Striking a Balance Understanding Pain Management and Opioids



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Dr. Hendershot declares that he has no relevant financial relationships with ineligible companies to disclose.



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https://opioidanalgesicrems.com/RpcUI/products.u.

Scan the QR code to go to the FDA OA REMS Blueprint



MATE ACT AND STATE REQUIREMENTS

MATE Act

As of June 27, 2023, DEA registrants are to have completed a total of at least 8 hours of training on treatment and management of patients with opioid or other substance use disorders. This activity meets the criteria outlined by SAMHSA to count toward this training requirement.

State Requirements

This course also meets many states' requirements for pain education.



Prescribing Limits, Status & Education Requirements

Seven-day (short-term pain), four-day (emergency room prescriptions), three-day (prescribed by dentists or optometrists)

	Physician	PA	Advanced Practice Nurse
Prescriber Status	Licensed	Schedule II-V	Schedule II-V
Education Requirements	3 hrs./2 yrs.	3 hrs./2 yrs.	3 hr. x 1, and then 1 hr /renewal

The Medication Access and Training Expansion (MATE) Act requires new or renewing Drug Enforcement Agency (DEA) registrants, as of June 27, 2023, to have completed a total of at least eight hours of training on opioid or other substance use disorders. This course meets the criteria outlined by Substance Abuse and Mental Health Services Administration (SAMHSA) to count toward this training requirement.

http://www.fsmb.org/siteassets/advocacy/key-issues/continuing-medical-education-by-state.pdf, January 2023 Opioid prescription limits and policies by state – Ballotpedia, April 4, 2022 www.netce.com/ce-requirements/ https://www.asam.org/education/dea-education-requirements



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THE CO*RE COLLABORATIVE

This course does not advocate for or against the use of opioids.

We intend to help clinicians 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.







American Association of NURSE PRACTITIONERS*

AAQOS American Academy of Orthopaedic Surgeons



A M E R I C A N OSTEOPATHIC ASSOCIATION





AMERICAN ACADEMY OF HOSPICE AND PALLIATIVE MEDICINE









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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.

This course is based on the FDA's Opioid Analgesic REMS (FDA Blueprint, Sept. 2018) and existing guidelines, including the 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain.





Barbara St. Marie, PhD, AGPCNP, FAANP, FAAN UNIVERSITY OF IOWA



Arianna Sampson Campbell, PA-C MARSHALL MEDICAL CANTER



Joseph Shega, MD

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

- 1. Describe the pathophysiology of pain as it relates to the concepts of pain management.
- 2. Accurately assess patients in pain.
- 3. Develop a safe and effective pain treatment plan.
- 4. Identify evidence-based non-opioid options for the treatment of pain.
- 5. Identify the risks and benefits of opioid therapy.
- 6. Manage ongoing opioid therapy.

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7. Recognize behaviors that may be associated with opioid use disorder.





*Provisional data for the 12-month period Jan. 2021–Dec. 2021 https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

Source: https://www.ama-assn.org/system/files/ama-overdose-epidemic-report.pdf







OPIOID OVERDOSE DEATHS BY TYPE OF OPIOID

HEROIN FENTAN

Figure 4. Age-adjusted rate of drug overdose deaths involving opioids, by type of opioid: US, 2001-2021



Source: https://www.cdc.gov/nchs/images/databriefs/451-500/db457-fig4.png

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CHAPTER 1 PAIN

Color of Pain by Dr. Kathleen A. Sluka <u>www.kathleenslukaart.com</u>

THE NEUROMECHANISMS OF PAIN



MEDIATORS OF PERIPHERAL NOCICEPTION



With thanks to Allan Basbaum and David Julius, University of California, San Francisco



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



CO*R

THE EXPERIENCE OF PAIN: A BIOPSYCHOSOCIAL MODEL





ADVERSE CHILDHOOD EXPERIENCES (ACEs)



CHAPTER 2 MULTI-DIMENSIONAL EVALUATION OF THE PATIENT WITH PAIN

HOW DO WE INITIATE DISCUSSION WITH A PATIENT?

Ask permission: "Is it okay if I ask you about alcohol or drugs?" Reframe your approach to avoid use of stigmatizing terms:

TERMS TO AVOID	PREFERRED TERM		
Addiction	Substance use disorder (SUD) or opioid use disorder (OUD) [from the <i>DSM-5-TR</i> [®]]		
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



HISTORY OF PRESENT ILLNESS

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PRE-SCREENERS COLLECTED IN ADVANCE (PHQ-2/9, BPI)

DESCRIPTION OF PAIN



WHAT RELIEVES THE PAIN?

WHAT CAUSES OR INCREASES THE PAIN?

PATIENT'S LEVEL OF PAIN AND THE EFFECT OF THE PAIN ON PHYSICAL, EMOTIONAL, AND PSYCHOSOCIAL FUNCTION (eg, PEG, BPI, MPI)

Source: Hogans, B., Barreveld, A. (Eds.). Pain Care Essentials, NY, NY: Oxford Univ. 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 clinicians 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)

A NON-PUNITIVE APPROACH TO PRESCRIBING ANALGESIC AGENTS

- Check when initiating opioid therapy regularly when continuing therapy
- · Improves patient communication, education, and safety
 - Confirm PDMP information with patient; do not dismiss from care
 - Identify drugs that increase overdose risk when taken together
 - Provide potentially life-saving information and interventions (safety concerns, provide naloxone)
- Discuss safety concerns with other clinicians
- Lowers rates of prescription opioid-related hospitalization and ED visits
- Most PDMPs allow you to appoint a delegate

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

Source: https://www.cdc.gov/opioids/healthcare-professionals/pdmps.html



PDMP: Prescription Drug Monitoring Program

General	 CSMP (Controlled Substance Monitoring Program) https://www.csappwv.com/Account/Login.aspx?ReturnUrl=%2f Administered by the Board of Pharmacy Schedule II-V are monitored Dispensers and prescribers are required to register and input data Before prescribing, there is an obligation to review under certain circumstances Prescribers can authorize a registered delegate
Reporting	 Must be entered into PDMP within 24 hours after dispensing Unsolicited reports/alerts are sent to prescribers, dispensers, law enforcement and licensing boards West Virginia does share data with other states' PDMP Out-of-state pharmacies are required to report to the patient's home state Patient will be notified if their record has been accessed

https://namsdl.org/doc-library/?fwp_document_type=map January 2019 http://www.pdmpassist.org/content/pdmp-maps-and-tables January 2023

Collaborative for REMS Education

OBTAIN A COMPLETE PSYCHOSOCIAL HISTORY

PSYCHOLOGICAL HISTORY

Screen for:

- Mental health diagnoses, depression, anxiety, PTSD, current treatments (using <u>PHQ-2, PHQ-9, GAD-7</u>, etc.)
- Alcohol, tobacco, and other drug use
- History of Adverse Childhood Experiences (ACEs) using <u>ACE</u> <u>Questionnaire</u>
- Family history of substance use disorder and psychiatric disorders

Depression and anxiety can be predictors of chronic pain

SOCIAL DETERMINANTS OF HEALTH (SDOH)

SDOH relate to pain in terms of

- Economic stability
- Education access & quality
- Health care access & quality
- Neighborhood & built environment
- Social & community context

Source: https://health.gov/healthypeople/priority-areas/social-determinants-health



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PHYSICAL EXAM AND ASSESSMENT

Seek objective data

Conduct physical exam and evaluate for pain Order diagnostic or confirmatory tests

General: vital signs, appearance, and pain behaviors

Neurologic exam

Musculoskeletal exam

- Inspection
- Gait and posture
- Range of motion
- Palpation
- Percussion
- Auscultation
- Provocative
 maneuvers

Cutaneous or trophic findings

Source: Hogans, B., Barreveld, A. (Eds.). Pain Care Essentials, NY, NY: Oxford Univ. Press. 2020.

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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

• P<u>EG</u>

Adverse Childhood Experiences Questionnaire

• ACE

Assessment in Patients Unable to Self-Report

Hierarchy of Pain Assessment or PAINAD





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Psychological Measurement Tools (PHQ-2, PHQ-9, GAD-7, etc.)

CHAPTER 3 CREATING THE PAIN TREATMENT PLAN













HOW IS PAIN MANAGED?



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COMPONENTS OF A MULTIMODAL TREATMENT PLAN FOR PAIN





PAIN MANAGEMENT GOALS AND TREATMENT OPTIONS: A MULTIMODAL APPROACH



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of Life

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

Source: https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/research



PHARMACOLOGIC TREATMENTS BY TYPE OF PAIN

Continue Effective Nonpharmacologic Options First





POTENTIAL SITES OF ACTION FOR ANALGESIC AGENTS

Peripherally Mediated Pain:

- Acetaminophen
- Anticonvulsants
- NSAIDs
- Opioids
- Topical anesthetics



Centrally Mediated Pain:

- Alpha-2 agonists
- Anticonvulsants
- Ca⁺ channel antagonists
- NMDA RAs
- Opioids
- TCA/SNRI antidepressants

Most commonly, pain conditions are a combination of peripherally and centrally mediated processes



DRUG CHARACTERISTICS TO CONSIDER BEFORE PRESCRIBING

Route of administration	Mechanism of action		Strength	Dosing interval
Key instructions (indications, uses, contraindications)	Specific drug interactions		Formulation	Product-specific safety concerns
Specific information about product conversions, if available		tc	ER/LA: Use only in opioid elerant patients	Relative potency to morphine (MME)

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

- Immediate Release (IR): rapid onset of analgesia, relatively short duration of effect
- Extended Release/Long-Acting (ER/LA): potentially longer onset of action, longer duration of effect; formulation allows for QD or BID dosing; less frequent dosing


WHEN TO CONSIDER A THERAPEUTIC TRIAL OF IR OPIOID

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

Patient has moderate to severe nociceptive or neuropathic pain

Potential benefits are likely to outweigh risks



 CDC Guideline recommendations do not apply to pain related to sickle cell disease or cancer or to patients receiving palliative or end-of-life care (separate guidelines apply to some). There are differences in benefits, risks, and expected outcomes for these patients compared to other patients with chronic pain.

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



RISKS VERSUS BENEFITS OF PRESCRIBED OPIOIDS

POTENTIAL RISKS

- Life-threatening respiratory depression/overdose, death
- SUD/OUD (assess using ORT-OUD or other validated tool)
- 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 nonopioid analgesics
- Relieves suffering
- May improve function and quality of life



ASSESS RISK FOR OPIOID USE DISORDER



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

DAST Drug Abuse Screening Test

CTQ Childhood Trauma Questionnaire

ACEs Adverse Childhood Experiences

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A CLOSER LOOK AT THE ORT-OUD

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., Compton, P.A., et al. J Pain 2019; Jan 26.

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

Scoring:

- ≤ 2: low risk
- \geq 3: high risk

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CATEGORIZATION OF OPIOIDS

Scan to view DEA Drug Scheduling



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

*These represent PAMORA: peripherally-acting mu opioid receptor antagonist $_{41}$ \mid ° CO*RE 2023



OPIOID SIDE EFFECTS AND ADVERSE EVENTS

SIDE EFFECTS	ADVERSE EVENTS	
Respiratory depression	Death	
GI effects: dry mouth, nausea/vomiting, opioid-induced constipation (most common; mitigate!)	Addiction	
Myoclonus (twitching or jerking)	Overdose	
Sedation, cognitive impairment	Hospitalization	
Sweating, miosis, urinary retention	Disability or permanent damage	
Allergic reactions	Falls or fractures	
Hypogonadism	Opioid-induced hyperalgesia	
Tolerance, physical dependence		
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 older, cachectic, or debilitated patients
- If given concomitantly with other drugs that depress respiration (such as benzodiazepines*)
- In patients who are opioidnaïve or have just had a dose increase
- In patients with conditions causing respiratory compromise (eg, obstructive sleep apnea)
- In patients with organ dysfunction

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



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





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 w/ 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 clinician who will ensure appropriate treatment for the baby

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

For women using opioids daily, 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





PEDIATRIC CONSIDERATIONS

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* 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

ADOLESCENTS ages 12-21: Identify and treat for OUD (use SBIRT)

SBIRT-Screening, Brief Intervention, Referral to Treatment. 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. <u>https://publications.aap.org/pediatrics/article/138/1/e20161210/52573/Substance-Use-Screening-Brief-Intervention-and</u> https://www.aap.org/en/patient-care/substance-use-and-prevention/resources-to-address-the-opioid-epidemic/



Scan to view SBIRT resource



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:









Telehealth technology allows new, effective, and efficient options for clinicians and patients to work in partnership to manage chronic medical issues



OPTIMIZING PATIENT CARE THROUGH I TELEHEATH



New CO*RE CE/CME Module

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

PATIENT PROVIDER AGREEMENT (PPA)

Reinforce Expectations For Appropriate And Safe Opioid Use

- Clarify treatment plans & 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) & 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 further inquiry: proceed with caution





CHAPTER 4 MANAGING PATIENTS ON OPIOID ANALGESICS

INITIATING IR OPIOIDS

- Prescribe the lowest effective dose for the shortest period of time based on the individual patient's condition
- 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 stimulant laxative

One- and 3-year probabilities of continued opioid use, by days' supply of first Rx



- 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

Source: https://www.cdc.gov/mmwr/volumes/66/wr/mm6610a1.htm



ONGOING MANAGEMENT OF PATIENTS ON OPIOID ANALGESICS

PERIODIC, CONTINUAL ASSESSMENT

- Is the patient making progress toward functional goals?
- Reassess to identify the underlying source of pain
- Reset goals if required or indicated; develop reasonable expectations
- Ask if patient is willing to engage with other modalities
- Monitor for breakthrough pain or comorbid conditions that may arise
- Review adverse events/side effects at each visit
 - Evaluate bowel function
 - Screen for endocrine function as needed
 - Implement opioid rotation, as indicated



ONGOING MANAGEMENT OF PATIENTS ON OPIOID ANALGESICS (cont.)

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

CONSIDERATIONS FOR TREATMENT MODIFICATION

- Continue IR
- Taper and discontinue (when opioid therapy is no longer necessary)
- Transition to ER/LA



TRANSITIONING FROM IR TO ER/LA OPIOID OPTIONS

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



CONSIDERATIONS FOR CHANGE FROM IR TO ER/LA OPIOIDS

DRUG SELECTION IS CRITICAL

Some ER/LA opioids or dosage forms are only recommended for opioid tolerant patients (ER/LA in opioid-naïve patients is controversial)

- ANY strength of transdermal fentanyl
- Certain strengths/doses of other ER/LA products (check drug prescribing information)
- Consider transition to buprenorphine (patch, film)

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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, <u>https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf;</u> <u>https://pubmed.ncbi.nlm.nih.gov/31917418/, https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/IB_1497_Provider_BupChronicPain.pdf</u>

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
- 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

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

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)







START WITH AN EDT FOR ADULTS

Practice Example: Transition an 80 y/o patient from morphine 180 mg/day to oxycodone

	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 muopioids

Incomplete cross tolerance among mu-opioids





GUIDELINES FOR OPIOID ROTATION

Practice Example! Transition an 80 y/o patient from morphine 180 mg/day to oxycodone

REDUCE CALCULATED EQUIANALGESIC DOSE BY 25%–50%*

SELECT % REDUCTION BASED ON CLINICAL JUDGMENT

Calculate equianalgesic dose of new opioid from EDT

CLOSER TO 50% REDUCTION CLOSER TO 25% REDUCTION

IF PATIENT...

 Is receiving a relatively high dose of current opioid regimen

Is an older adult or

IF PATIENT...

- Does not have these characteristics
- Is changing route of administration



medically frail

*75%–90% reduction for methadone



VIDEO: EQUIANALGESIC DOSING EXAMPLE

Optional Slide





IF SWITCHING TO **METHADONE**:

- Do not give methadone to opioid-naïve patients
- 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; EKG monitoring controversial

IF SWITCHING TO	IF SWITCHING TO
BUPRENORPHINE:	TRANSDERMAL FENTANYL:
Consider cross-taper with buccal film or transdermal patch; see guidelines for switch to higher dose	Calculate dose conversion based on equianalgesic dose ratios included in the drug package insert

SOURCES: <u>https://pubmed.ncbi.nlm.nih.gov/31917418/</u>, https://www.pbm.va.gov/PBM/AcademicDetailingService/ Documents/Academic_Detailing_Educational_Material_Catalog/IB_1497_Provider_BupChronicPain.pdf <u>https://accpjournals.onlinelibrary.wiley.com/doi/full/10.1002/phar.2676</u>, CDC 2022 Guideline for Prescribing Opioids for Pain, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4078896/




GUIDELINES FOR OPIOID ROTATION: SUMMARY



Practice Example! Transition an 80 y/o patient from morphine 180 mg/day to oxycodone

VALUES FROM EDT*	PATI	ENT OPIOID VALUES	SOLVE FO	OR X	AUTOMATICALLY REDUCE DOSE
Value of current opioid Value of new opioid	24-hr dose of current opioid X amount of new opioid				
Frequently assess initial response		Titrate dose of new opioid to optimize outcomes		Calcu resc titrat tc	ulate supplemental sue dose used for ion at 5%–15% of otal daily dose [‡]

- * If switching to transdermal fentanyl, use equianalgesic dose ratios provided in PI.
- [†] If switching to methadone, reduce dose by 75%–90%.
- [‡] If oral transmucosal fentanyl used as rescue, begin at lowest dose irrespective of baseline opioid.



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 OPTIMIZING

- 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 (not punitive)
- Helps to identify drug misuse/addiction



Scan to view Urine Drug Screen Video

• 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 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	Cost/OtherLower cost; intended for a drug- free population; may not be useful in pain medicine	



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

Source: http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/DrugsofAbuseTests/ucm125722.htm



EXAMPLES OF OPIOID METABOLISM



*6-MAM = 6-Monoacetylmorphine

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CONSIDERATIONS FOR RE-EVALUATING OPIOID USE

THERAPEUTIC GOALS ARE ACHIEVED 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





Scan to view CO*RE Tools



PATIENT-CENTERED APPROACH TO TAPERING

No single approach is appropriate for all patients

- Discontinue through a taper schedule
- If OUD suspected:
 - Begin treatment: Medications for Opioid Use Disorder (MOUD)
 - Consider referral to an addiction or OUD specialist if appropriate
- Consider rotation to partial agonist (e.g., buprenorphine)
- 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)

Source: https://pubmed.ncbi.nlm.nih.gov/37356051/



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





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



CHAPTER 5 EDUCATING YOUR PATIENTS AND THEIR CAREGIVERS

COUNSEL PATIENTS

Proper Use

- Take opioid as prescribed
- If a dose is missed: do not take extra, contact HCP
- Use least amount of medication necessary for shortest time
- Long-term opioid use: avoid abrupt discontinuation, taper safely to avoid withdrawal symptoms

Monitoring/Side Effects

- Notify HCP if pain is uncontrolled
- Go over all side effects (previous chapter)

Safety

- Inform HCP of ALL side effects, other meds/supplements taken
- Use caution when operating heavy machinery and driving

Scan to view Patient Counseling Guide





Storage

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

Sources: https://www.accessdata.fda.gov/drugsatfda_docs/rems/opioid_Analgesic_2018_09_18_Patient_Counseling_Guide.pdf & McDonald E, Kennedy-Hendrick A, McGinty E, Shields W, Barry C, Gielen A. Pediatrics. 2017;139(3):e20162161



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
- Sedation, cognitive impairment
- Falls and fractures
- Never share medications
 with others



OPIOID-INDUCED RESPIRATORY DEPRESSION

Distribute, dispense, or prescribe naloxone to patient or caregiver. Teach proper administration.

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:

- 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





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 and Nalmefene





Naloxone Regulation

Effective date	• June 2018
Criminal Immunity	 Prescribers: Yes Dispensers: Yes Lay People: Yes
Also Available	 Without Prescription: Yes To 3rd Party: Yes By Standing Order: Yes
Carried by First Responders	• Yes

On March 29, 2023, FDA announced approval of Narcan (naloxone hydrochloride) Nasal Spray (NNS) for use as a nonprescription opioid overdose reversal agent. OTC NNS commercially available Sept 2023. Other naloxone products will remain prescription drugs.

<u>State Naloxone Access Rules and Resources - SAFE Project</u>, January 2023 <u>http://legislativeanalysis.org/wp-content/uploads/2023/02/Naloxone-Access-Summary-of-State-Laws.pdf</u> https://www.thefdalawblog.com/2023/03/2023-is-the-year-for-otc-naloxone 3/30/2023

Collaborative for REMS Education

WHERE AND HOW TO DISPOSE OF UNUSED OPIOIDS



Authorized Collection Sites

 Use the DEA disposal locator website to find sites near you (QR code to right) or search Google Maps for "drug disposal nearby"



Scan to view disposal locator

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 compost)



Mail-Back Packages

• Obtain from authorized collectors

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



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CHAPTER 6 UNDERSTANDING OPIOID USE DISORDER (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 = mild4-5 = moderate $\ge 6 = severe$

Not valid if
 opioid is taken
 as prescribed



WORDS MATTER – PEOPLE MATTER







HOW TO IDENTIFY RISK FOR MY PATIENTS

10%–26% of patients on chronic opioid therapy (COT) for chronic noncancer pain (CNCP) may develop 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 Binge/ Intoxication Opioid peptides Corticotropin-releasing factor Dynorphin Glutamate N. Withdrawall Barive Effect Preoccupation CO*RE

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 you can save a life!

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?





HOW BUPRENORPHINE WORKS







Source: https://www.naabt.org/education/images/Receptors_HiRes.jpg, https://pubmed.ncbi.nlm.nih.gov/16547090/



BUPRENORPHINE

- Most commonly prescribed pharmacotherapy for treatment of OUD
- Good efficacy and safety profile
- "Plateau effect" for respiratory depression
- Congress eliminated the X-waiver requirement to prescribe Bup
- All DEA-licensed HCPs can prescribe without patient number caps
- Long-acting injectable and sublingual form indicated to treat opioid withdrawal and craving

FDA-approved bup products for pain:

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

Source: https://pubmed.ncbi.nlm.nih.gov/16547090/



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)
- Evaluate for SUD 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 nonpharma 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



RESOURCES TO HELP YOU TREAT OR TO REFER:

TREATMENT SUPPORT

SAMHSA – Training Materials & Resources

REFERRAL SUPPORT

ASAM – Physician Finder



SAMHSA – Find Treatment



AAAP – Specialist Finder





NIDA – Treatment Resources



PCSS – Providers Clinical Support System





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 OUD, begin treatment





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



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FULL LIST OF SOURCES AVAILABLE UPON REQUEST

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