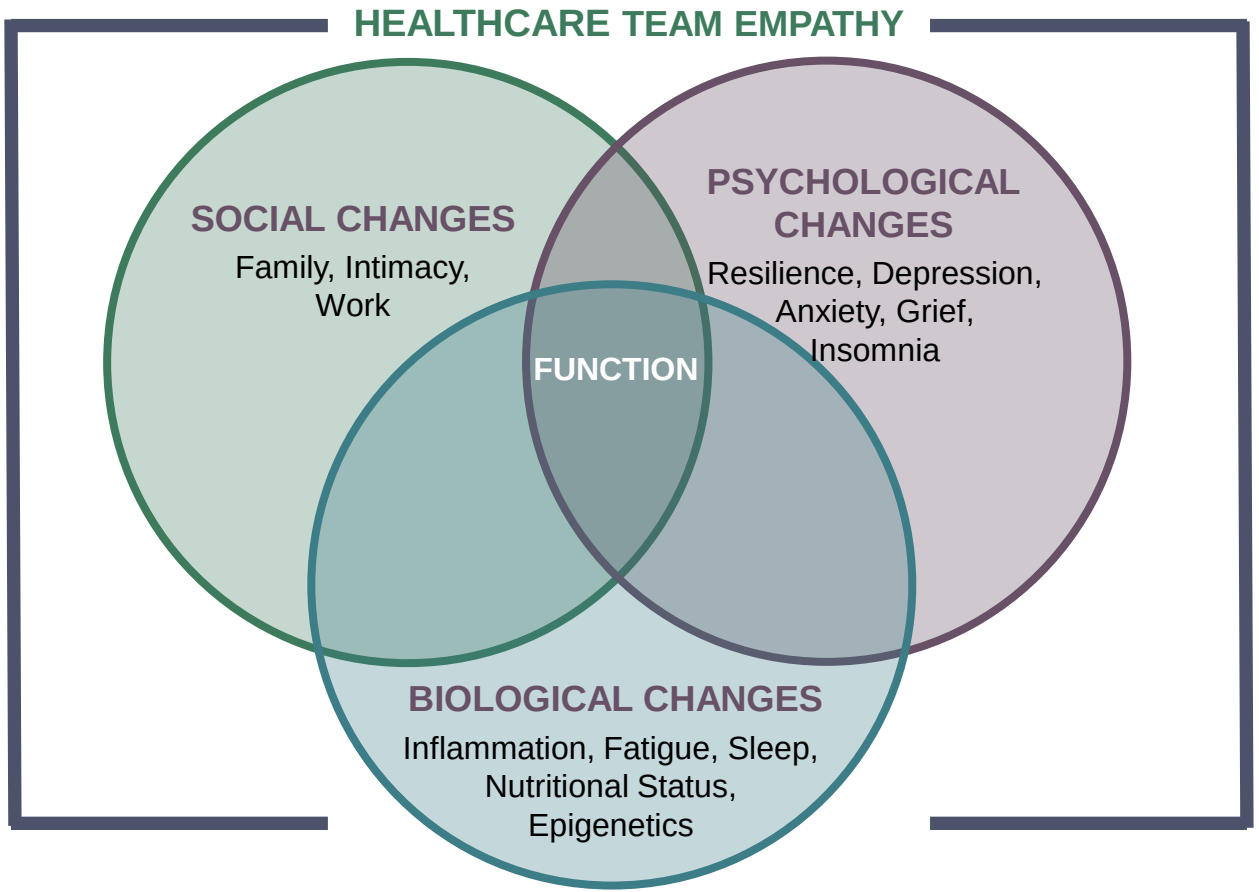
—IASP (July 2020)

ACUTE	CHRONIC
• Acute pain duration of < 1 month • Sudden onset, self-limiting • Ideally resolves with healing • Triggered by tissue damage and inflammation • Has protective value • Inflammatory mediation • **Subacute**, pain that continues for 1-3 months, can become chronic	• Lasting 3 months or longer • Generally steady-state or worsening • Persists beyond normal healing period • Serves no value • Peripheral and central sensitization

TYPES OF PAIN

NOCICEPTIVE / INFLAMMATORY	NOCIPLASTIC	NEUROPATHIC	MIXED TYPES (NOCICEPTIVE / NEUROPATHIC)
Pain in response to an injury or stimuli; *typically* acute	Pain that arises from altered nociceptive function; *typically* chronic	Pain that develops when the nervous system is damaged; chronic	Primary injury and secondary effects
Post-operative pain, sports injuries, arthritis, sickle cell disease, mechanical low back pain	Fibromyalgia, irritable bowel syndrome, nonspecific low back pain	Post-herpetic neuralgia, trigeminal neuralgia, distal polyneuropathy, CRPS, neuropathic low back pain	

THE EXPERIENCE OF PAIN: A BIOPSYCHOSOCIAL MODEL

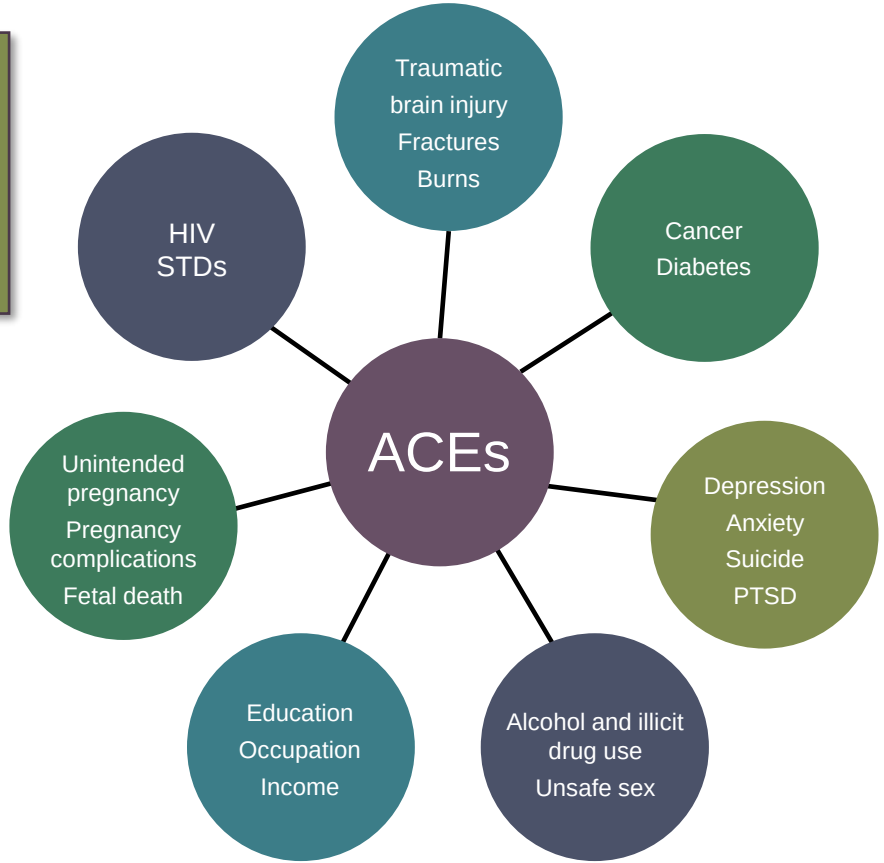


ADVERSE CHILDHOOD EXPERIENCES (ACEs)

A shift in focus…

from *“what’s wrong with this patient?”*

to *“what happened to this patient?”*



CHAPTER 2

TERMINOLOGY

WORDS MATTER: LANGUAGE CHOICE CAN REDUCE STIGMA

"*If you want to care for something, you call it a flower; if you want to kill something, you call it a weed.*"
—DON COYHIS

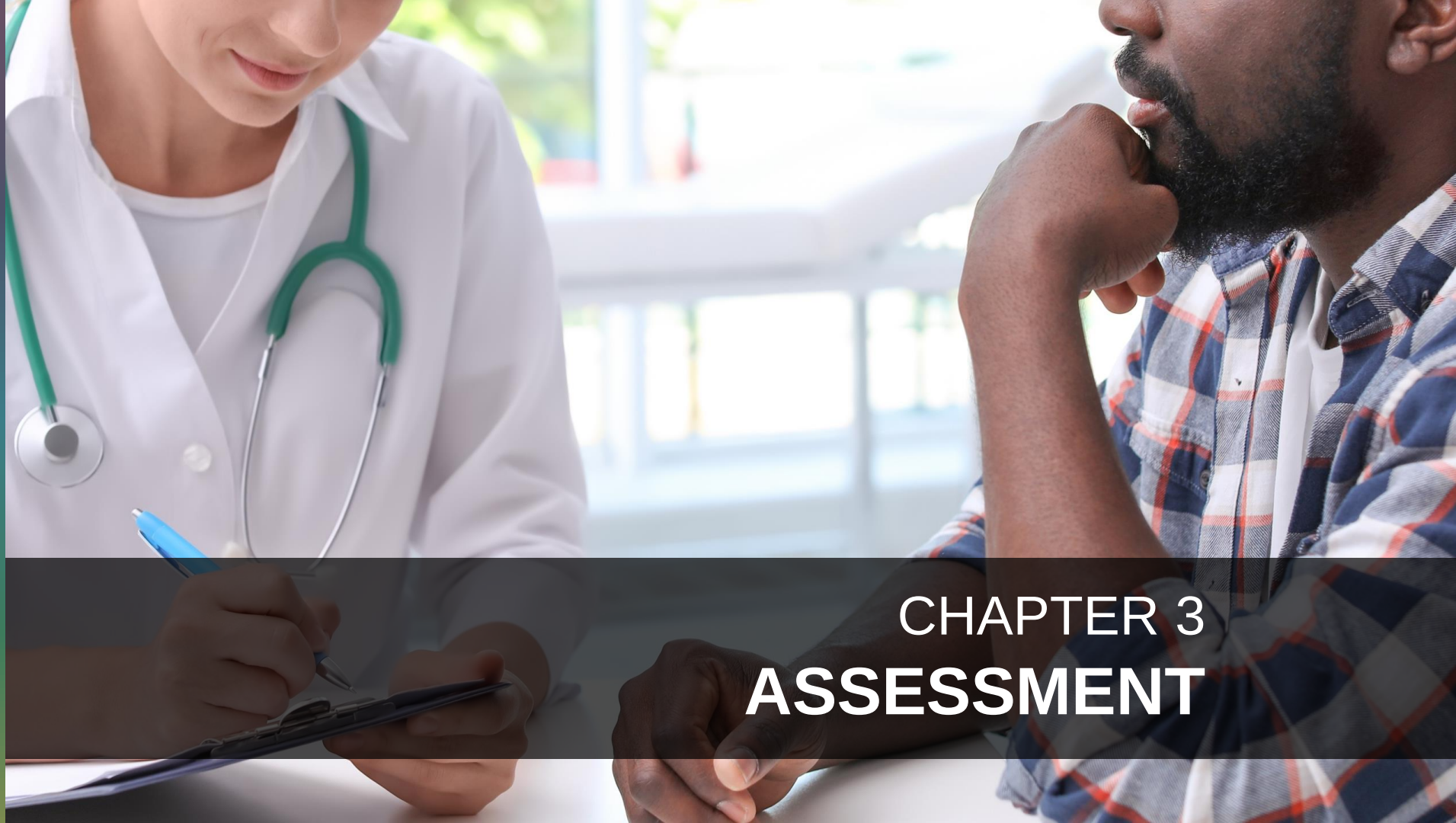
COMMONLY USED TERM	PREFERRED TERM
Addiction	Substance use disorder (SUD) or opioid use disorder (OUD) [from the *DSM-5-TR*®]
Drug-seeking, aberrant/problematic behavior	Using medication not as prescribed
Addict/user	Person with a substance use disorder (SUD) or an opioid use disorder (OUD)
Dirty urine/failing a drug test	Testing positive on a urine drug screen
Abuse or habit	Misuse or "use other than prescribed"

SOURCE: https://nida.nih.gov/research-topics/addiction-science/words-matter-preferred-language-talking-about-addiction

WORDS MATTER: DEFINITIONS

Misuse	Use of a medication in a way other than the way it is prescribed
Tolerance	Increased dosage needed to produce a specific effect
Dependence	State in which an organism only functions normally in the presence of a substance
Diversion	Transfer of a legally controlled substance, prescribed to one person, to another person for illicit (forbidden by law) use
Withdrawal	Occurrence of uncomfortable symptoms or physiological changes caused by an abrupt discontinuation or dosage decrease of a pharmacologic agent
MOUD	Medication for Opioid Use Disorder, an approach to treating Opioid Use Disorder that combines FDA-approved medication with counseling and behavioral therapies
MME	Morphine milligram equivalents; a standard opioid dose value based on morphine and its potency; allows for ease of comparison and risk evaluations
Chronic non-cancer pain (CNCP)	Any painful condition that persists for ≥ 3 months, or past the time of normal tissue healing, that is not associated with a cancer diagnosis

SOURCE: NIDA, https://nida.nih.gov/research-topics/addiction-science/words-matter-preferred-language-talking-about-addiction



CHAPTER 3

ASSESSMENT

PAIN ASSESSMENT

DESCRIPTION OF PAIN

Location

Intensity

Quality

Onset/
duration

Variations/
patterns/rhythms

WHAT RELIEVES THE PAIN?

WHAT CAUSES OR INCREASES THE PAIN?

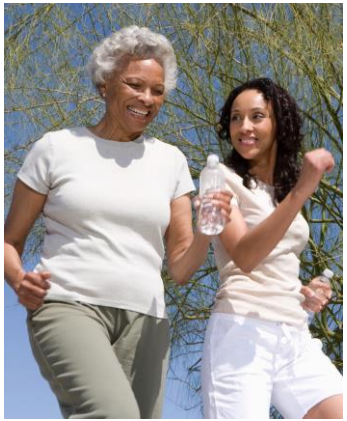
EFFECTS OF PAIN ON PHYSICAL, EMOTIONAL AND PSYCHOSOCIAL FUNCTION

PATIENT'S CURRENT LEVEL OF PAIN AND FUNCTION

SOURCE: Hogans, B., Barreveld, A. (Eds.). *Pain Care Essentials*, New York, NY: Oxford University Press. 2020.

MEDICAL AND TREATMENT HISTORY

RELEVANT ILLNESSES



PAST AND CURRENT OPIOID USE

- Query your state's Prescription Drug Monitoring Program (**PDMP)** to confirm patient report
- Contact past providers and obtain prior medical records
- For opioids currently prescribed, note the opioid, dose, regimen, and duration
- Determine whether the patient is **opioid-tolerant**

NONPHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

PHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

BARRIERS TO PREVIOUS TREATMENT STRATEGIES

PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs)

PDMP DATABASES	BENEFITS
• Reports on opioid prescriptions filled by patient • Nearly all are available online 24/7 • 54 operational PDMPs in the U.S. • In some states, prescribers are required to access; know your state laws • Will not have data on medications dispensed in OTPs	• Lower rates of prescription opioid-related hospitalization and ED visits • Reduction in “doctor shopping” • Reduction in prescribing high doses and over-prescribing • Identify drugs that increase overdose risk when taken together (such as benzodiazepines, gabapentinoids, opioids, and other sedatives)

Limitations: Often under-used, can be time consuming, will not have data on medications dispensed in OTPs, may not have access to bordering state data, lack of intuitive format, privacy issues, no national PDMP connection

Multiple prescriptions from different providers is most predictive of opioid misuse.

OBTAIN A COMPLETE SOCIAL AND PSYCHOLOGICAL HISTORY

SOCIAL HISTORY

Employment, cultural background, social network, relationship history, legal history, and other behavioral patterns

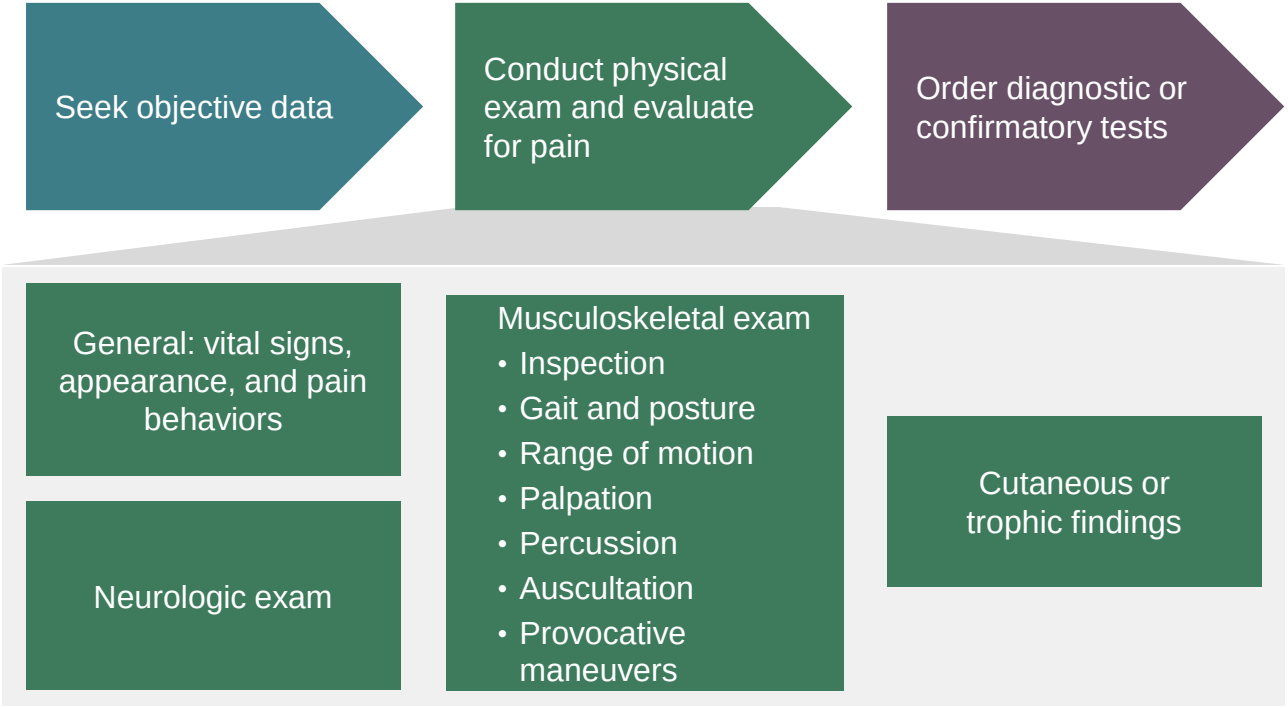
PSYCHOLOGICAL HISTORY

Screen for:

- Mental health diagnoses, depression, anxiety, PTSD, current treatments
- Alcohol, tobacco, and other drug use
- History of Adverse Childhood Experiences (ACES)
- Family history of substance use disorder and psychiatric disorders

Depression and anxiety can be predictors of chronic pain

PHYSICAL EXAM AND ASSESSMENT



SOURCE: Hogans, B., Barreveld, A. (Eds.). Pain Care Essentials, New York, NY: Oxford University Press. 2020.

PAIN ASSESSMENT TOOLBOX

http://core-rems.org/opioid-education/tools/

Pain Assessment Tools

BPI or 5 A's

Functional Assessment

SF-36, PPS, Geriatric Assessment

Pain intensity, Enjoyment of life, General activity

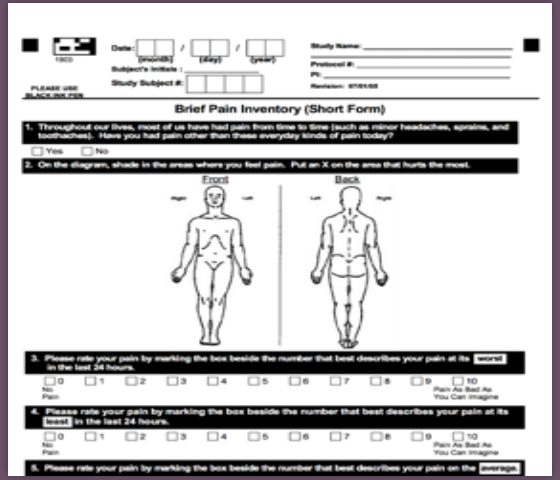
PEG

Adverse Childhood Experience Questionnaire

ACE

Assessment in Patients Unable to Self-Report

Hierarchy of Pain Assessment | **PAINAD**



Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

Yes No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

Front Back

3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average

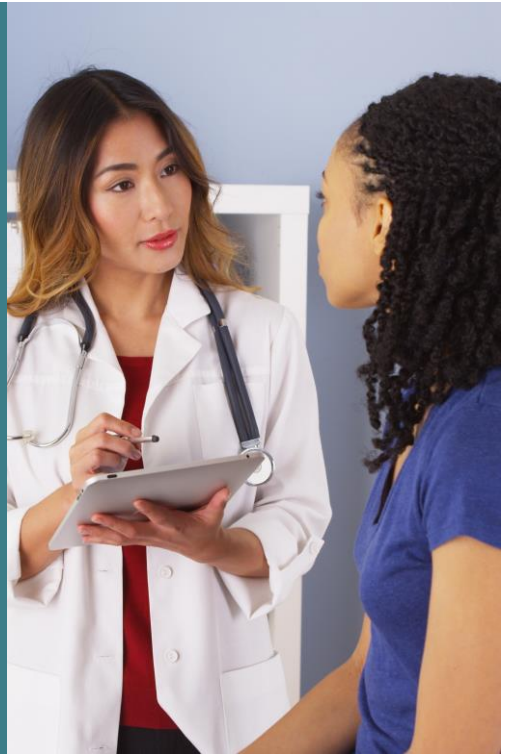
Brief Pain Inventory (BPI)

Psychological Measurement Tools (PHQ-9, GAD-7, etc.)

ASSESSMENT IS NOT A ONE-TIME OCCURRENCE

Assessment of a patient's response to pain treatment is a continual process:

- Routinely check the PDMP
- Check in with your patients
- Reassess to identify the underlying source of pain
- Investigate comorbid conditions that may arise
- Ask if patient is willing to engage with other modalities
- Modify plans as needed

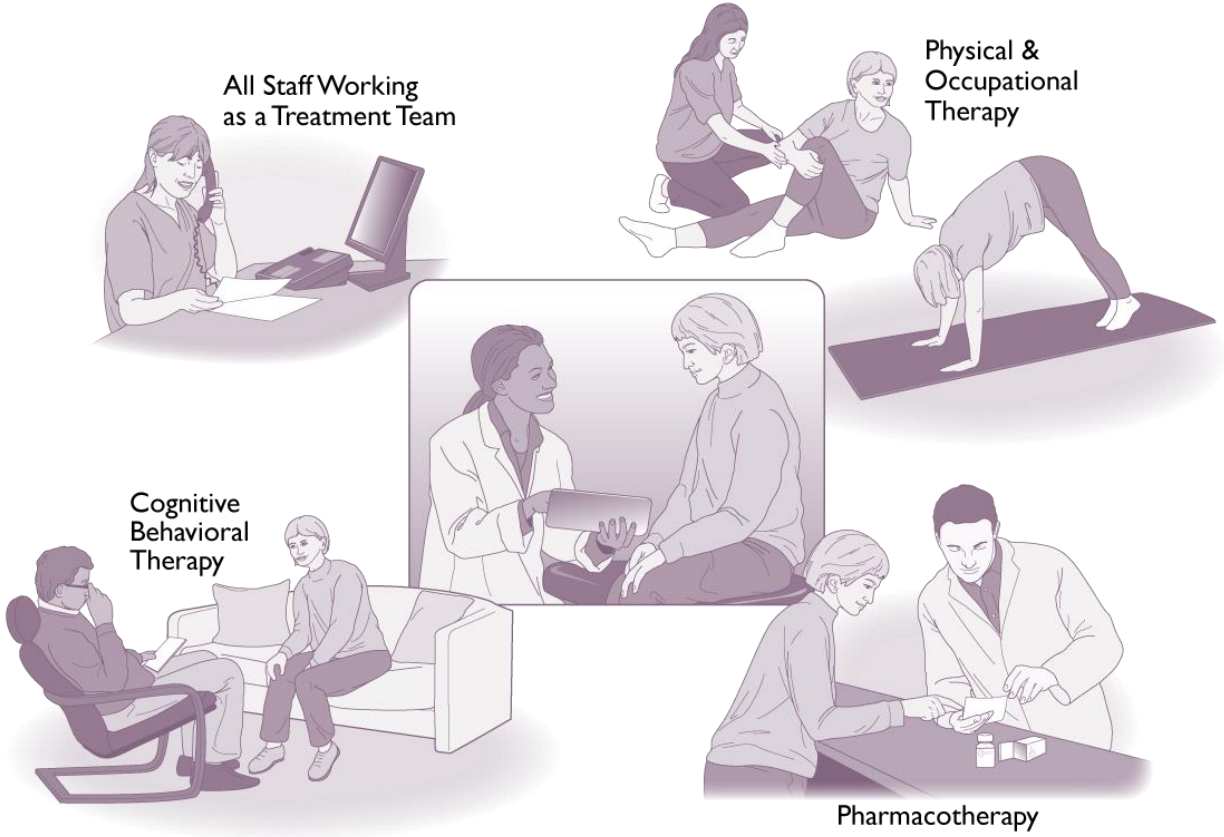


CHAPTER 4

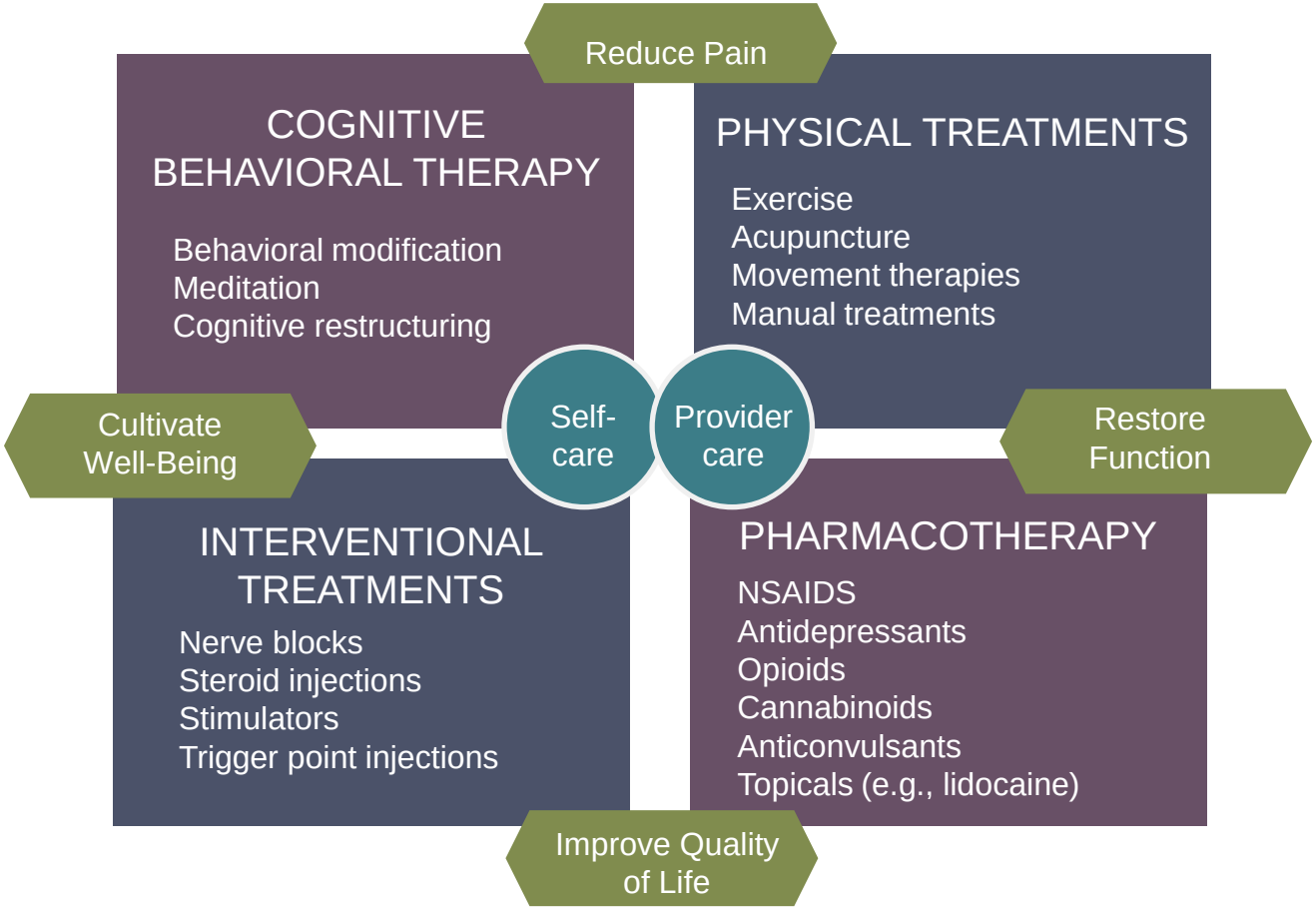
CREATING THE PAIN TREATMENT PLAN

HOW IS PAIN MANAGED?

COMPONENTS OF A MULTIMODAL TREATMENT PLAN FOR PAIN



PAIN MANAGEMENT GOALS AND TREATMENT OPTIONS: A MULTIMODAL APPROACH



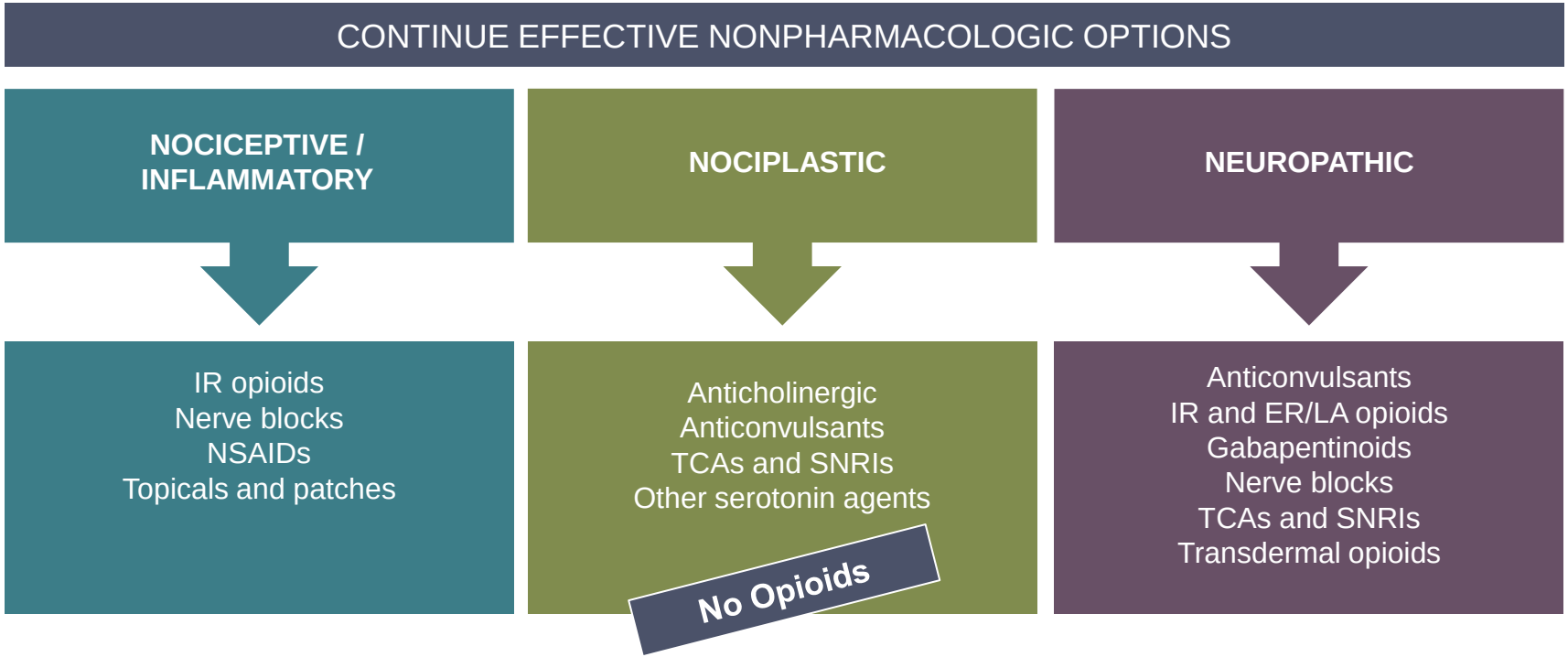
EVIDENCE-BASED NONPHARMACOLOGIC TREATMENTS

What is appropriate for your patient?

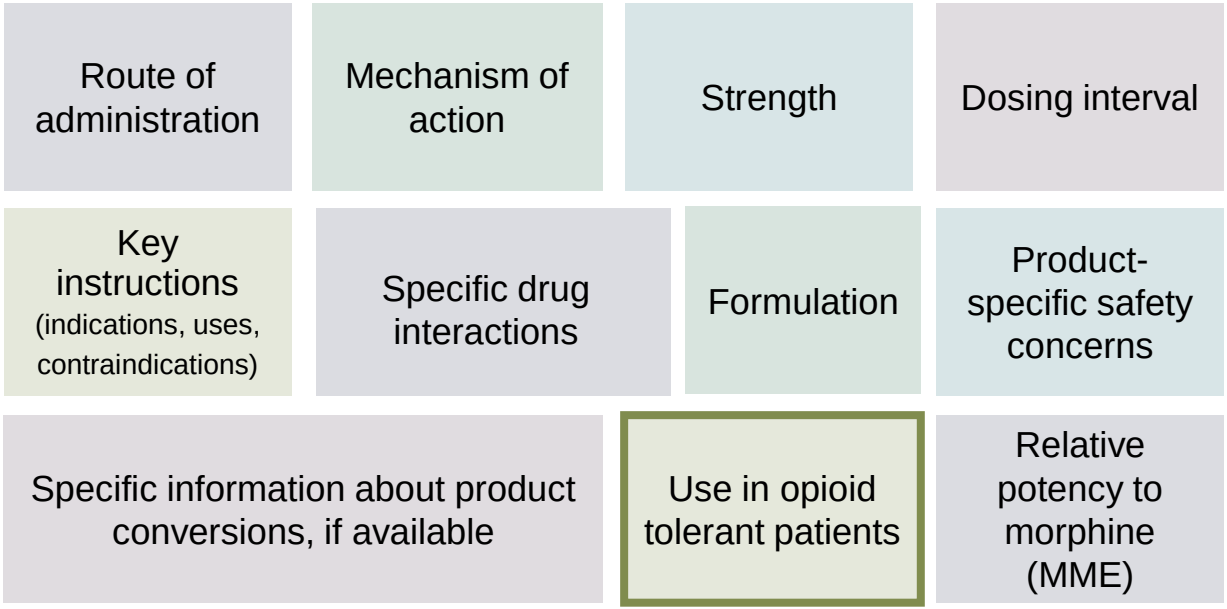
- Tai Chi
- Yoga
- CBT and ACT
- Acupuncture
- PT/OT/aquatic
- Mindfulness meditation
- OMT
- Massage therapy
- Chiropractic
- Neuromodulation or surgical approaches (in some situations)

CBT = cognitive behavioral therapy; ACT = acceptance commitment therapy; OMT = osteopathic manipulative therapy

PHARMACOLOGIC TREATMENTS BY TYPE OF PAIN



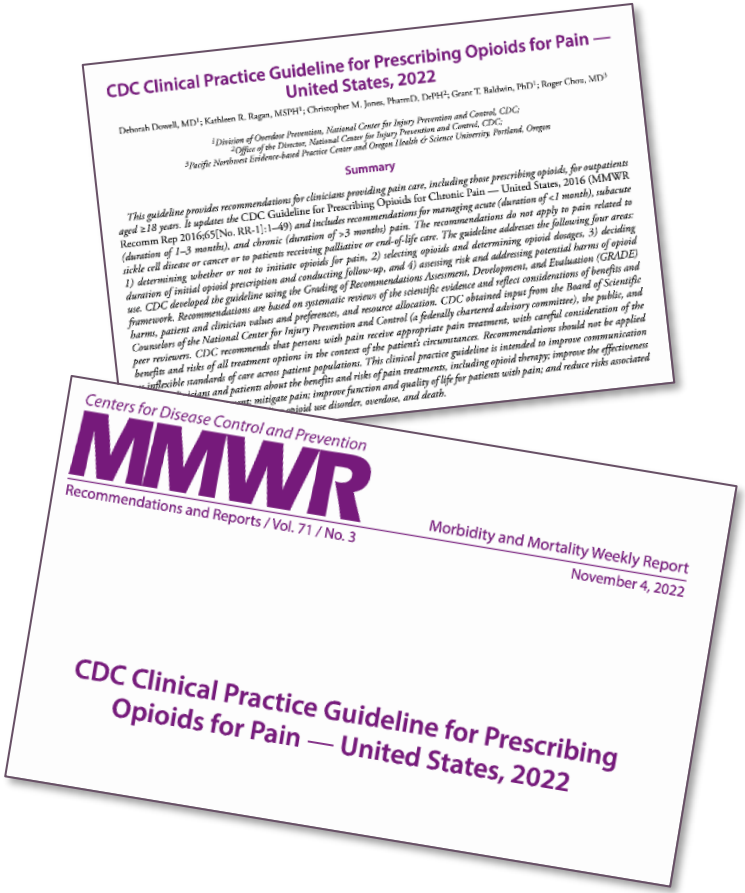
DRUG CHARACTERISTICS TO CONSIDER BEFORE PRESCRIBING



Opioid product information available at https://opioidanalgesicrems.com/products.html.

2022 CDC GUIDELINE

- Clinician recommendations for patients aged ≥18 years
- Summary of current research
- Flexible; encourages patient-centered decision making
- Emphasizes the importance of the individual & clinical judgement
- This is a clinical tool, not a law, regulation or policy



https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm

2022 CDC GUIDELINE: WHAT'S NEW?

- Broader Clinical Audience
- More delineation between initial & ongoing opioid therapy
- Revised and expanded guidance on opioid tapering
- Expanded guidance on nonopioid options for pain
- Opioid dosage guidance was updated regarding:
  - Suggestions for the lowest starting dose for opioid-naïve patients.
  - Morphine milligram equivalent doses for commonly prescribed opioids.
  - The approach to potential dosage increases, emphasizing principles of safe and effective pain treatment that allow for individual circumstances and flexibility in care.

https://www.cdc.gov/opioids/healthcare-professionals/prescribing/guideline/whats-changed.html

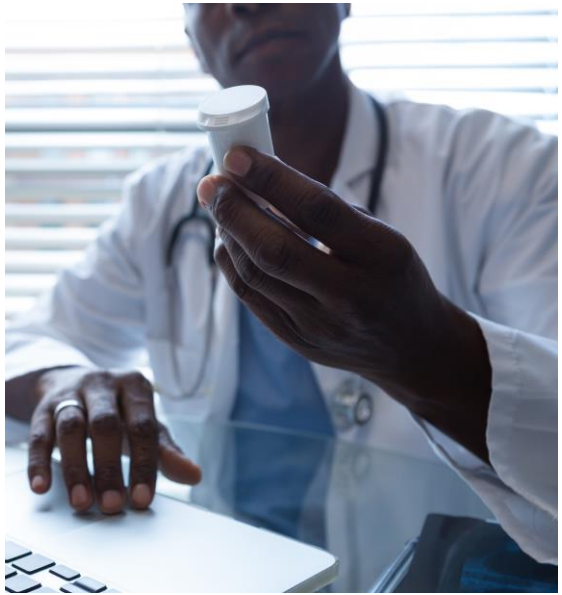
CO*RE

CONSIDER AN OPIOID ONLY WHEN:

Potential benefits are likely to outweigh risks

Patient has failed to adequately respond to non-opioid and nonpharmacological interventions

Patient has moderate to severe nociceptive or neuropathic pain



Begin as a therapeutic trial

SOURCES: Chou R, et al. J Pain. 2009;10:113-130. Department of Veterans Affairs, Department of Defense. VA/DoD Clinical Practice Guideline for Management of Opioid Therapy for Chronic Pain. 2017.

OPIOID MISUSE RISK ASSESSMENT TOOLS

http://core-rems.org/opioid-education/tools/

TOOLS FOR PATIENTS CONSIDERED FOR OPIOID THERAPY
ORT-OUD Opioid Risk Tool
SOAPP® Screener and Opioid Assessment for Patients with Pain
DIRE Diagnosis, Intractability, Risk, and Efficacy score

TOOLS FOR SUBSTANCE USE DISORDER
CAGE-AID Cut down, Annoyed, Guilty, Eye-Opener tool, Adapted to Include Drugs
TAPS Tobacco, Alcohol, Prescription Medication and Other Substances Tool
DAST Drug Abuse Screening Test
CTQ Childhood Trauma Questionnaire
ACEs Adverse Childhood Experiences

A CLOSER LOOK AT THE ORT-OUD

Opioid Risk Tool – OUD (ORT-OUD)

This tool should be administered to patients upon an initial visit prior to beginning or continuing opioid therapy for pain management. A score of 2 or lower indicates low risk for future opioid use disorder; a score of >/= 3 indicates high risk for opioid use disorder.

Mark each box that applies	YES	NO
Family history of substance abuse		
Alcohol	1	0
Illegal drugs	1	0
Rx drugs	1	0
Personal history of substance abuse		
Alcohol	1	0
Illegal drugs	1	0
Rx drugs	1	0
Age between 16-45 years	1	0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	1	0
Depression	1	0
Scoring totals		

SOURCE: Cheatle, M., et al. J Pain 2019; Jan 26.

Substance use disorder history does not prohibit treatment with opioids but may require additional monitoring and expert consultation or referral.

Scoring:

- **≤ 2: low risk**
- **≥ 3: high risk**

OPIOID SIDE EFFECTS AND ADVERSE EVENTS

SIDE EFFECTS	ADVERSE EVENTS
Respiratory depression	Death
Opioid-induced constipation (OIC) (most common)	Addiction
Myoclonus (twitching or jerking)	Overdose
Sedation, cognitive impairment	Hospitalization
Sweating, miosis, urinary retention	Disability or permanent damage
Allergic reactions	Falls or fractures
Hypogonadism	
Tolerance, physical dependence, hyperalgesia	

Prescribers should report serious AEs and medication errors to the FDA:
https://www.fda.gov/media/76299/download or 1-800-FDA-1088

OPIOID-INDUCED RESPIRATORY DEPRESSION

MORE LIKELY TO OCCUR:

- In elderly, cachectic, or debilitated patients
- If given concomitantly with other drugs that depress respiration (such as benzodiazepines*)
- In patients who are opioid-naïve or have just had a dose increase
- In patients with conditions causing respiratory compromise

HOW TO REDUCE RISK:

- Ensure proper dosing and titration
- **Do not overestimate** dose when converting dosage from another opioid product
  - Can result in fatal overdose with first dose
- Avoid co-prescribing benzodiazepines*
- Instruct patients to swallow tablets/capsules whole
  - Dose from cut, crushed, dissolved, or chewed tablets/capsules may be fatal, particularly in opioid-naïve individuals

***Greatest risk of respiratory depression**

DRUG INTERACTIONS COMMON TO OPIOIDS

Other CNS Depressants

- Increased risk of respiratory depression, hypotension, profound sedation, or coma
- Reduce initial dose

Partial Agonists* or Mixed Agonist/Antagonists†

- Use caution with full opioid agonist
- May reduce analgesic effect and/or precipitate withdrawal

Skeletal Muscle Relaxants

- Concurrent use may enhance neuromuscular blocking action and increase respiratory depression

Anticholinergic Medication

- Concurrent use increases risk of urinary retention and severe constipation
- May lead to paralytic ileus

*Buprenorphine; †Pentazocine, nalbuphine, butorphanol

FOR SAFER USE: KNOW DRUG INTERACTIONS, PHARMACODYNAMICS, AND PHARMACOKINETICS

CNS depressants can potentiate sedation and respiratory depression (e.g., benzodiazepines, gabapentin)

Some ER/LA products rapidly release opioid (dose dump) when exposed to alcohol

Some drug levels may increase without dose dumping

Opioid use with MAOIs may increase respiratory depression

Certain opioids with MAOIs can cause serotonin syndrome (e.g., tramadol)

Opioid use can reduce efficacy of diuretics

Inducing release of antidiuretic hormone

Many opioids can prolong QTc interval, check the PI;
methadone requires extra caution

Drugs that inhibit or induce CYP enzymes can increase
or lower blood levels of
some opioids

OPIOIDS AND CYP450 ENZYME INTERACTIONS

Metabolism of several commonly used opioids occurs through the cytochrome P450 system

Be aware of potential inhibitors (e.g., macrolides, azole antifungals) and inducers (e.g., carbamazepine)

Genetic and phenotypic variations in patient response to certain opioids

Refer to product-specific information in the drug package insert before prescribing

SOURCE: https://dailymed.nlm.nih.gov/dailymed/index.cfm

TRANSDERMAL/TRANSMUCOSAL DOSAGE FORMS

Do not cut, damage, chew, or swallow

Prepare skin: clip (not shave) hair and wash area with water

Rotate location of application

Do not apply buccal film products if film is cut, damaged, or changed in any way—use the entire film

Note that metal foil backings are not safe for use in MRIs

Monitor patients with fever for signs or symptoms of increased opioid exposure

Note that exertion or exposure to external heat can lead to fatal overdose


SPECIAL
POPULATIONS

OLDER ADULTS

RISK FOR RESPIRATORY DEPRESSION

- Age-related changes in distribution, metabolism, excretion; absorption less affected

ACTIONS

- Monitor
  - Initiation and titration
  - Concomitant medications (polypharmacy)
  - Falls risk, cognitive change, psychosocial status
- Reduce starting dose to 1/3 to 1/2 the usual dosage in debilitated, non-opioid-tolerant patients
- Start low, go slow, but GO
- Routinely initiate a bowel regimen
- Patient and caregiver reliability/risk of diversion

SOURCEs: American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. J Am Geriatr Soc. 2009;57:1331-46; Chou R, et al. J Pain. 2009;10:113-30.

WOMEN OF CHILDBEARING POTENTIAL

Neonatal opioid withdrawal syndrome is a potential risk of opioid therapy

GIVEN THIS POTENTIAL RISK, CLINICIANS SHOULD:

- Discuss family planning, contraceptives, breastfeeding plans with patients
- Counsel women of childbearing potential about risks and benefits of opioid therapy during pregnancy and after delivery
- Encourage minimal/no opioid use during pregnancy, unless potential benefits outweigh risks to fetus
- Refer to a qualified provider who will ensure appropriate treatment for the baby

- Perform universal screening to avoid neonatal opioid withdrawal syndrome (NOWS)

- **For women using opioids on a daily basis, ACOG recommends buprenorphine or methadone**

ACOG = American College of Obstetricians and Gynecologists

SOURCES: Chou R, et al. J Pain. 2009;10:113-30; ACOG Committee on Obstetric Practice, August 2017

CHILDREN AND ADOLESCENTS

HANDLE WITH CARE: JUDICIOUS AND LOW-DOSE USE OF IR FOR BRIEF THERAPY

THE SAFETY AND EFFECTIVENESS OF MOST OPIOIDS ARE UNESTABLISHED

- Pediatric analgesic trials pose challenges
- Transdermal fentanyl approved in children ≥ 2 years
- Oxycodone ER dosing changes for children ≥ 11 years

ER/LA OPIOID INDICATIONS ARE PRIMARILY LIFE-LIMITING CONDITIONS

WHEN PRESCRIBING ER/LA OPIOIDS TO CHILDREN:

- Consult pediatric palliative care team or pediatric pain specialist or refer to a specialized multidisciplinary pain clinic

SOURCES: Berde CB, et al. *Pediatrics.* 2012;129:354-364; Gregoire MC, et al. Pain Res Manag 2013;18:47-50; Mc Donnell C. Pain Res Manag. 2011;16:93-98; Slater ME, et al. Pain Med. 2010;11:207-14.

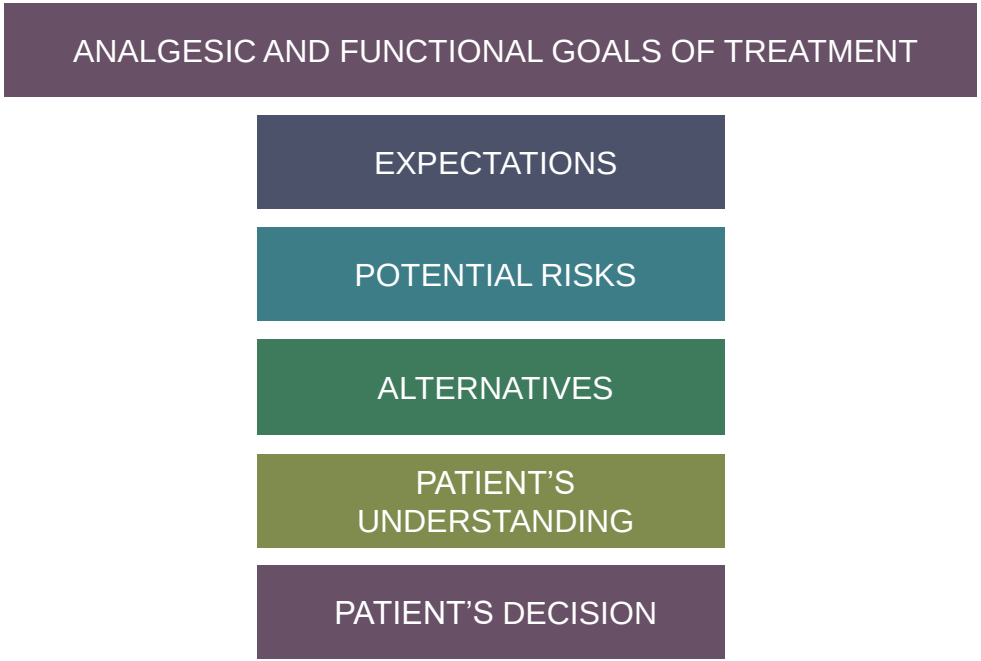
OTHER POPULATIONS NEEDING SPECIAL TREATMENT CONSIDERATIONS

Persons with…

- Sleep disorders or sleep-disordered breathing (sleep apnea)
- Dementia/nonverbal patients
- Obesity
- Renal/hepatic impairment
- Psychiatric disorders
- Life-limiting illness
- Substance use disorder

INFORMED CONSENT

When initiating a pain treatment plan, confirm patient understanding of informed consent to establish:



OPTIMIZING PATIENT CARE THROUGH TELEHEATH

New CO*RE CE/CME Module

- Series of four short videos
- Help HCPs conduct successful telehealth patient visits
- Available online https://learningipma.org

PATIENT PROVIDER AGREEMENT (PPA)

Reinforce Expectations For Appropriate And Safe Opioid Use

- Clarify treatment plans and goals
- One prescriber
- Consider one pharmacy
- Safeguards
  - Do not store in medicine cabinet
  - Keep locked (medication safe)
  - Do not share or sell
- Instructions for disposal when no longer needed
- Prescriber notification for any event resulting in a pain medication prescription
- Follow-up plan
- Monitoring
  - Random urine drug test (UDT) and pill counts
- Refill procedure
- Identify behaviors indicating need for discontinuation
- Exit strategy
- Signed by both

PATIENT PROVIDER AGREEMENT NONADHERENCE

Behavior outside the boundaries of agreed-on treatment plan

- Unsanctioned dose escalations or other noncompliance with therapy on 1 or 2 occasions
- Unapproved use of the drug to treat another symptom
- Openly acquiring similar drugs from other medical sources

- Multiple dose escalations or other noncompliance with therapy despite warnings
- Prescription forgery
- Obtaining prescription drugs from nonmedical sources

Any of the above behaviors merits **investigation**: proceed with caution

CHAPTER 5

MANAGING PATIENTS ON OPIOID ANALGESICS

INITIATING OPIOIDS

- Begin a therapeutic trial with an immediate release (IR) opioid
- Prescribe the lowest effective dosage
- Use caution at any dosage, but particularly when:
  - Anytime the opioid dose is increased
  - Carefully justify a decision to titrate dosage to ≥ 50 MME/day
- Always include dosing instructions, including daily maximum
- Be aware of interindividual variability of response
- Have PPA, baseline UDT, and informed consent in place
- Co-prescribe naloxone and bowel regimen
- Re-evaluate risks/benefits within 1–4 weeks (could be as soon as 3–5 days) of initiation or dose escalation
- Re-evaluate risks/benefits every 1–3 months; if benefits do not outweigh harms, optimize other therapies and work to taper and discontinue

There are differences in benefits, risks, and expected outcomes for patients with chronic pain and cancer pain, as well as for hospice and palliative care patients.

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ONGOING AND LONG-TERM MANAGEMENT OF PATIENTS ON OPIOID ANALGESICS

PERIODIC REVIEW OF PAIN

- Is the patient making progress toward functional goals?
- Reset goals if required or indicated; develop reasonable expectations
- Monitor for breakthrough pain
- Review adverse events/side effects at each visit
  - Evaluate bowel function
  - Screen for endocrine function as needed
  - Report adverse events to the FDA website
  - Implement opioid rotation, as indicated

Prescribers should report serious AEs and medication errors to the FDA:
https://www.fda.gov/media/76299/download or 1-800-FDA-1088

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ONGOING AND LONG-TERM MANAGEMENT OF PATIENTS ON OPIOID ANALGESICS

MONITORING FOR SAFETY

- Check Prescription Drug Monitoring Program (PDMP)
- Use urine drug testing (UDT)
- Reassess risk of substance use disorder (SUD) and/or OUD
- Monitor adherence to the treatment plan
  - Medication reconciliation
  - Evaluate for nonadherence

DISCONTINUING AND TAPERING

- When is opioid therapy no longer necessary?

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MONITORING PAIN AND SUBSTANCE USE DISORDER

PAIN – 5 A's	SUD – 5 C's
• **A**nalgesia • **A**ctivity/Function • **A**berrant/Problematic behavior, not present • **A**dverse events • **A**ffect	• **C**ontrol, loss of • **C**ompulsive use • **C**raving drug • **C**ontinued use • **C**hronic problem

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WHEN TO MOVE FROM IR TO ER/LA OPIOIDS

PRIMARY REASONS

- Maintain stable blood levels (steady state plasma)
- Longer duration of action
- Multiple IR doses needed to achieve effective analgesia
- Poor analgesic efficacy despite dose titration
- Less sleep disruption

OTHER POTENTIAL REASONS

- Patient desire or need to try a new formulation
- Cost or insurance issues
- Adherence issues
- Change in clinical status requiring an opioid with different pharmacokinetics
- Problematic drug-drug interactions

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CONSIDERATIONS FOR CHANGE FROM IR TO ER/LA OPIOIDS

DRUG AND DOSE SELECTION IS CRITICAL

Some ER/LA opioids or dosage forms are only recommended for opioid tolerant patients

- ANY strength of transdermal fentanyl or hydromorphone ER
- Certain strengths/ doses of other ER/LA products (check drug prescribing information)

MONITOR PATIENTS CLOSELY FOR RESPIRATORY DEPRESSION

- Especially within 24–72 hours of initiating therapy and increasing dosage

INDIVIDUALIZE DOSAGE BY TITRATION BASED ON EFFICACY, TOLERABILITY, AND PRESENCE OF ADVERSE EVENTS

- Check ER/LA opioid product PI for minimum titration intervals
- Supplement with IR analgesics (opioid and non-opioid) if pain is not controlled during titration

SOURCES: Chou R, et al. J Pain. 2009;10:113-130; FDA. Education Blueprint Healthcare Providers Involved in the Treatment and Monitoring of Patients with Pain 09/2018, https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf

EMERGENCE OF OPIOID-INDUCED HYPERALGESIA

- An increased sensitivity to pain
- Usually occurs at high MME dosages and over long periods of time
- A physiological phenomenon that can happen to anyone
- Consider this explanation if:
  - Pain increases despite dose increases
  - Pain appears in new locations
  - Patient becomes more sensitive to painful stimuli
  - Patient is not improving in the absence of underlying cause or disease progression

SOURCE: Yi P, Pryzbylkowski P. Opioid induced hyperalgesia. Pain Medicine 2015; 16: S32-S36

OPIOID TOLERANCE

If opioid tolerant, still use caution at higher doses

Patients considered opioid tolerant are taking at least

- 60 mg oral morphine/day
- 25 mcg transdermal fentanyl/hour
- 30 mg oral oxycodone/day
- 8 mg oral hydromorphone/day
- 25 mg oral oxymorphone/day
- An equianalgesic dose of another opioid

Also use caution when rotating a patient on an IR opioid to a different ER/LA opioid

FOR 1 WEEK
OR LONGER

Products restricted to opioid tolerant individuals include transdermal fentanyl (Duragesic) and hydromorphone (Exalgo).

SOURCE: The Opioid Analgesics Risk Evaluation & Mitigation Strategy product search, https://opioidanalgesicrems.com/products.html

OPIOID TOLERANCE VERSUS PHYSICAL DEPENDENCE

TOLERANCE

- Occurs when increased dose is needed to maintain the functional status no longer achieved by current dose
- Remember CNS and respiratory depression can develop with dose increase

PHYSICAL DEPENDENCE

- Occurs when an individual only functions normally in the presence of the substance
- Abrupt discontinuation or dosage decrease causes uncomfortable symptoms of withdrawal

Both **tolerance** and **physical dependence** are physiological adaptations to chronic opioid exposure and **DO NOT** equal addiction or opioid use disorder

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OPIOID ROTATION

DEFINITION

A change from an existing opioid regimen to another opioid with the goal of improving therapeutic outcomes or to avoid AEs attributed to the existing drug

RATIONALE

Used when differences in pharmacologic or other effects make it likely that a switch will improve outcomes

- Effectiveness and AEs of different mu-opioids vary among patients
- Patient tolerant to first opioid might have improved analgesia from second opioid at a dose lower than calculated from an equianalgesic dosing table (EDT)

SOURCES: Fine PG, et al. J Pain Symptom Manage. 2009;38:418-425; Knotkova H, et al. J Pain Symptom Manage. 2009;38:426-439; Pasternak GW. Neuropharmacol. 2004;47(suppl 1):312-323.

EQUIANALGESIC DOSING TABLES (EDTs)

Many different versions:

- Published
- Online calculators
- Smartphone apps

Vary in terms of:

- Equianalgesic values
- Whether ranges are used
- **Which opioids are included:** May or may not include transdermal opioids, rapid-onset fentanyl, ER/LA opioids, or opioid agonist-antagonists

START WITH AN EDT FOR ADULTS

	EQUIANALGESIC DOSE		USUAL STARTING DOSE	
DRUG	SC/IV	PO	PARENTERAL	PO
Morphine	10 mg	30 mg	2.5–5 mg SC/IV q3–4hr (1.25–2.5 mg)	5–15 mg q3–4hr (IR or oral solution) (2.5–7.5 mg)
Oxycodone	NA	20 mg	NA	5–10 mg q3–4hr (2.5 mg)
Hydrocodone	NA	30 mg	NA	5 mg q3–4hr (2.5 mg)
Hydromorphone	1.5 mg	7.5 mg	0.2–0.6 mg SC/IV q2–3hr (0.2 mg)	1–2 mg q3–4hr (0.5–1 mg)

MU-OPIOID RECEPTORS AND INCOMPLETE CROSS TOLERANCE

MU-OPIOIDS BIND TO MU RECEPTORS

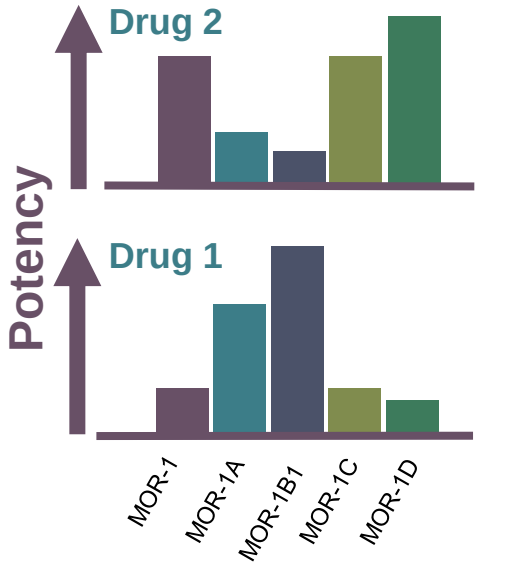
MANY MU RECEPTOR SUBTYPES

Mu-opioids produce **subtly different** pharmacologic responses based on distinct activation profiles of mu receptor subtypes

MAY HELP EXPLAIN:

Interpatient variability in response to mu-opioids

Incomplete cross tolerance among mu-opioids



GUIDELINES FOR OPIOID ROTATION

Calculate equianalgesic dose of new opioid from EDT

REDUCE CALCULATED EQUIANALGESIC DOSE BY 25%–50%*

SELECT % REDUCTION BASED ON CLINICAL JUDGMENT

CLOSER TO 50% REDUCTION	CLOSER TO 25% REDUCTION
IF PATIENT…	IF PATIENT…
• Is receiving a relatively high dose of current opioid regimen	• Does not have these characteristics
• Is elderly or medically frail	• Is changing route of administration

*75%–90% reduction for methadone

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GUIDELINES FOR OPIOID ROTATION *(continued)*

IF SWITCHING TO METHADONE:

- Standard equianalgesic dosing tables are less helpful in opioid rotation to methadone
- For opioid tolerant patients, methadone doses should **not** exceed 30–40 mg/day upon rotation
    - Consider inpatient monitoring, including serial EKG monitoring
- For opioid-naïve patients, do **not** give methadone as an initial drug

IF SWITCHING TO TRANSDERMAL:

- **Fentanyl:** calculate dose conversion based on equianalgesic dose ratios included in the drug package insert

BREAKTHROUGH PAIN (BTP)

PATIENTS ON STABLE ATC OPIOIDS MAY EXPERIENCE BTP

- Due to disease progression or a new or unrelated pain
  - Target cause or precipitating factors
- Dose for BTP: Using an **IR, 5%–15%** of total daily opioid dose, administered at an appropriate interval
- **Never use ER/LA for BTP**

CONSIDER ADDING

- PRN IR opioid trial based on analysis of benefit versus risk
  - There is a risk for problematic drug-related behaviors
  - High-risk: Add only in conjunction with frequent monitoring
  - and follow-up
  - Low-risk: Add with routine follow-up and monitoring
- Consider non-opioid drug therapies and nonpharmacologic treatments

ABUSE-DETERRENT FORMULATION (ADF) OPIOIDS

Drug formulations designed to discourage misuse

- An ER/LA opioid with properties to meaningfully deter misuse (less likely to be crushed, injected, or snorted)
- Consider as one part of an overall strategy
- Mixed evidence on the impact of ADF on misuse
- Overdose is still possible if taken orally in excessive amounts
- These products are expensive with no generic equivalents

URINE DRUG TESTING (UDT)

- Urine testing is done **FOR** the patient, not **TO** the patient
- Helps to identify drug misuse/addiction
- Assists in assessing and documenting adherence

CLINICAL CONSIDERATIONS

- Recommend UDT before first prescription (baseline), then intermittently, depending on clinical judgment and state regulations
- Document time and date of last dose taken
- Be aware of possible false positives or negatives
- Clarify unexpected results with the lab before confronting patient to rule out poor specimen or error

SCREENING VERSUS CONFIRMATORY UDTs

	SCREENING (Office-based)	CONFIRMATORY (Send to lab)
Analysis technique	Immunoassay	GC-MS or HPLC
Sensitivity (power to detect a class of drugs)	Low or none when testing for semi-synthetic or synthetic opioids	High
Specificity (power to detect an individual drug)	Varies (can result in false positives or false negatives)	High
Turnaround	Rapid	Slow
Cost/Other	Lower cost; intended for a drug-free population; may not be useful in pain medicine	Higher cost; legally defensible results

GC-MS = gas chromatograph-mass spectrometry; HPLC = high-performance liquid chromatography

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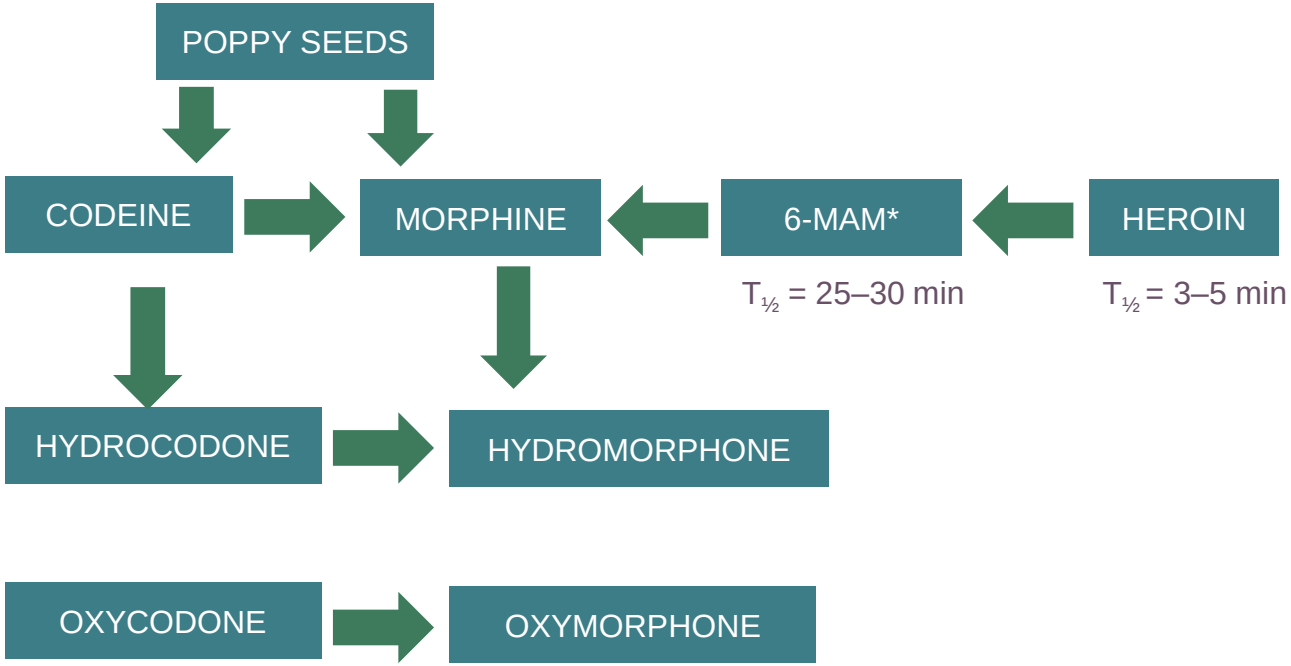
WINDOWS OF SPECIFIC DRUG DETECTION

Drug	How soon after taking drug will there be a positive drug test?	How long after taking drug will there continue to be a positive drug test?
Cannabis/ Tetrahydrocannabinol (THC)	1–3 hours	1–7 days (can be up to 1 month if long-term use)
Crack (cocaine)	2–6 hours	2–3 days
Heroin (opiates)	2–6 hours	1–3 days
Speed/uppers (amphetamine, methamphetamine)	4–6 hours	2–3 days
Angel dust/PCP	4–6 hours	7–14 days
Ecstasy	2–7 hours	2–4 days
Benzodiazepine	2–7 hours	1–4 days
Barbiturates	2–4 hours	1–3 weeks
Methadone	3–8 hours	1–3 days (up to 2 weeks)
Tricyclic antidepressants	8–12 hours	2–7 days
Oxycodone	1–3 hours	1–2 days
Fentanyl/Norfentanyl	1–3 hours	30 days

SOURCES: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/DrugsofAbuseTests/ucm125722.htm and https://doi.org/10.1016/j.drugalcdep.2020.108147

EXAMPLES OF OPIOID METABOLISM



*6-MAM = 6-Monoacetylmorphine

CONSIDERATIONS FOR RE-EVALUATING OPIOID USE

PATIENT MOVES PAST THE POINT OF NEED	INTOLERABLE AND UNMANAGEABLE AEs	NO PROGRESS TOWARD THERAPEUTIC GOALS	RISKS OUTWEIGH BENEFITS

MISUSE BEHAVIORS

- One or two episodes of increasing dose without prescriber knowledge
- Sharing medications
- Unapproved opioid use to treat another symptom (e.g., insomnia)
- Use of illicit drugs or unprescribed opioids
- Repeatedly obtaining opioids from multiple outside sources
- Prescription forgery
- Multiple episodes of prescription loss
- Diversion

Even at prescribed doses, opioids carry the risk of misuse, abuse, opioid use disorder, overdose, and death

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TOOLS TO REASSESS OUD/SUD RISK

SBIRT
Screening, Brief Intervention, and Referral to Treatment

TAPS
Tobacco, Alcohol, Rx, and Other Substances

PDUQ
Prescription Drug Use Questionnaire

PMQ
Pain Medication Questionnaire

COMM
Current Opioid Misuse Measure

APPROACHES TO SUPPORT THE DISCONTINUATION DECISION

- Discontinue through a taper schedule

- If OUD suspected:
  - Begin treatment: Medications for Opioid Use Disorder (MOUD)
  - Refer to an OUD specialist

- Consider rotation to partial agonist (e.g., buprenorphine)

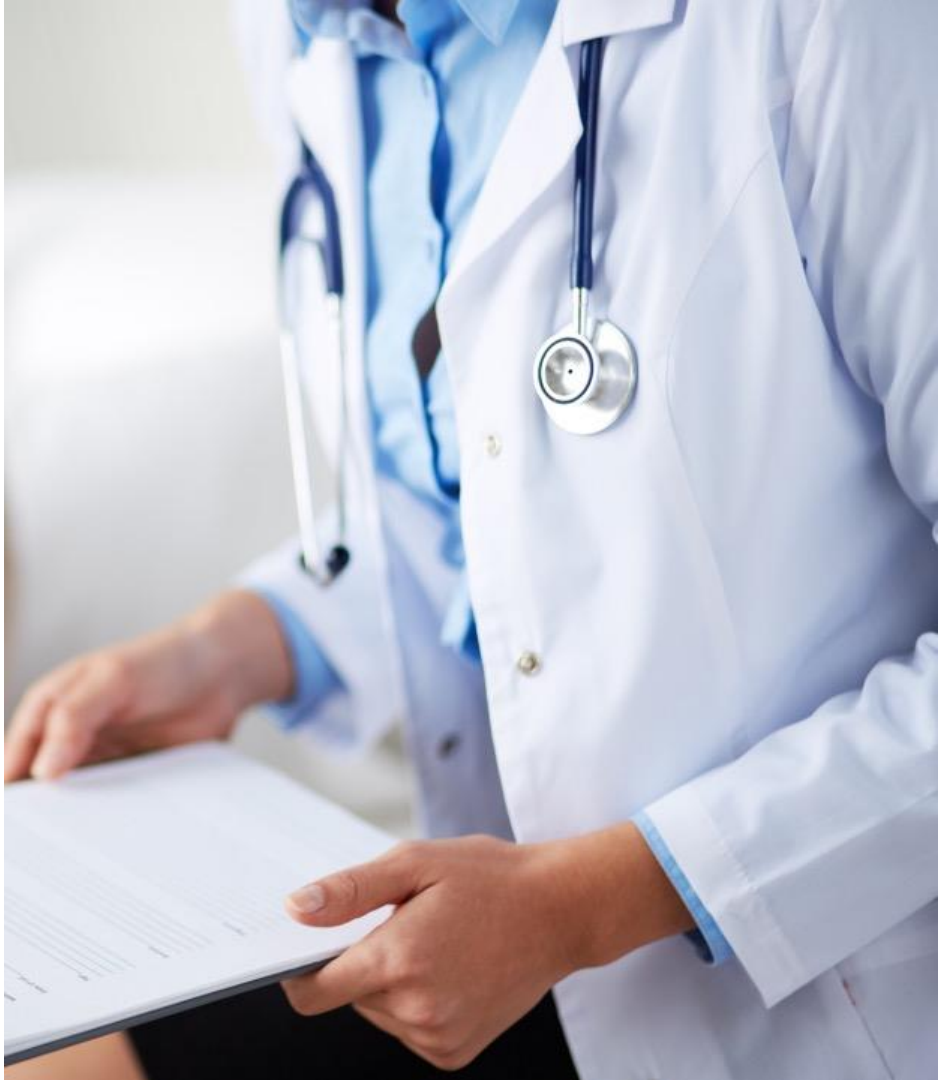
- No single approach is appropriate for all patients

- May use a range of approaches, from a slow 10% dose reduction per week to a more rapid 25%–50% reduction every few days

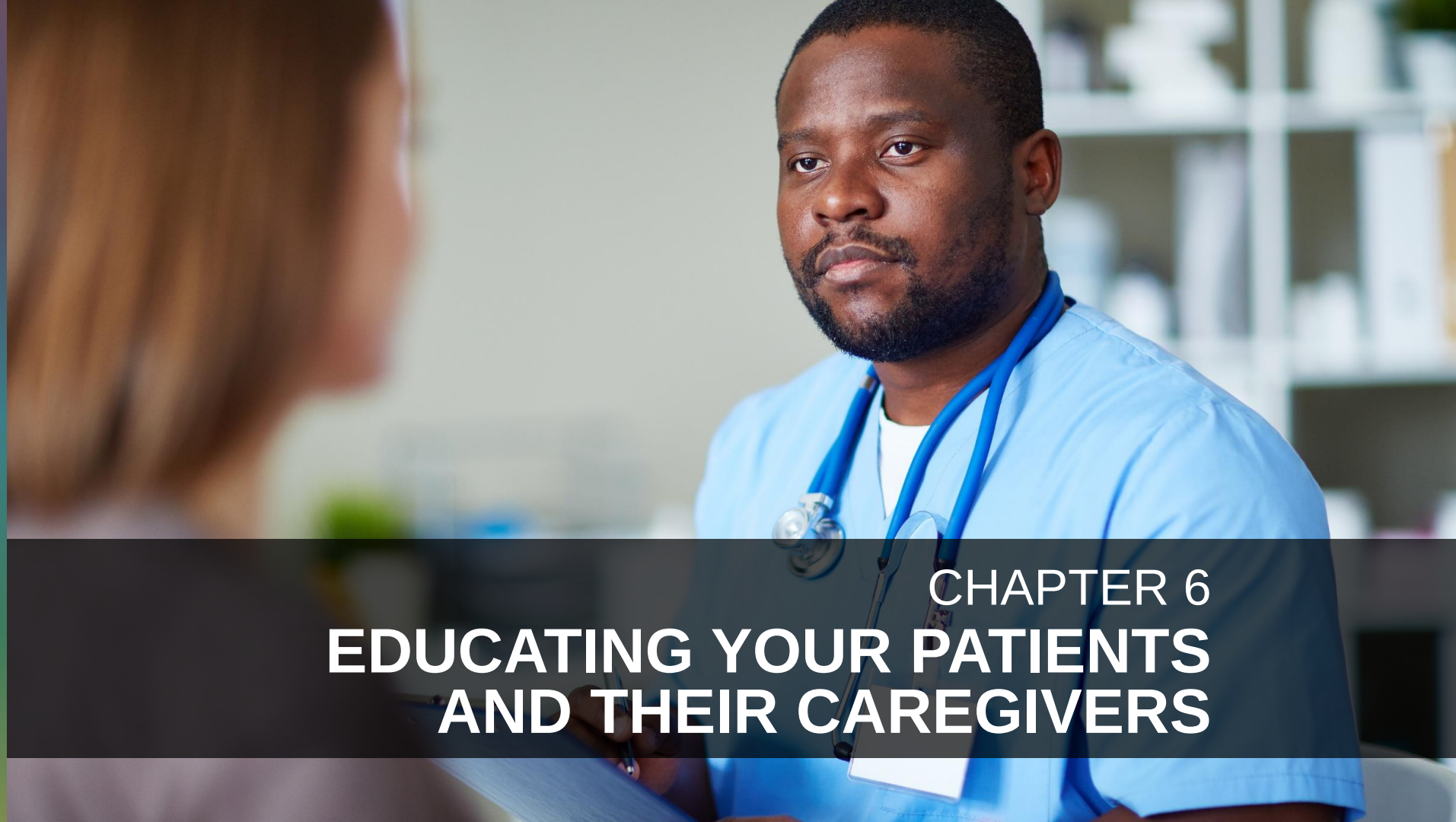
- To minimize withdrawal symptoms in patients physically dependent on opioids, consider medications to assist with withdrawal (clonidine, NSAIDs, antiemetics, antidiarrheal agents)

CONSULTING A PAIN SPECIALIST

- Appropriate when you feel you cannot provide the level of care needed
- First ensure you have a reliable specialist to refer to
- To find a pain specialist in your area:
    - Consult with state boards
    - Consult with colleagues
    - Use online resources
    - Consult payment source
- Prior to referral, contact the specialist and ask what is needed for referral
- If there are concerns about the development of an opioid use disorder, consult ASAM's website and an addiction specialist.



Adequately **DOCUMENT**
all patient interactions,
assessments, test results,
treatment plans,
and expectations.



CHAPTER 6

EDUCATING YOUR PATIENTS AND THEIR CAREGIVERS

COUNSEL PATIENTS ABOUT PROPER USE

- Take opioid as prescribed
- Use least amount of medication necessary for shortest time
- Use caution with long-term opioid use patients; avoid abrupt discontinuation or dose reduction; taper safely to avoid withdrawal symptoms
- Notify HCP if pain is uncontrolled
- Report side effects to HCP
- Inform HCP of ALL meds and supplements being taken
- Never share or sell opioids: can lead to others' deaths, against the law
- Use caution when operating heavy machinery and driving

USE FDA PATIENT COUNSELING DOCUMENT

- What are opioids?
- What are the risks and benefits?
- How to take safely

https://tinyurl.com/5n6z2dta

What You Need to Know About Opioid Pain Medicines

This guide is for you! Keep this guide and the Medication Guide that comes with your medicine so you can better understand what you need to know about your opioid pain medicine. Go over this information with your healthcare provider. Then, ask your healthcare provider about anything that you do not understand.

What are opioids?

Opioids are strong prescription medicines that are used to manage severe pain.

What are the serious risks of using opioids?

- Opioids have serious risks of addiction and overdose.
- **Too much opioid medicine in your body can cause your breathing to stop – which could lead to death.** This risk is greater for people taking other medicines that make you feel sleepy or people with sleep apnea.
- **Addiction** is when you crave drugs (like opioid pain medicines) because they make you feel good in some way. You keep taking the drug even though you know it is not a good idea and bad things are happening to you. Addiction is a brain disease that may require ongoing treatment.

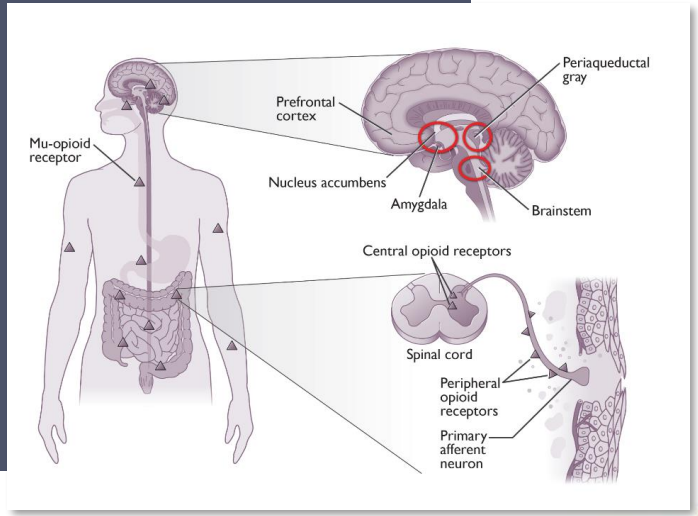
Risk Factors for Opioid Abuse:

- You have:
  - a history of addiction
  - a family history of addiction

- Take your opioid medicine exactly as prescribed.
- Do not cut, break, chew, crush, or dissolve your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- When your healthcare provider gives you the prescription, ask:
  - How long should I take it?
  - What should I do if I need to taper off the opioid medicine (slowly take less medicine)?
- Call your healthcare provider if the opioid medicine is not controlling your pain. Do not increase the dose on your own.
- Do not share or give your opioid medicine to anyone else. Your healthcare provider selected this opioid and the dose just for you. A dose that is okay for you could cause an overdose and death for someone else. Also, it is against the law.
- Store your opioid medicine in a safe place where it cannot be reached by children or stolen by family or visitors to your home. Many teenagers like to experiment with pain medicines. Use a lock- box to keep your opioid

PROVIDE ANTICIPATORY GUIDANCE ON OPIOID SIDE EFFECTS AND ADVERSE EVENTS

- Overdose and death: respiratory depression
- Opioid-induced constipation (OIC): most common
- Nausea, vomiting, GERD
- Sexual dysfunction and other endocrine abnormalities (hypogonadism)
- Tolerance, physical dependence
- Hyperalgesia
- Allergic reactions
- Sedation, cognitive impairment
- Falls and fractures
- Sweating, miosis, urinary retention
- Myoclonus (twitching or jerking)
- Opioid use disorder (OUD)



COUNSEL PATIENTS AND CAREGIVERS

WARNINGS
(Safe Administration)

- Never break, chew, crush, or snort an opioid tablet/capsule
- Never cut or tear patches or buccal films
- If patient cannot swallow, determine if appropriate to sprinkle contents on applesauce or administer via feeding tube
- Use of CNS depressants or alcohol with opioids can cause overdose

WHAT TO LOOK FOR
(Safety Concerns)

- Cravings
- Being unable to fulfill work/family obligations
- Nodding off
- Taking more than prescribed

OPIOID-INDUCED RESPIRATORY DEPRESSION

If not immediately recognized and treated, may lead to respiratory arrest and death

More likely to occur in opioid-naïve patients during initiation or after dose increase

Instruct patients/family members to:

- Screen for shallow or slowed breathing
- Deliver NALOXONE
- **CALL 911**

Instructions may differ if patient is on hospice or near end of life

Greatest risk: when co-prescribed with a benzodiazepine

SIGNS OF ACCIDENTAL OPIOID POISONING: CALL 911

- Person cannot be aroused or is unable to talk
- Any trouble with breathing, heavy snoring is warning sign
- Gurgling noises coming from mouth or throat
- Body is limp, seems lifeless; face is pale, clammy
- Fingernails or lips turn blue/purple
- Slow, unusual heartbeat or stopped heartbeat

Administer Naloxone

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NALOXONE

WHAT IT IS:

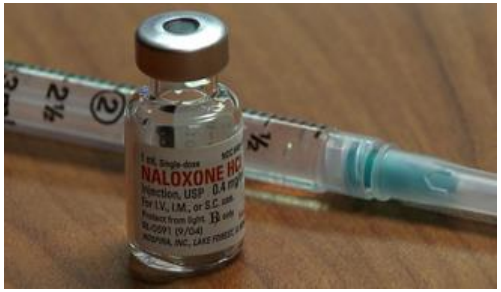
- An opioid antagonist administered intranasally (most common) or parenterally
- Reverses acute opioid-induced respiratory depression but will also reverse analgesia; may precipitate acute opioid withdrawal
- No misuse potential

WHAT TO DO:

- Discuss an overdose plan with patients; involve family/caregivers
- Ensure family/caregivers have access to naloxone; some states *require* co-prescribing
- Involve and train family, friends, partners, and/or caregivers in the proper administration of naloxone
- Know your local naloxone resources (e.g., the library, community centers)
- Check expiration dates and replace expired naloxone
- In the event of known or suspected overdose, **call 911** and administer naloxone

NALOXONE OPTIONS

- Available as auto-injector, intramuscular injection, or nasal spray
- Cost and insurance coverage vary
- Make use of tutorial videos or live demonstration to educate patient/family/caregiver on proper administration
- Store at room temperature



Naloxone vials

Narcan nasal spray

Evzio (auto-injector)

Trade names are used for identification purposes only and do not imply endorsement.

SOURCE: FDA Information About Naloxone, https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm472923.htm

SAFE OPIOID STORAGE AND DISPOSAL

STEP 1: MONITOR

- Note how many pills are in each prescription
- Keep track of dosage and refills
- Make sure everyone in the home knows meds are tracked (if appropriate)

STEP 2: SECURE

- Keep meds in a safe place (locked cabinet or box)
- Store away from children, family, visitors, and pets
- Extra precautions needed with adolescents in the home

STEP 3: DISPOSE

- Discard expired or unused meds
- Check your local disposal options (e.g., pharmacy, police)

SOURCE: McDonald E, Kennedy-Hendrick A, McGinty E, Shields W, Barry C, Gielen A. Pediatrics. 2017;139(3):e20162161

WHERE AND HOW TO DISPOSE OF UNUSED OPIOIDS

Authorized Collection Sites

- Use the DEA disposal locator website to find sites near you: https://apps.deadiversion.usdoj.gov/pubdispsearch
- Search Google Maps for ”drug disposal nearby”

Options

- Check with local pharmacy for disposal options
- Flush
  - Fold patch in half so sticky sides meet, then flush
- Trash (mix with noxious element like kitty litter or dirt)

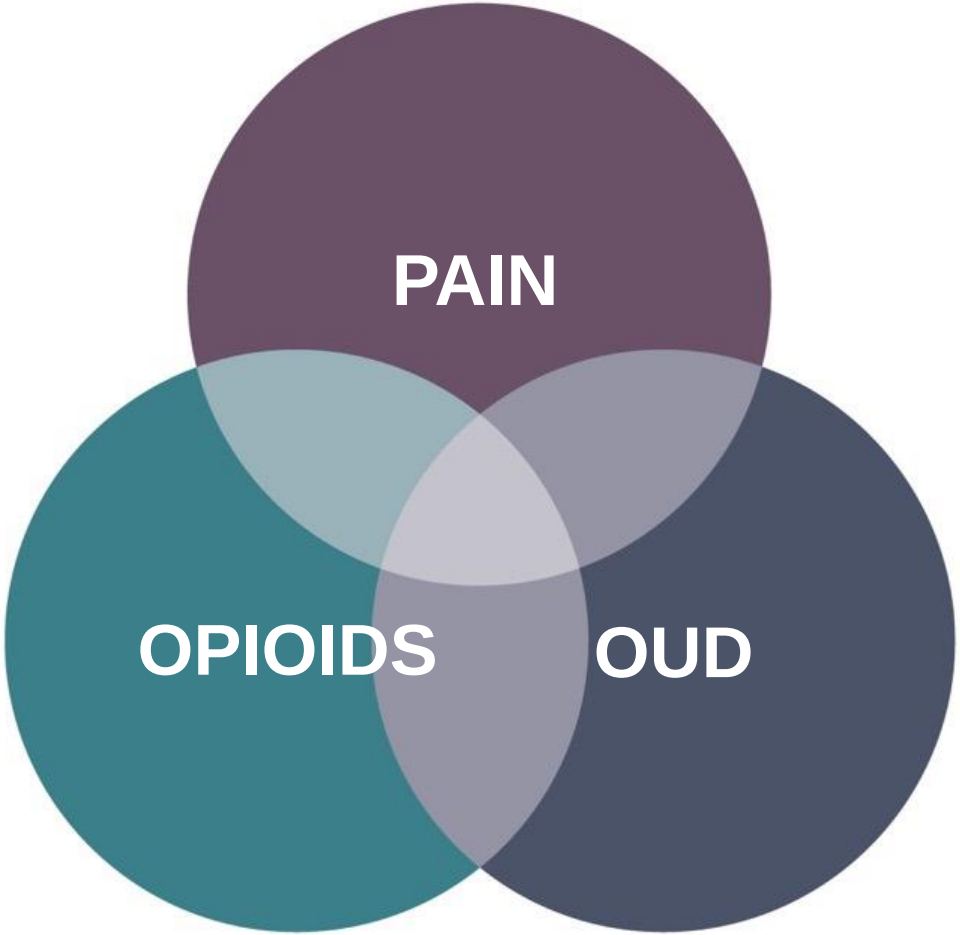
Mail-Back Packages

- Obtain from authorized collectors

SOURCES: FDA. Where and How to Dispose of Unused Medicines. https://www.fda.gov/consumers/consumer-updates/where-and-how-dispose-unused-medicines
EPA. How to Dispose of Medicines Properly. https://archive.epa.gov/region02/capp/web/pdf/ppcpflyer.pdf

CHAPTER 7

UNDERSTANDING OPIOID USE DISORDER (OUD)


PAIN
OPIOIDS
OUD

WHAT IS ADDICTION?

PRACTICAL DEFINITION:

Addiction is the continued use of drugs or activities, despite knowledge of continued **harm** to oneself or others.

OFFICIAL ASAM DEFINITION:

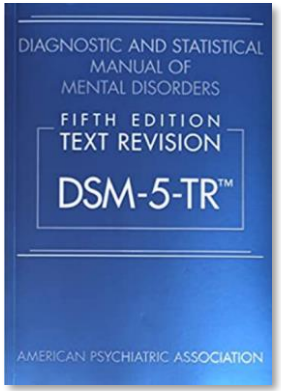
Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences. Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

OPIOID USE DISORDER: DSM-5-TR CRITERIA

Be alert to these factors in your patients on long-term opioid therapy

1. Taking larger amounts and/or for longer periods than intended
2. Persistent desire or inability to cut down or control use
3. Increased time spent obtaining, using, or recovering
4. Craving/compulsion to use opioids
5. Role failure at work, home, school
6. Social or interpersonal problems
7. Reducing social, work, recreational activity
8. Physical hazards
9. Physical or psychological harm

- ❖ Tolerance
- ❖ Withdrawal



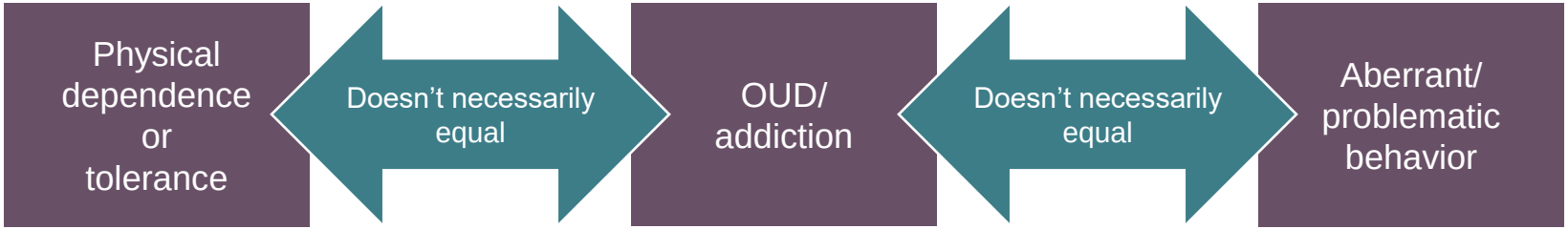
- 2–3 = mild
- 4–5 = moderate
- ≥6 = severe

- ❖ **Not valid if opioid is taken as prescribed**

SOURCE: APA. Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR). 2022

CO*RE

WORDS MATTER



HOW TO IDENTIFY RISK FOR MY PATIENTS

10%–26% of patients on chronic opioid therapy (COT) for chronic noncancer pain (CNCP) may develop an OUD

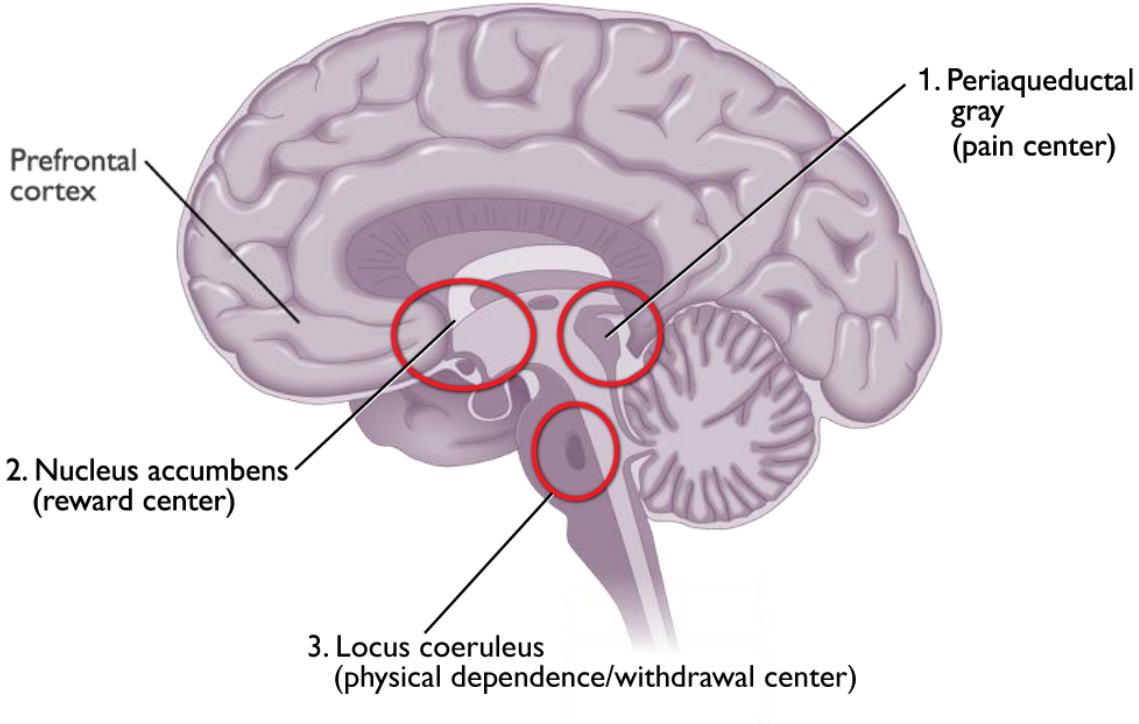
What to look for:

- High dosages
- Prolonged use
- Low hedonic tone
- Mental health disorders
- Past history of substance use disorder

Clinical judgment is key.

SOURCE: Chou R, et al. Ann Intern Med. 2015;162:276-86

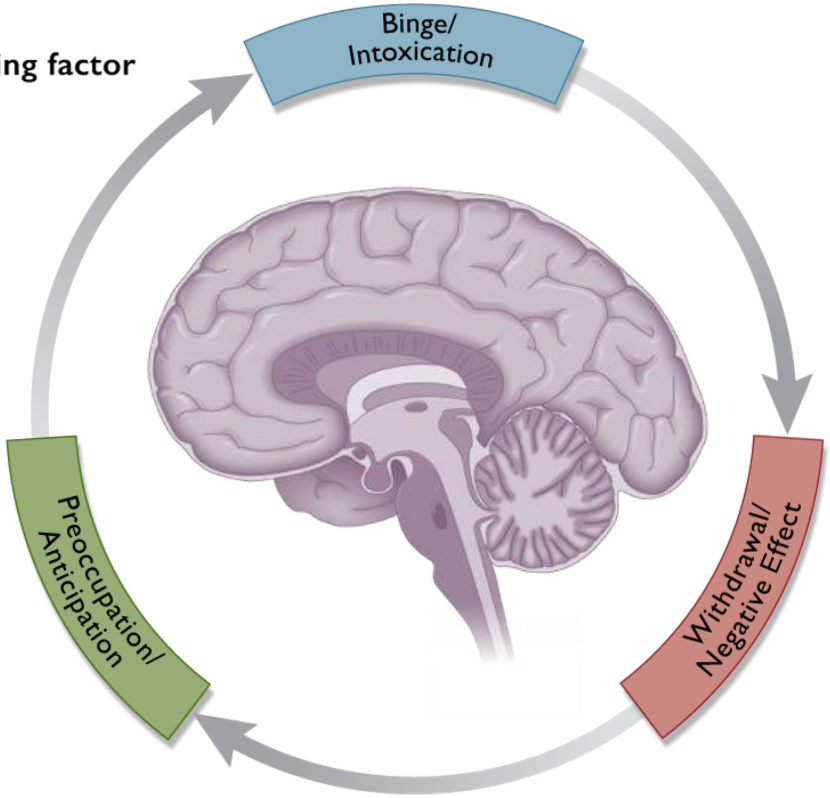
OPIOID RECEPTORS IN THE BRAIN: RELATIONSHIP TO ANALGESIA, OUD, AND WITHDRAWAL



THE CYCLE OF SUBSTANCE USE DISORDER

NEUROTRANSMITTERS

- Dopamine
- Opioid peptides
- Corticotropin-releasing factor
- Dynorphin
- Glutamate



MEDICATION FOR OPIOID USE DISORDER (MOUD)

- Important and evidence-based medication that saves lives
- You can start from your office, as an outpatient
- Patients with OUD have decreased mortality when treated

There are three medication options:

1. Buprenorphine (Schedule III)
2. Methadone (Schedule II)
3. Naltrexone (not a controlled substance)

Are we just replacing one drug with another? Myth or fact?

BUPRENORPHINE

- The most commonly prescribed pharmacotherapy for the treatment of OUD
- Partial mu-agonist with “plateau effect” for respiratory depression
- Good efficacy and safety profile
- Congress eliminated the X-waiver requirement to prescribe Bup
- All DEA-licensed HCPs can prescribe without patient number caps
- FDA Approved Formulations to Treat OUD: Long-acting and sublingual form
- Can prescribe OUD formulations off-label for chronic pain
- Cannot prescribe Pain formulations off-label for OUD

FDA-approved buprenorphine products for pain:

- Butrans: 7-day transdermal patch and Belbuca: buccal mucosal film; BID dosing

AVOID OTHER SUBSTANCES THAT COULD CONTRIBUTE TO AN ACCIDENTAL OVERDOSE

- Benzodiazepines (BZDs), sedatives, muscle relaxants; they are CNS depressants
- More than 30% of opioid overdoses involve benzodiazepines (BZDs)
- Use a comprehensive SUD evaluation to support recovery efforts for all substances

SOURCE: NIDA. Takaki H, et al. Am Journal Addictions. 2019;1-8.

USE A WHOLE-PERSON APPROACH WHEN TREATING A PATIENT WITH OUD FOR PAIN

- Must address *both* pain and opioid use disorder
- Remember that untreated pain is a trigger for return to use
- Avoid other potentially problematic medications
- Consider a multimodal pain program, including non-pharma options
- Avoid stigmatizing patients who are on long-term opioids for pain

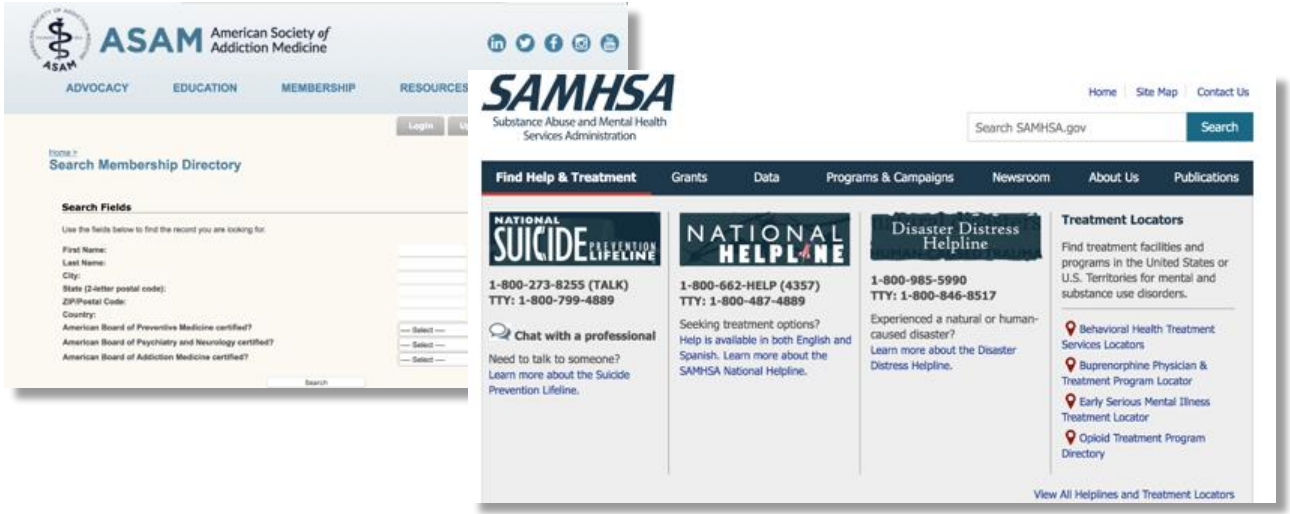
- Consider buprenorphine for both pain and OUD
- Enlist patient's family/caregivers to secure and dispense opioids
- Recommend an active recovery program
- Remember to use PDMP
- Use screening methods (UDT, pill counts, PPA) to identify challenges and initiate discussion

SOURCE: Bailey J, et al. Pain Med 2010;11:1803-1818.

REFERRALS AND TREATMENT CENTERS

ASAM, SAMHSA, and AAAP are all helpful referral resources.

ASAM resources: https://asam.ps.membersuite.com/directory/SearchDirectory_Criteria.aspx
SAMHSA locator: https://findtreatment.samhsa.gov/locator
AAAP locator: https://www.aaap.org/patients/find-a-specialist/

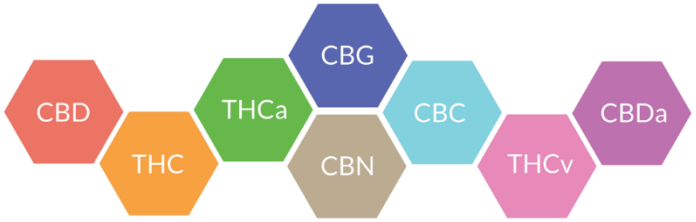


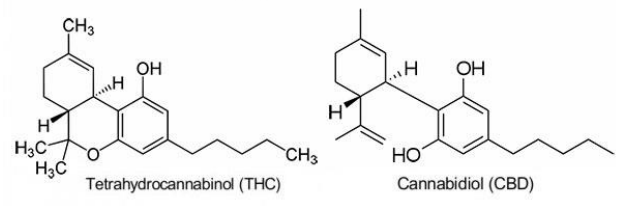
CHAPTER 8

PAIN, CANNABIS, & KRATOM

CHEMICAL COMPOSITION

- Over 100 cannabinoids in cannabis plants, most unstudied
- THC associated with more negative effects (high, addiction)
- CBD thought to be potentially more therapeutic
- Preparations often labeled with inaccurate THC & CBD content
- Varying concentration, other cannabinoids may have health effects

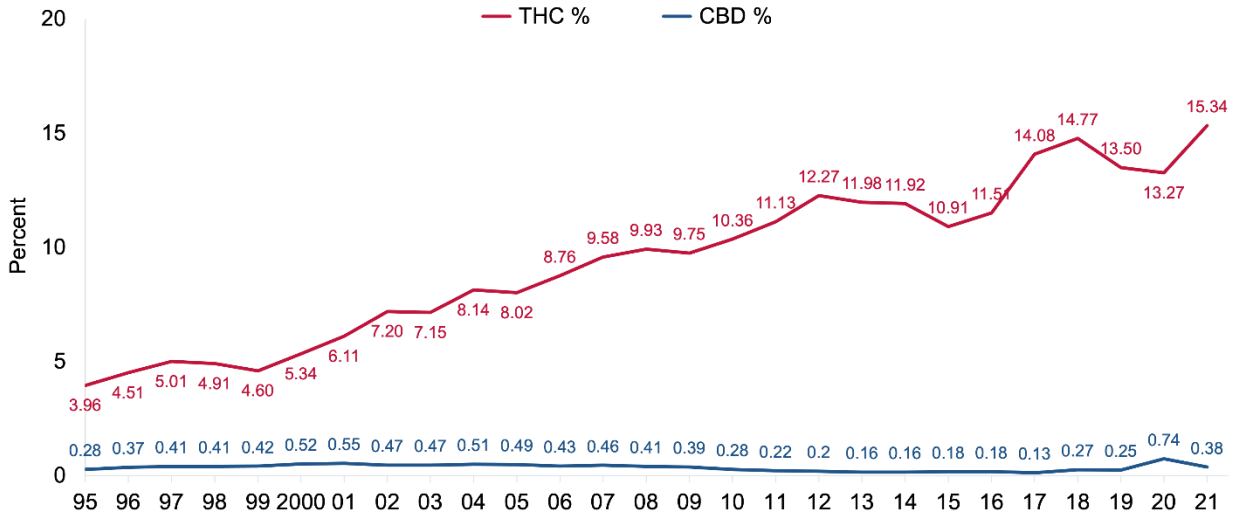




SOURCE: Hayakawa, K. et al. Therapeutic Potential of Non-Psychotropic Cannabidiol in Ischemic Stroke. Pharmaceuticals **2010**, 3, 2197-2212

INCREASED THC POTENCY OVER TIME

THC concentration increased 5% → > 30% in recent years



SOURCE: U Miss, Potency Monitoring Project

PREPARATIONS

PREPARATIONS	DESCRIPTION	USE
MARIJUANA	Dried plant product consisting of leaves, stems, and flowers	Smoked or vaporized
HASHISH	Concentrated resin cake	Ingested or smoked
TINCTURE	Cannabinoid liquid extracted from plant	Consumed sublingually
HASHISH OIL	Oil obtained from Cannabis plant by solvent extraction	Smoked or vaporized
INFUSION	Plant material mixed with nonvolatile solvents (e.g., butter, cooking oil)	Ingested

SOURCE: Hill 2015, JAMA

PERCEPTIONS OF MEDICAL EFFICACY vs DATA

Perceptions

- 81% of patients believe marijuana has at least one benefit
- 66% of patients believe in pain benefit

Data

- Systematic Review of RTCs: 2021: Outcomes had low or very low-quality evidence, neither supporting nor refuting efficacy
- Meta analysis 2022: Placebo contributes significantly to pain reduction in cannabis clinical trials
- Review 2022: High THC:CBD products (>98% THC) associated with 25% reduction in pain in short-term studies of variable quality

SOURCE: Keyhani et al, Annals of Int Med 2018; Fisher et al Pain 2021; Gedin et al, JAMA 2022, , McDonagh Ananls 2022

OPIOID-SPARING THEORY vs DATA

Theory

If cannabis products treat pain, patient may use these products and reduce their use of opioids

Data

- States with medical cannabis have modestly lower rates of opioid prescribing and risky opioid prescribing
- **2019 Study:** Association between med cannabis and reduced opioid mortality has **reversed** over time
- **2021 Meta Analysis**: Opioid-sparing effects remain uncertain due to very low evidence
- **2022 Meta Analysis:** Preclinical/observational studies show opioid-sparing effect, but higher-quality RCTs do not

SOURCE: Shah et al, JGIM 2019, Noori et al BMJ Open 2021; Nielsen Neuropsychopharm 2022

CANNABIS AND PAIN

- There is limited evidence that marijuana works to treat most types of acute or chronic pain.
- A few studies have found that marijuana can be helpful in treating neuropathic pain (a specific type of chronic pain caused by damaged nerves).
- However, more research is needed to know whether marijuana works better than other options to manage pain.

SOURCE: https://www.cdc.gov/marijuana/health-effects/chronic-pain.html

KRATOM PHARMACOLOGY

- Low Dose: 1-5g: Stimulant resembling caffeine/cocaine: MOA
- High Dose: 5-15g: Opioid Like Effects
- μ and δ Opioid (?k) Receptor Agonist/?Partial Agonist: G-protein biased signaling
- 7-OH Mitragynine 13 and 46 > Potent: Morphine: Mitrgynine
- α2 Adrenergic Agonist, Descending Pathway-NE, 5HT
- Animal self-administration
- Analgesic and Sedation Effect Reversed by Naloxone
- Onset of action: 30 minutes: ½ life ~4 hrs
- Mitragynine inhibits CYP 3A4, 2D6, 2C9, 1A2
- Hepatic Cholestasis—dose dependent

KRATOM CHRONIC USE

- Anorexia, Weight Loss, Constipation, Dark Pigmentation of the Face(Increased Melanocyte Stim)
- Deaths: Generally in combination with alcohol, other opioids, benzos, others
- Typical, but Milder, Opioid Physical Dependence, Tolerance, and Withdrawal Syndrome
- Secondary Hypogonadism

KRATOM DETECTION AND TREATMENT

DETECTION

- Not detected on routine screening immunoassays
- Mitragynine and 7-OH Mitragynine detected on GC-MS testing
- May be used by patients in treatment for OUD
- Detected up to 6 weeks post cessation - lipophilic

TREATMENT

- Buprenorphine most commonly reported
- OUD paradigm
- Maintenance or withdrawal management

IN SUMMARY

- There is a place for opioids, but use caution
- Use multimodal therapies as part of the pain management care plan
- Screen for OUD risk with a validated instrument
- Continually reassess patients using opioids
- Patient and family/caregiver education is essential
- If you suspect an OUD, begin treatment

THANK YOU!

WWW.CORE-REMS.ORG

Please complete your post-test 😁

Complete the brief post-test for CE/CME credit
Your participation helps the FDA reach its goals for REMS education

