Pain Management and Opioids:

Balancing Risks and Benefits

Wendy L. Wright,
DNP, FNP-BC, FAANP, FAAN, FNAP
Owner and FNP
Wright & Associates Family Healthcare @ Amherst and @ Concord, New Hampshire

1

FACULTY INFORMATION

Wendy L. Wright,
DNP, FNP-BC, FAANP, FAAN, FNAP
Owner and FNP
Wright & Associates Family Healthcare @ Amherst and @ Concord, New Hampshire

DISCLOSURE:
Speaker bureau: Sanofi, Pfizer, and Merck: Vaccines; AbbVie and Biohaven -Migraines
Consultant: Sanofi, Pfizer, and Merck: Vaccines; GSK-OA/pain

2

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.*

3

WHY ARE WE HERE?

4

CO*RE STATEMENT

Misuse, abuse, diversion, addiction, and overdose of opioids in the United States have created a serious public health epidemic.

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

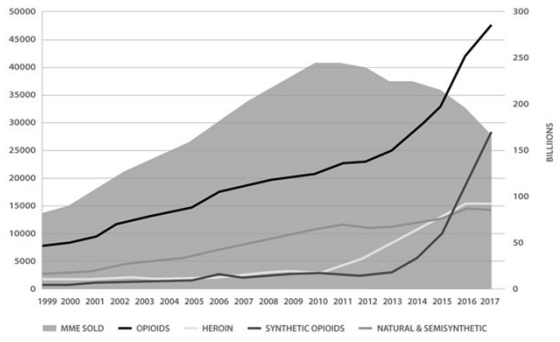
There is potential for unintended consequences of inadequately managed pain from far-reaching prescribing restrictions.

This course is in alignment with the FDA Opioid Analgesics REMS Education Blueprint.

This course does not advocate for or against the use of opioids. We intend to help healthcare 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.

5

PRESCRIBING PATTERNS AND OPIOID-RELATED DEATHS



SOURCE: CDC, Prescription Opioid Data

6

OPIOID ANALGESICS ARE SCHEDULE II SUBSTANCES

SCHEDULE	DESCRIPTION	EXAMPLES
I	High potential for abuse; no currently accepted medical use	Heroin, LSD, cannabis, ecstasy, peyote
II	High potential for abuse, which may lead to severe psychological or physical dependence	Hydromorphone, methadone, meperidine, oxycodone, fentanyl, morphine, opium, codeine, hydrocodone combination products
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, benzodiazepines, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, tramadol
V	Low potential for abuse	Gabapentin, pregabalin, cough preparations containing ≤ 200 mg codeine/100 ml

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

7

FENTANYL AND FENTANYL ANALOGUES

OD deaths from fentanyl and fentanyl analogues, such as carfentanil, have increased 540% in three years.

Street fentanyl is illegally manufactured; it is generally NOT a diverted pharmaceutical product.

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.

Fentanyl is also found in heroin, cocaine, and methamphetamine.

Photo source: New Hampshire State Drug Laboratory

8

RISKS VERSUS BENEFITS

RISKS

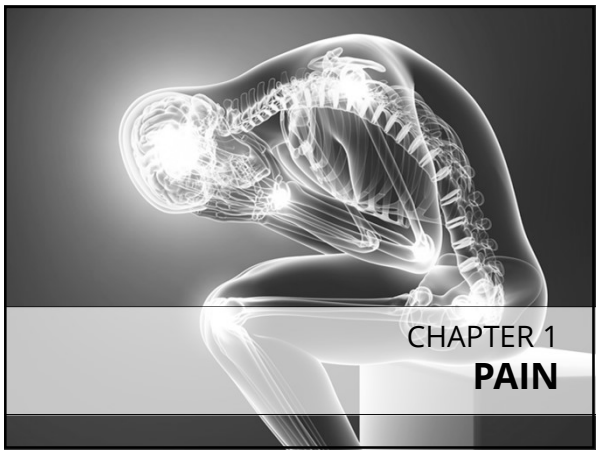
- Misuse, diversion, and addiction
- Abuse by patient or household contacts
- Interactions with other meds and substances
- Risk of neonatal abstinence syndrome
- Inadvertent exposure/ingestion by household contacts, especially children
- Life-threatening respiratory depression
- Overdose, especially as ER/LA formulations contain more MME than IR

BENEFITS

- Analgesia
  - Reliable pain control
  - Quick analgesia (particularly with IRs)
- Continuous, predictable (with ER/LAs)
- Improved function
- Improved quality of life

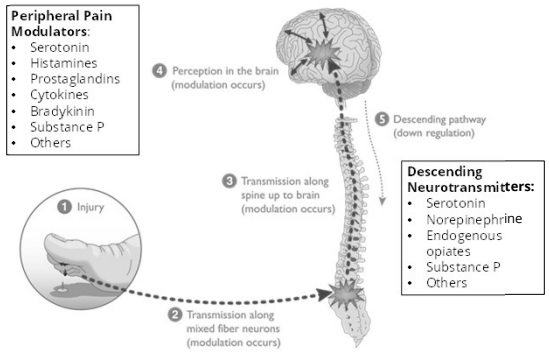
SOURCE: Nicholson, B. Pain Pract. 2009;9(1):71-81. http://onlinelibrary.wiley.com/doi/10.1111/j.1533-2500.2008.00232.x/abstract

9



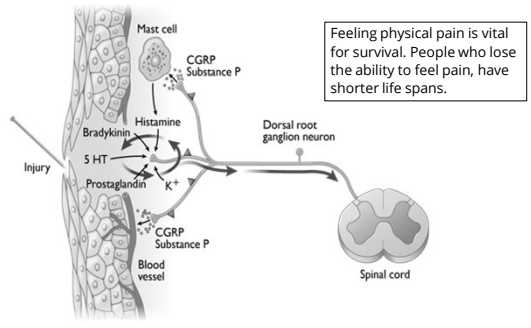
10

THE NEUROMECHANISMS OF PAIN



11

MEDIATORS OF PERIPHERAL NOCICEPTION

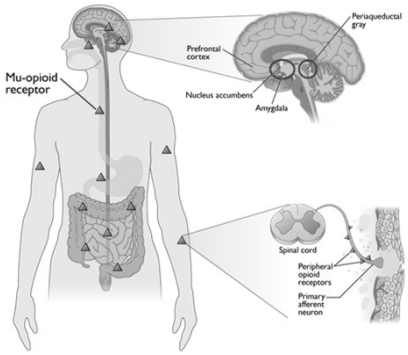


Feeling physical pain is vital for survival. People who lose the ability to feel pain, have shorter life spans.

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

12

OPIOID RECEPTOR LOCATIONS



13

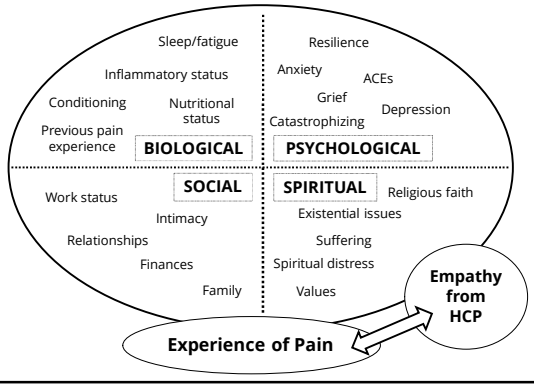
TYPES OF PAIN

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; *typically* chronic	Primary injury and secondary effects
Postoperative pain, sports injuries, arthritis, sickle cell disease, mechanical low back pain	Fibromyalgia, irritable bowel syndrome, CRPS, non-specific low back pain	Post-herpetic neuralgia, trigeminal neuralgia, distal polyneuropathy, neuropathic low back pain	

Possible development of chronic pain after an acute injury.

14

THE BIOPSYCHOSOCIAL SPIRITUAL CONTEXT OF PAIN



15

PAIN CATASTROPHIZING

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	0	1	2	3	4
I feel I can't go on	0	1	2	3	4
It's terrible and I think it's never going to get any better	0	1	2	3	4
It's awful and I feel that it overwhelms me	0	1	2	3	4
I feel I can't stand it anymore	0	1	2	3	4
I become afraid that the pain will get worse	0	1	2	3	4
I keep thinking of other painful events	0	1	2	3	4
I anxiously want the pain to go away	0	1	2	3	4
I can't seem to keep it out of my mind	0	1	2	3	4
I keep thinking about how much it hurts	0	1	2	3	4
I keep thinking about how badly I want the pain to stop	0	1	2	3	4
There's nothing I can do to reduce the intensity of the pain	0	1	2	3	4
I wonder whether something serious may happen	0	1	2	3	4

SOURCE: Pain Catastrophizing Scale © 2009 Dr. Michael JL Sullivan

- *"Tell me about your pain…"*
- Listen for rumination, feelings of hopelessness, or anticipation of negative outcomes.
- These feelings are important to identify because they can prolong and intensify pain; or lead to higher levels of suffering and altered perception of pain.
- If identified, shift to *"tell me about your life."*

16

HOW IS PAIN RESOLVED?

17

CHAPTER 2
TERMINOLOGY

18

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) [from the *DSM-5*®]
Drug-seeking, aberrant/problematic behavior	Using medication not as prescribed
Addict	Person with substance use disorder (SUD)
Clean/dirty urine	Positive/negative urine drug screen

SOURCES: SAMHSHA Resource: https://www.samhsa.gov/capt/sites/default/files/resources/sud-stigma-tool.pdf
Scholten W. Public Health. 2017;153:147-153. DOI: 10.1016/j.puhe.2017.08.021

19

WORDS MATTER: DEFINITIONS

Misuse	Use of a medication in a way other than the way it is prescribed
Abuse	Use of a substance with the intent of getting high
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
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

SOURCES: SAMHSHA Resource: https://www.samhsa.gov/capt/sites/default/files/resources/sud-stigma-tool.pdf
World Health Organization, Ensuring Balance in National Policies on Controlled Substances.
https://www.who.int/medicines/areas/quality_safety/GLs_Ens_Balance_NOCP_Col_EN_sanend.pdf

20

CHAPTER 3
ASSESSMENT

21

PAIN ASSESSMENT

DESCRIPTION OF PAIN

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

SOURCES: Heapy A, Kerns RD. Psychological and behavioral assessment. In: Raj's Practical Management of Pain. 4th ed. 2008:279-295; Zacharoff KL, et al. Managing Chronic Pain with Opioids in Primary Care. 2nd ed. Newton, MA: Inflexion, Inc.;2010.

22

PAST MEDICAL AND TREATMENT HISTORY

NONPHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

PHARMACOLOGIC STRATEGIES AND EFFECTIVENESS

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**

GENERAL EFFECTIVENESS OF CURRENT PRESCRIPTIONS

23

PRESCRIPTION DRUG MONITORING PROGRAMS (PDMPs)

PDMPs are state-run, electronic databases that track controlled substance prescriptions in a state.

PDMP DATABASES	BENEFITS
• Provide a full accounting of the controlled substance prescriptions filled by a patient • Nearly all are available online 24/7 • Required in most states; know your state laws	• Identify potential drug misuse/abuse • Discover existing prescriptions not reported by patient • Opportunity to discuss with patient • Determine if patient is using multiple prescribers/pharmacies • Identify drugs that increase overdose risk when taken together

24

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 recreational drug use
- History of adverse childhood experiences
- Family history of substance use disorder and psychiatric disorders

25

PHYSICAL EXAM AND ASSESSMENT

Seek objective data → Conduct physical exam and evaluate for pain → Order diagnostic tests (appropriate to complaint)

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

SOURCES: Lalani I, Argoff CE. History and Physical Examination of the Pain Patient. In: Raj's Practical Management of Pain. 4th ed. 2008:177-188; Chou R, et al. J Pain. 2009;10:113-130.

26

PAIN ASSESSMENT TOOL BOX

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

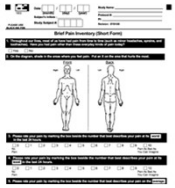
Pain Assessment Tools
BPI or 5 A's

Functional Assessment
SF-36, PPS, Geriatric Assessment

Pain intensity, Enjoyment of life, General activity
PEG

Childhood Trauma Questionnaire
ACE

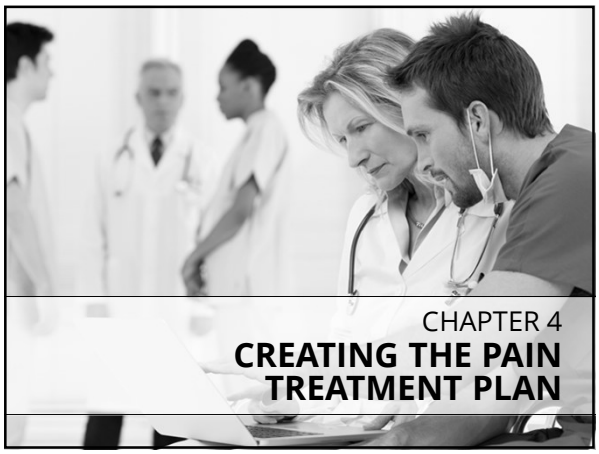
Assessment in Advanced Dementia
PAINAD



Brief Pain Inventory

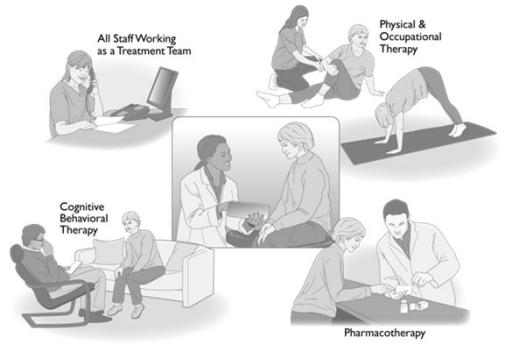
Psychological Measurement Tools (PHQ-9, GAD-7, etc.)

27



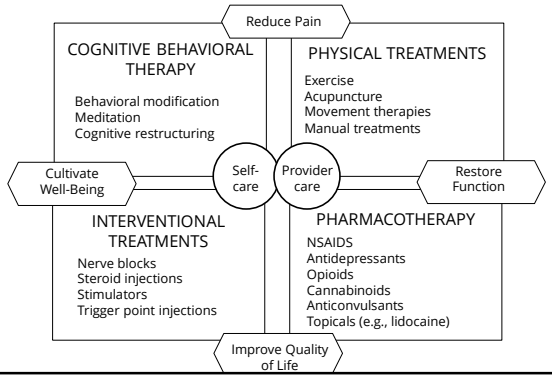
28

COMPONENTS OF A MULTIMODAL TREATMENT PLAN FOR PAIN



29

PAIN MANAGEMENT GOALS AND TREATMENT OPTIONS: A MULTIMODAL APPROACH



30

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

31

PHARMACOLOGIC TREATMENTS BY TYPE OF PAIN

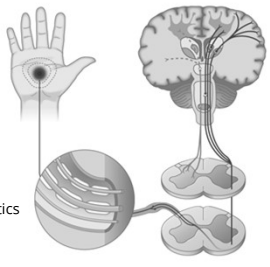
NOCICEPTIVE / INFLAMMATORY	NOCIPLASTIC	NEUROPATHIC
Antihistamine IR opioids Nerve blocks NSAIDs Topical / transdermal	Anticholinergic Anticonvulsants TCAs and SNRIs Other serotonin agents No Opioids	Anticonvulsants IR and ER/LA opioids Nerve blocks TCAs and SNRIs Transdermal opioids

CONTINUE EFFECTIVE NONPHARMACOLOGIC OPTIONS

32

APPROPRIATE MEDICATIONS FOR PERIPHERALLY MEDIATED VERSUS CENTRALLY MEDIATED PAIN

Peripherally Mediated Pain:
- Acetaminophen
- Antihistamines
- NSAIDs
- Opioids
- Topical anesthetics



Centrally Mediated Pain:
- Alpha-2 agonists
- Anticonvulsants
- Ca^{+} channel antagonists
- NMDA
- Opioids
- TCA/SNRI antidepressants

33

DRUG CHARACTERISTICS TO CONSIDER BEFORE PRESCRIBING

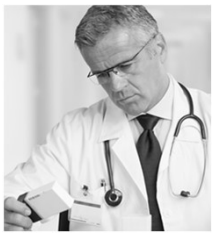
Route of administration	Formulation	Strength	Dosing interval
Key instructions (indications, uses, contraindications)	Specific drug interactions	MOA	Product-specific safety concerns
Specific information about product conversions, if available		Use in opioid-tolerant patients	Relative potency to morphine

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

34

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 neuropathic or nociceptive pain that is moderate to severe



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. 2010.

35

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
RAFFT Relax, Alone, Friends, Family, Trouble
DAST Drug Abuse Screening Test
CTQ Childhood Trauma Questionnaire
ACEs Adverse Childhood Experiences

Also for patients with chronic pain:
- Get a baseline UDT
- Check the PDMP

36

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. JPain 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**

37

OPIOID SIDE EFFECTS AND ADVERSE EVENTS

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

38

OPIOID-INDUCED RESPIRATORY DEPRESSION

MORE LIKELY TO OCCUR:

- In elderly, cachectic, or debilitated patients
- If given concomitantly with other drugs that depress respiration
- In patients who are opioid-naïve or have just had a dose increase
- Opioids are **contraindicated** in patients with respiratory depression or conditions that increase risk

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
- Instruct patients to swallow tablets/capsules whole
  - Dose from cut, crushed, dissolved, or chewed tablets/capsules may be fatal, particularly in opioid-naïve individuals

39

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		

40

FOR SAFER USE: KNOW DRUG INTERACTIONS, PK, AND PD

CNS depressants can potentiate sedation and respiratory depression	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	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

41

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

42

DRUG INTERACTIONS COMMON TO OPIOIDS

Other CNS Depressants
- Concurrent use can increase risk of respiratory depression, hypotension, profound sedation, or coma
- Reduce initial dose of one or both agents

Partial Agonists* or Mixed Agonist/Antagonists †
- Avoid concurrent use 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

43

44

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

SOURCE: 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.

45

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, breast feeding 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 high-risk OB/Gyn who will ensure appropriate treatment for the baby

- Perform universal screening to avoid neonatal abstinence syndrome

- For women using opioids on a daily basis, consider methadone or buprenorphine

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

46

CHILDREN AND ADOLESCENTS

HANDLE WITH CARE: JUDICIOUS & 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
- Oxycodone ER dosing changes for children ≥ 11

ER/LA OPIOID INDICATIONS ARE PRIMARILY LIFE-LIMITING CONDITIONS

WHEN PRESCRIBING ER/LA OPIOIDS TO CHILDREN:

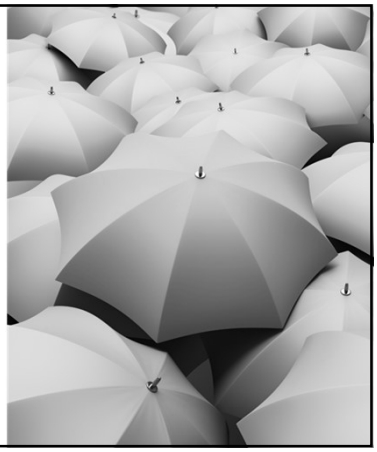
- Consult pediatric palliative care team or pediatric pain specialist or refer to a specialized multidisciplinary pain clinic

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.

47

OTHER POPULATIONS NEEDING SPECIAL TREATMENT CONSIDERATIONS

- Persons with sleep disorders or sleep-disordered breathing (sleep apnea)
- Persons with dementia/ nonverbal patients
- Persons with obesity
- Persons with renal/ hepatic impairment
- Persons with psychiatric disorders
- Persons at end-of-life
- Persons with substance use disorder



48

INFORMED CONSENT

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

- ANALGESIC AND FUNCTIONAL GOALS OF TREATMENT
- EXPECTATIONS
- POTENTIAL RISKS
- ALTERNATIVES
- PATIENT'S UNDERSTANDING
- PATIENT'S DECISION

49

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 UDT and pill counts
- Refill procedure
- Identify behaviors indicating need for discontinuation
- Exit strategy
- Signed by both

50

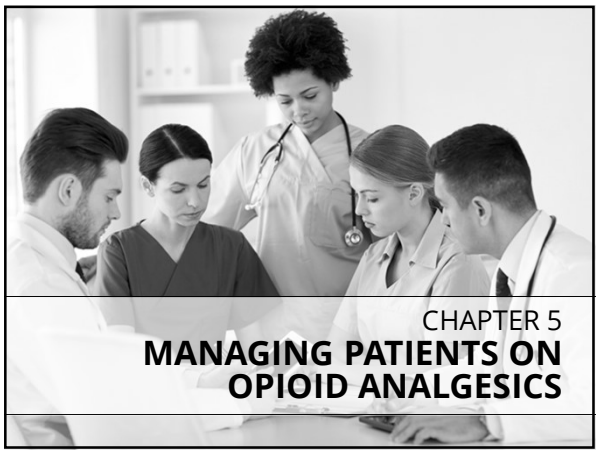
PPA NONADHERENCE

Behavior outside the boundaries of agreed-on treatment plan

Unsanctioned dose escalations or other noncompliance with therapy on 1 or 2 occasions	Multiple dose escalations or other noncompliance with therapy despite warnings
Unapproved use of the drug to treat another symptom	Prescription forgery
Openly acquiring similar drugs from other medical sources	Obtaining prescription drugs from nonmedical sources

Any of these behaviors merits **investigation**: proceed with caution

51



CHAPTER 5

MANAGING PATIENTS ON OPIOID ANALGESICS

52

INITIATING OPIOIDS

- Begin with IR
- Prescribe the lowest effective dosage
- Use caution at any dosage, but particularly when:
  - Increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day
  - Carefully justify a decision to titrate dosage to ≥ 90 MME/day
- Always include dosing instructions, including daily maximum
- Be aware of interindividual variability of response
- Co-prescribe naloxone (if indicated)
- Co-prescribe 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 3 months; if benefits do not outweigh harms, optimize other therapies and work to taper and discontinue

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

53

ONGOING AND LONG-TERM MANAGEMENT OF PATIENTS ON OPIOID ANALGESICS

PERIODIC REVIEW OF PAIN

- Is the patient making progress toward their 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

54

ONGOING AND LONG-TERM MANAGEMENT OF PATIENTS ON OPIOID ANALGESICS

MONITORING FOR SAFETY

- Check PDMP (when clinically indicated or legally mandated)
- Use urine drug testing (UDT)
- Reassess risk of 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?

55

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

56

WHEN TO MOVE FROM IR TO ER/LA OPIOIDS

PRIMARY REASONS	OTHER POTENTIAL 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	• 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

57

CONSIDERATIONS FOR CHANGE FROM IR TO ER/LA OPIOIDS

DRUG AND DOSE SELECTION IS CRITICAL	MONITOR PATIENTS CLOSELY FOR RESPIRATORY DEPRESSION	INDIVIDUALIZE DOSAGE BY TITRATION BASED ON EFFICACY, TOLERABILITY, AND PRESENCE OF AEs
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)	• Especially within 24 – 72 hours of initiating therapy and increasing dosage	• 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

58

OPIOID-INDUCED HYPERALGESIA

- An increased sensitivity to pain
- 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 progression
- Usually occurs at high MME dosages and over long periods of time
- A physiological phenomenon that can happen to anyone

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

59

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

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/RpcUI/products.u

60

OPIOID TOLERANCE VERSUS PHYSICAL DEPENDENCE

TOLERANCE

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

⟺

PHYSICAL DEPENDENCE

- Occurs when an organism 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

61

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.

62

EQUIANALGESIC DOSING TABLES (EDT)

Many different versions:

Published	Online
Online interactive	Smart-phone 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

63

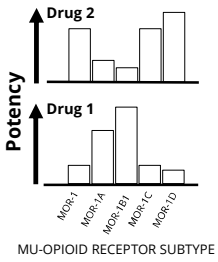
EXAMPLE OF AN EDT FOR ADULTS

	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)

64

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



MU-OPIOID RECEPTOR SUBTYPE

65

GUIDELINES FOR OPIOID ROTATION

Calculate equianal-gesic dose of new opioid from EDT

REDUCE CALCULATED EQUIANALGESIC DOSE BY 25% – 50%*

SELECT % REDUCTION BASED ON CLINICAL JUDGMENT

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

*75% – 90% reduction for methadone

66

GUIDELINES FOR OPIOID ROTATION *(continued)*

IF SWITCHING TO METHADONE:

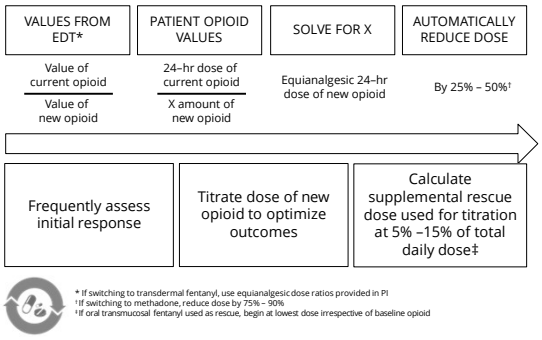
- Standard EDTs are less helpful in opioid rotation to methadone
- For opioid tolerant patients, methadone doses should **not** exceed 30 – 40 mg/day upon rotation
  - Consider inpatient monitoring, including serial EKG monitoring
- For opioid-naïve patients, do **not** give methadone as an initial drug

IF SWITCHING TO TRANSDERMAL:

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

67

GUIDELINES FOR OPIOID ROTATION: SUMMARY



* 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

68

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 aberrant/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

69

ABUSE-DETERRENT FORMULATION (ADF) OPIOIDS

- Response to growing non-medical-use problem
- An ER/LA opioid with properties to meaningfully deter abuse, even if they do not fully prevent abuse
  - 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

70

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

71

SCREENING VERSUS CONFIRMATORY UDTS

	SCREENING	CONFIRMATORY
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
Other	Intended for a drug-free population, may not be useful in pain medicine.	Legally defensible results

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

72

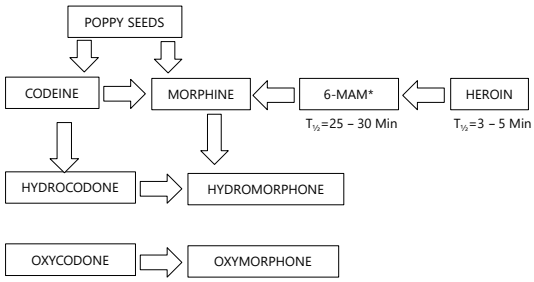
WINDOWS OF SPECIFIC DRUG DETECTION

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/pot	1 – 3 hours	1 – 7 days
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
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

73

EXAMPLES OF OPIOID METABOLISM



*6-MAM=6-Monoacetylmorphine

74

REASONS FOR DISCONTINUING OPIOIDS

PAIN LEVEL DECREASE IN STABLE PATIENTS	INTOLERABLE AND UNMANAGEABLE AEs	NO PROGRESS TOWARD THERAPEUTIC GOALS

MISUSE OR ABERRANT 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

75

OUD/SUD RISK ASSESSMENT TOOLS (ONCE TREATMENT BEGINS)

PMQ Pain Medication Questionnaire	**COMM** Current Opioid Misuse Measure
PDUQ Prescription Drug Use Questionnaire	**SBIRT** Screening, Brief Intervention, and Referral to Treatment

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

76

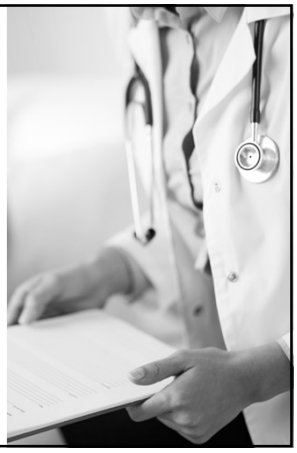
TAPER DOSE WHEN DISCONTINUING

- 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
- If opioid use disorder or a failed taper, refer to an addiction specialist or consider opioid agonist therapy
- Counseling and relaxation strategies needed

77

CONSULTING A PAIN SPECIALIST

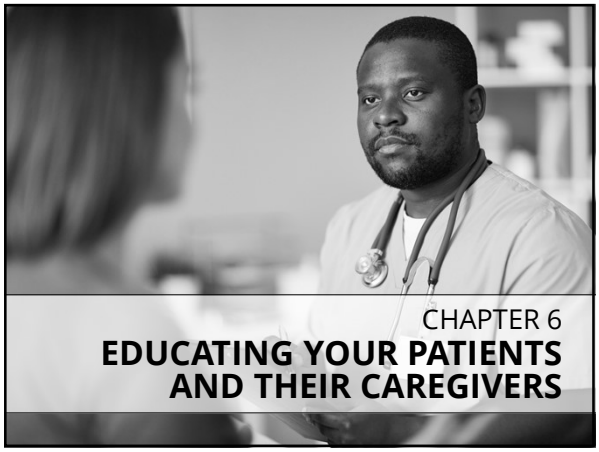
- Appropriate when you feel you cannot provide the level of care needed
- First ensure you have a reliable specialist to refer to
- To find a pain specialist in your area:
  - Consult with state boards
  - Consult with colleagues
  - Use online resources
  - Consult payment source
- Prior to referral, contact the specialist and ask what is needed for referral



78

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

79



CHAPTER 6

EDUCATING YOUR PATIENTS AND THEIR CAREGIVERS

80

COUNSEL PATIENTS ABOUT PROPER USE

- Take opioid as prescribed
- Adhere to dose regimen
- Use least amount of medication necessary for shortest time
- Do not abruptly discontinue or reduce dose; taper safely to avoid withdrawal symptoms
- Properly handle missed doses
- Notify HCP if pain is uncontrolled
- Manage side effects
- Inform HCP of ALL meds being taken
- Never share or sell opioids: can lead to others' deaths, against the law
- Use caution when operating heavy machinery and driving

Read the opioid **drug package insert** received from the pharmacy **every time** an opioid is dispensed

81

USE PATIENT COUNSELING DOCUMENT

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

CLICK TO DOWNLOAD

https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_Analgesic_2018_09_18_Patient_Counseling_Guide.pdf

82

PROVIDE ANTICIPATORY GUIDANCE ON OPIOID SIDE EFFECTS AND ADVERSE EVENTS

- Respiratory depression: most serious
- Opioid-induced constipation (OIC): most common
- Sexual dysfunction and other endocrine abnormalities
- Tolerance, physical dependence, hyperalgesia
- Allergic reactions
- Sedation, cognitive impairment
- Falls and fractures
- Sweating, miosis, urinary retention
- Hypogonadism
- Myoclonus (twitching or jerking)
- Addiction in vulnerable patients
- Overdose and death

83

WARN PATIENTS

Never break, chew, crush, or snort an opioid tablet/capsule, or cut or tear patches or buccal films prior to use

- May lead to rapid release of opioid, causing overdose and death
- If patient is unable to swallow a capsule whole, refer to drug package insert to determine if appropriate to sprinkle contents on applesauce or administer via feeding tube

Use of CNS depressants or alcohol with opioids can cause overdose and death

- Use with alcohol may result in rapid release and absorption of a potentially fatal opioid dose, known as "dose dumping"
- Use with other depressants such as sedative-hypnotics (benzodiazepines), anxiolytics, or illegal drugs can cause life-threatening respiratory depression

84

OPIOID-INDUCED RESPIRATORY DEPRESSION

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

Greatest risk: during initiation of therapy 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

85

SIGNS OF OVERDOSE POISONING CALL 911

- Person cannot be aroused or awakened 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

86

NALOXONE

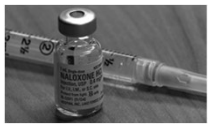
What it is:
- An opioid antagonist administered intranasally (most common) or parenterally
- Reverses acute opioid-induced respiratory depression but will also reverse analgesia; may precipitate acute opioid withdrawal

What to do:
- Discuss an overdose plan with patients
- Consider offering a naloxone prescription to all patients prescribed opioids; some states *require* co-prescribing
- Involve and train family, friends, partners, and/or caregivers in the proper administration of naloxone
- Check to see if pharmacy dispenses it
- Check expiration dates and replace expired naloxone
- In the event of known or suspected overdose **call 911** and administer naloxone

87

NALOXONE OPTIONS

- Available as auto-injector, intramuscular injection, or nasal spray
- Cost and insurance coverage vary
- Make use of tutorial videos to demonstrate administration
- Store at room temperature
- Dispose of used containers safely



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

88

SAFE OPIOID STORAGE AND DISPOSAL

STEP 1: MONITOR	STEP 2: SECURE	STEP 3: DISPOSE
• Note how many pills are in each prescription • Keep track of dosage and refills • Make sure everyone in the home knows	• Keep meds in a safe place (locked cabinet or box) • Store away from children, family, visitors, and pets • Encourage parents of your teen's friends to secure their prescription	• Discard expired or unused meds • Consult drug package insert for best disposal method

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

89

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"

Mail-Back Packages

- Obtain from authorized collectors

Other Options

- Drug take-back days (local pharmacies or local law enforcement)
- Flush
- Trash (mix with noxious element)
- Fold patch in half so sticky sides meet, then flush

SOURCES. Department of Justice, Diversion Control Division, Disposal Act: General Public Fact Sheet (June 2018), https://www.deadiversion.usdoj.gov/drug_disposal/fact_sheets/disposal_public_06222018.pdf, FDA. Where and How to Dispose of Unused Medicines, https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm101653.htm

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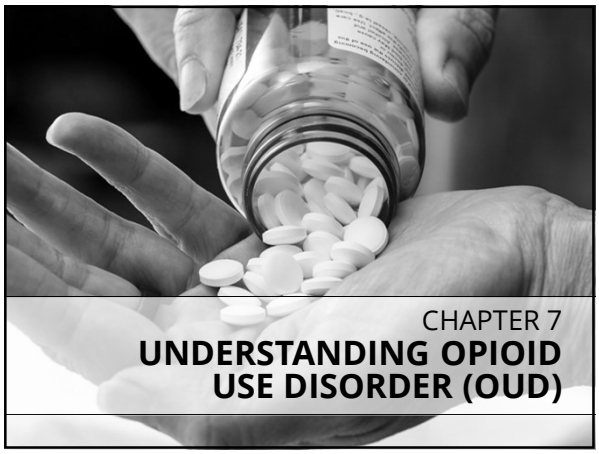
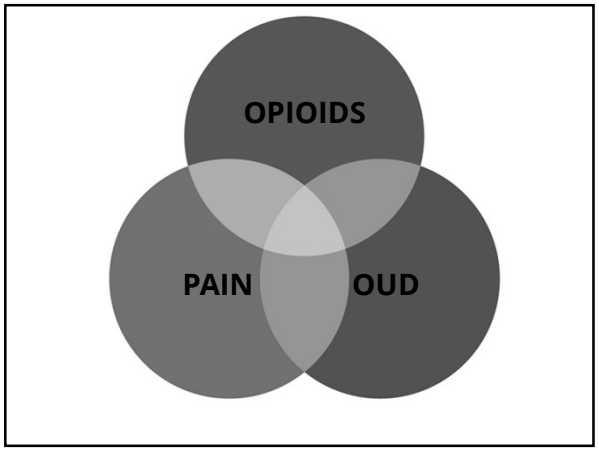


CHAPTER 7
UNDERSTANDING OPIOID USE DISORDER (OUD)

91



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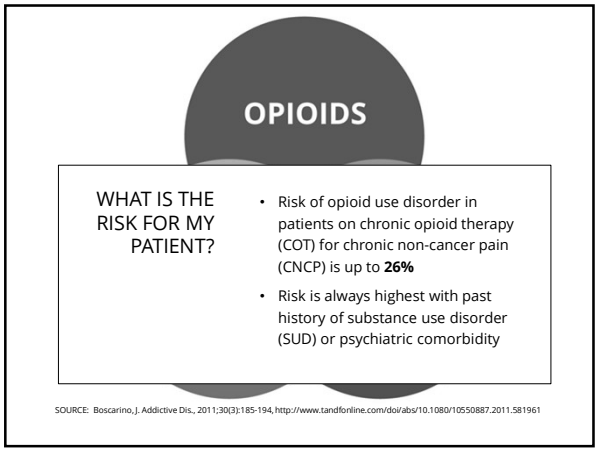


93

WHAT IS ADDICTION?

OFFICIAL ASAM DEFINITION:	PRACTICAL DEFINITION:
Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors.	Addiction is the continued use of drugs or activities, despite knowledge of continued **harm** to one's self or others.

94

SUBSTANCE USE DISORDER: DSM-5 CRITERIA

1. Tolerance*
2. Withdrawal*

LOSS OF CONTROL

3. Using larger amounts and/or for longer periods
4. Inability to cut down on or control use
5. Increased time spent obtaining, using, or recovering
6. Craving/compulsion

USE DESPITE NEGATIVE CONSEQUENCES

7. Role failure at work, home, school
8. Social, interpersonal problems
9. Reducing social, work, recreational activity
10. Physical hazards
11. Physical or psychological harm

- 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). 2013

95

PAIN, OUD, AND OPIOIDS

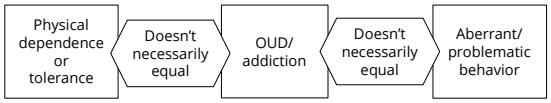
The DSM-5 criteria for opioid use disorder may be misleading in the context of *prescribed opioids* for the treatment of pain.

The usual illegal, illicit issues do not pertain.

Harm may be masked under these conditions.

96

WORDS MATTER



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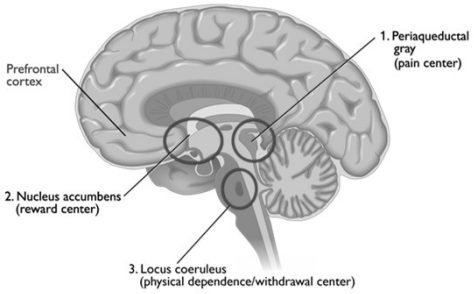
OPIOID RECEPTORS IN THE BRAIN: RELATIONSHIP TO ANALGESIA, OUD, AND WITHDRAWAL

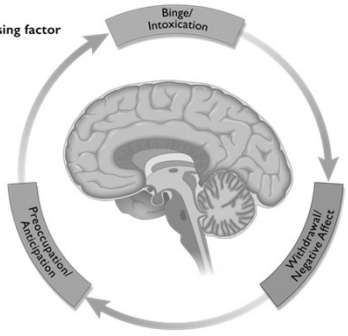


98

THE CYCLE OF SUBSTANCE USE DISORDER

NEUROTRANSMITTERS

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



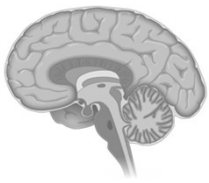
99

WHO IS VULNERABLE TO OPIOID MISUSE OR OUD?

Those with psychiatric comorbidities

19% of people who have mental health disorders in United States receive 51% of the prescribed opioids.

The probability of long-term opioid use increases most sharply in the first days of therapy, particularly after 5 days or 1 month of opioids has been prescribed.



100

TREATMENT OF OPIOID USE DISORDER

- Medication options for addiction treatment (MAT)
  - Methadone (Schedule II)
  - Buprenorphine (Schedule III)
  - Naltrexone (not a controlled substance)
- Supplementary psychosocial and recovery support services
  - Housing, childcare, support groups, employment services
- Temporal considerations
  - Frequency of administration (daily versus long-acting formulations)
  - Length of treatment
    - No recommended time period for treatment
    - Patients who discontinue and resume risk overdose and death

101

TREATING PAIN IN THE PATIENT WITH OUD

- Remember that untreated pain is a trigger for relapse
- Must address *both* pain and opioid use disorder
- Avoid other potentially problematic medications
- Consider a multidisciplinary pain program

- Consider buprenorphine for both pain and OUD
- Consider using opioids that do not metabolize to other prescribed medications
- Enlist patient's family/ significant other to secure and dispense opioids
- Recommend an active recovery program
- Remember to use UDT, PDMP, pill counts, PPA

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

102

OPIOID ANALGESICS WITH BENZODIAZEPINES, NICOTINE, AND ALCOHOL

- More than 30% of opioid overdoses involve benzodiazepines (BZDs); both are CNS depressants
- Nicotine and alcohol use are risk factors for misuse of prescribed opioids
- Nicotine users are co-prescribed BZDs and muscle relaxants (MRs) with opioids to a greater extent than non-nicotine users

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

103

BUPRENORPHINE

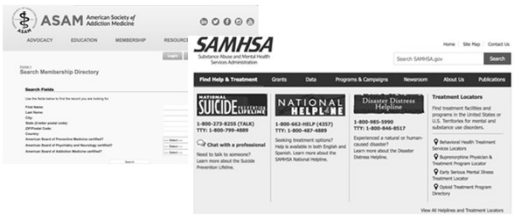
- If using for pain, you don't need a waiver
- If using to treat OUD, you need a waiver
- The most commonly prescribed pharmacotherapy for the treatment of OUD
- Partial mu-agonist with "plateau effect" for respiratory depression
- Good efficacy and safety profile
- FDA-approved buprenorphine products for pain:
  - Butrans: 7-day transdermal patch
  - Belbuca: buccal mucosal film; BID dosing

104

REFERRALS AND TREATMENT CENTERS

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

ASAM resources: https://www.asam.org/resources/resource-links
SAMHSA locator: https://findtreatment.samhsa.gov/locator
AAAP locator: https://www.aaap.org/patients/find-a-specialist/



105

Case-Based Learning
Acute Pain from End-Stage OA

106

Clinical Case: End-Stage Osteoarthritis (OA)

- Mrs. R is a 72-year-old woman presenting to her primary care provider with a 2-week history of swelling on the lateral aspect of her right knee and painless right sided foot drop
- Imaging studies revealed end-stage osteoarthritis with swelling over the fibular head
- The patient rated her pain a 7 out of 10

107

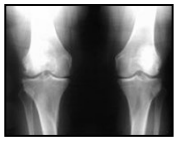
Clinical Case: End-Stage Osteoarthritis (OA)

- Mrs. R is a candidate for primary replacement of her knee
  - She will undergo surgery in two weeks
- Previously maintained on daily NSAID doses
  - Patient must discontinue NSAID in preparation for surgery to avoid interference with coagulation

108

Osteoarthritis (OA)

- A degenerative disorder that results from breakdown of articular cartilage in the synovial joints
  - Thought to be due primarily to wear and tear
  - Non-specific inflammatory changes may also affect the joints



Stacy SG, et al. Emedicine. Osteoarthritis, primary. http://emedicine.medscape.com/article/392096-overview

109

Clinical Case: Osteoarthritis

What is the BEST pharmacologic treatment for the patient's end-stage OA pain during the 10-day time period prior to her knee replacement surgery?

a. Continue NSAIDs with acetaminophen at higher and more frequent doses
b. Opioid therapy
c. Antidepressants
d. Topical anesthetics
e. None of the above

110

Pharmacological Therapy for Acute Pain

Medication Class	Action	Side Effects
Opioids	Agonistic effect ; acts at the mu receptor	Respiratory depression, GI irritation
Nonopioids (NSAIDs, COX-2, acetaminophen)	Principle mechanism of action is prostaglandin synthesis	Impaired hemostasis, GI irritation/bleeding, cardiovascular risk, renal toxicity
Dual-mechanism	Target multiple pain mechanism	Similar to opioids with better GI tolerability
Anticonvulsants	Decrease excitability of neurons by modulating sodium channels	Sleepiness, dizziness, fatigue
Antidepressants	Inhibit both NE and serotonin reuptake	Vary by class, include, dry mouth, blurred vision, nausea, constipation
Topical anesthetics	Modulate sodium channels; interrupts some nerve conduction	Local reactions at application site

Brunto LL, Lazo SS, Parker KL. Goodman & Gillman's The Pharmacological Basis of Therapeutics, 11th ed. New York, NY: McGraw Hill; 2006.

111

What's Coming Soon?

- Nerve growth factor inhibitors
  - **Tanezumab**
  - **Fasinumab**

112

How do you want to treat this patient?

113

Case Based Learning
Postherpetic Neuralgia

114

Clinical Case: Cancer-related Pain and Post-herpetic Neuralgia

- Mrs. M is 56-year-old woman with advanced breast cancer with bony metastases in the right femur and iliac crest and hepatic metastases maintained on stable doses of opioids
- Four months ago, she developed acute herpes zoster (shingles) treated only with antiviral therapy and additional intermittent opioids with little relief
- She arrives at her medical oncologist's office reporting steadily increasing pain in the area of her torso, unrelieved by her opioid medication
- She states that wearing clothing over that area of her body causes excruciating pain

115

115

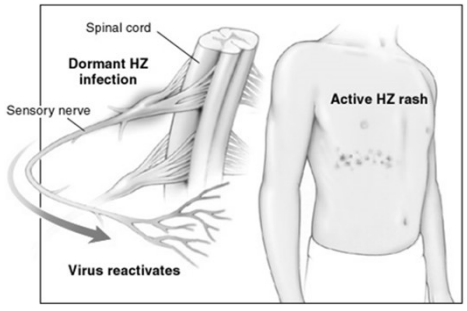
Clinical Case: Breast Cancer
History

- Current pain status
  - Severe pain in the torso and upper limbs
  - Average pain intensity 6 to 8 (0 to 10)
  - Worst pain intensity 8 to 10
- Health history
  - Advanced but relatively stable breast cancer
  - Recent recovery from varicella zoster infection
- Analgesic therapy
  - Extended-release morphine 60 mg q12h
  - Short-acting morphine 15 mg q2h PRN

116

116

Schematic of VZV Latency and Reactivation



Adapted from http://merck.micromedex.com/images/bhg/BHG01D10F02.gif.

117

Clinical Case: Breast Cancer
Initial Assessment

- Patient reports excruciating pain in her torso and upper arms

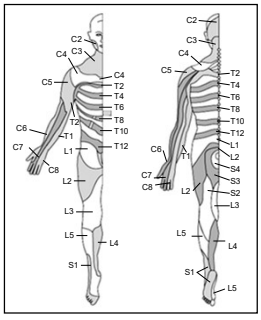
What type of pain is she experiencing?

a)Chronic cancer pain (somatic and visceral in origin)
b) Postherpetic neuralgia (PHN)
c) Cutaneous hypersensitivity (allodynia and hyperalgesia)
d) All of the above

118

Typical Locations of Herpes Zoster

- 56% thoracic
- 13% lumbar
- 13% cranial
- 11% cervical
- 4% sacral
- 3% other sites



Raggozzino MW, et al. *Medicine (Baltimore)*. 1982;61:310-316.

119

Characterization of Pain Associated With PHN

- Dysesthesia: an unpleasant abnormal sensation, spontaneous or evoked[1]
- Hyperalgesia: pain of exaggerated severity in response to normally painful stimulation[1]
- Allodynia: pain evoked by a normally innocuous stimulus[1]
  - Allodynia in some patients with PHN is a form of chronic secondary hyperalgesia maintained by input from intact and possibly "irritable" primary afferent nociceptors to a sensitized CNS[2]

1. Merskey H, Bogduk N. Classification of Chronic Pain. 2nd ed. Ann Arbor, Michigan: *IASP Press;* 1994;209-214.
2. Petersen KL, et al. *Pain.* 2000;88:125-133.

120

120

PHN: Risk Factors

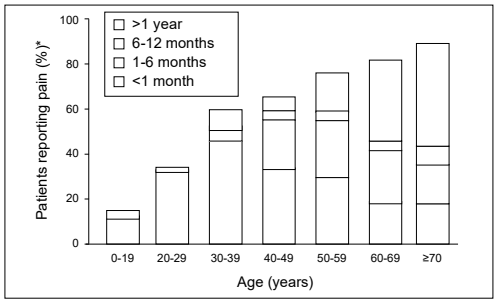
- Age[1,2]
- Severity of acute pain[1,2]
- Severity of acute rash[1,2]
- Painful prodrome[1]
- Gender – Female[1]

1. Jung B. *Neurology*. 2004;62:1545-1551.
2. Dworkin R, et al. *J Infect Dis*. 1998;178:S76-S80.

121

121

Duration of Pain Associated With PHN and Increased Age



*Population represents those referred to a pain clinic.
Modified from Kost RG, Strauss SE. *N Engl J Med*. 1996;335:32-42.

122

122

Evaluating Outcomes With PHN

- Worst pain intensity levels moderate to severe[1]
- Pain caused measurable interference with general activity (40%), mood (45%), and enjoyment of life (48%)[1]
- 31% had relatively low levels of satisfaction with pain medication[1]
- 44% moderate anxiety and depression[1]
- Brief Pain Inventory (BPI) utilized to evaluate pain in recent herpes zoster vaccine trial[2]

1. Oster G, et al. *J Pain*. 2005;6:356-363.
2. Oxman M, et al. *N Eng J Med*. 2005;352:2271-2284.

123

Clinical Case: Breast Cancer Treatment Plan

How would you manage this patient's PHN pain?

a) Lidocaine 5% patch
b) Opioid analgesics
c) Tricyclic antidepressants (TCAs)
d) Anticonvulsants
e) Multimodal therapy

124

Management Strategies for PHN

Therapy	Limitations
Lidocaine 5% patch	• Erythema or rash • Caution in patients receiving class I antiarrhythmics
Antidepressants	• Anticholinergic AEs, sedation, cardiac conduction abnormalities
Anticonvulsants	• Somnolence, dizziness, gait disturbances, GI upset
Opioid analgesics	• CNS- and GI-related AEs
Dual mechanism agents	• Similar to opioids but with better GI profile

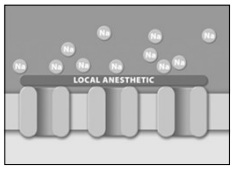
Kost R, et al. *N Engl J Med.* 1996;355:32-42. 125

125

Classes of Pain Medications: Local Anesthetics

Examples: lidocaine, bupivacaine

- Modulate sodium channels
- When administered peripherally, may produce differential—also known as sensory—block
  - Interrupts some nerve conduction, but leaves motor function unaffected
  - Some nerves are more readily blocked than others, depending on size and myelination
- Interrupts pain input at the nerve roots
- Associated with few adverse effects

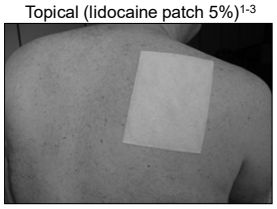


Brunto LL, Lazo SS, Parker KL. Goodman & Gillman's The Pharmacological Basis of Therapeutics, 11th ed. New York, NY: McGraw Hill; 2006.

126

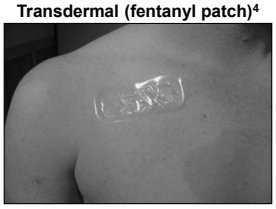
Topical vs Transdermal Medication Delivery Systems

Topical (lidocaine patch 5%)[1-3]



Peripheral tissue activity
Applied directly over painful site
Minimal systemic absorption
Systemic AEs rare

Transdermal (fentanyl patch)[4]



Systemic activity
Applied away from painful site
Serum levels necessary
Systemic AEs common

1. Argoff CE. *Clin J Pain*. 2000;16(2 suppl):S62-S66.
2. Galer BS, Rowbotham MC, Perander J, Friedman E. *Pain*. 1999;80:533-538.
3. Galer BS, Dworkin RH. *A Clinical Guide to Neuropathic Pain*. 2000:61-64.
4. Duragesic [package insert]. Pharmaceutica; 1999.

127

Lidocaine Patch 5%

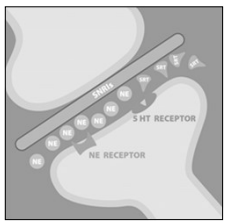
- Lidocaine 5% in pliable patch[1]
- Up to 3 patches applied once daily directly over painful site[2,3]
  - 12 h on, 12 h off (FDA-approved label)
  - Recently published data indicate 4 patches (18–24 h) safe
- Efficacy demonstrated in 3 randomized controlled trials on PHN[3-5]
- Drug interactions and systemic side effects unlikely[6-8]
  - Most common side effect: application-site sensitivity
- Clinically insignificant serum lidocaine levels[7]
- Mechanical barrier decreases allodynia[4]

1. Lidoderm (lidocaine patch 5%) [package insert].
2. Alvarez NA, et al. *Programs and Abstracts of the IASP 10th World Congress on Pain*. 2002. Abstract 175-P171.
3. Rowbotham MC, et al. In: *Programs and Abstracts of the 8th World Congress on Pain*. 1996. Abstract 274.
4. Rowbotham MC, et al. *Pain*. 1996;65:39-44.
5. Galer BS, et al. *Pain*. 1999;80:533-538.
6. Argoff CE. *Clin J Pain*. 2000;16(2 suppl):S62-S66.
7. Galer BS, et al. *A Clinical Guide to Neuropathic Pain*. 2000:61-64;
8. Gammaitoni AR, et al. *Ann Pharmacother*. 2002;36:236-240.

128

Classes of Pain Medications: Antidepressants

- Tricyclics
  - Examples: amytriptyline, nortriptyline, desipramine
  - Inhibit both norepinephrine (NE) and serotonin reuptake to varying degrees
  - Possess other properties (eg, local anesthetic-like activity)
- SNRIs (serotonin norepinephrine reuptake inhibitors)
  - Examples: venlafaxine, duloxetine, bupropion
  - Selective serotonin reuptake inhibitors (SSRIs) have not been shown to be particularly effective as pain therapy



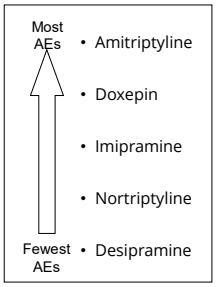
- Adverse effects vary by class of agent, and include dry mouth, blurred vision, nausea, constipation, agitation, dizziness, and drowsiness

Brunto LL, Lazo SS, Parker KL. Goodman & Gillman's The Pharmacological Basis of Therapeutics, 11th ed. New York, NY: McGraw Hill; 2006.

129

Tricyclic Antidepressants: Adverse Effects

- Commonly reported AEs (generally anticholinergic):
  - Blurred vision
  - Cognitive changes
  - Constipation
  - Dry mouth
  - Orthostatic hypotension
  - Sedation
  - Sexual dysfunction
  - Tachycardia
  - Urinary retention

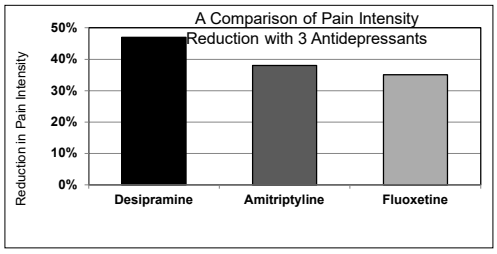


Brunto LL, Lazo SS, Parker KL. Goodman & Gillman's The Pharmacological Basis of Therapeutics, 11th ed. New York, NY: McGraw Hill; 2006.

130

Antidepressant Use for PHN

- 2005 study revealed that TCA's and SSRI's reduced PHN pain, with desipramine providing satisfactory relief in 80% of those treated



Rowbotham MC. *J Pain.* 2005;6:741-746.

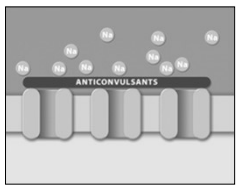
Wright, 2021

131

Classes of Pain Medications: Anticonvulsants

Examples: gabapentin, pregabalin, lamotrigine, topiramate

- Decrease excitability of neurons by modulating sodium channels; do not act on GABA
- Emerging as top-line adjunct in acute pain and first-line therapy in chronic pain
- Adverse effects/limitations
  - Most common adverse effects are CNS related, including sleepiness, dizziness, and fatigue



Brunto LL, Lazo SS, Parker KL. Goodman & Gillman's The Pharmacological Basis of Therapeutics, 11th ed. New York, NY: McGraw Hill; 2006.

132

Treatment Plan and Outcome for Mrs. M.

- 56-year-old breast cancer patient with PHN
  - After weighing treatment options, the patient was eventually treated with multimodal therapy
    - Continue current opioid therapy
    - Gabapentin was given and topical lidocaine was given for local relief

    OR
    - Consider treatment with a single acting dual mechanism agent
  - The patient recovered comfortably over the next 3 weeks

133

Case-Based Learning Chronic Low Back Pain

134

Clinical Case: Chronic Lower Back Pain (CLBP)

- Mr. L is 46-year-old man with history of CLBP, Type 2 diabetes, and osteoarthritis
- Presents with an acute episode (onset 1 day prior) of low back pain
- Body mass index (BMI): 38
- History of depression (currently taking sertraline)

135

Clinical Case: CLBP
History

- Current pain status
  - Intermittent unilateral pain in the left leg with radiating weakness to the foot
  - Intensity ranges from 5/10 to 9/10
- Health history
  - Moderate osteoarthritis in the knees
  - Moderate chronic low back pain for approximately 5 years after an automobile accident
- Medication history
  - Increasing doses of extended-release Oxycodone over past year
  - Diclofenac sodium topical gel 4 g qid to each knee
  - Oxycodone extended-release 80 mg q12h with short-acting oxycodone 15 to 30 mg every 3 to 4 hours as needed

136

136

Clinical Case: CLBP
Initial Assessment

Current Status

- Currently patient presents with unrelieved intermittent unilateral radiating pain down the left leg and increased pain in both knees from osteoarthritis
- Mr. L. is insisting that doses of his opioids be increased as he cannot stand the pain
- He reports that he is tired of being on disability and wants to have a better quality of life

137

Clinical Case: CLBP
Initial Assessment

Identify the possible pathophysiological mechanisms for his pain

Why is this patient not achieving adequate pain relief with his opioid regimen?

a) Opioid-nonresponsive neuropathic pain
b) Opioid tolerance
c) Worsening depression
d) Opioid hyperalgesia
e) Aberrant drug-seeking behaviors

138

Does This Patient Have Opioid Nonresponsive Neuropathic Pain?

Examples: morphine, oxycodone, fentanyl

- Remain therapeutic mainstay for moderate to severe pain management[1]
- Most common agents in the class act at the mu receptor[1]
- Agonistic effects both in peripheral nociceptors and centrally (spinal cord and descending pathway)[1]
- Prescribed as part of multimodal and interdisciplinary treatment plan[2]
- Some severe chronic neuropathic pain conditions can be successfully managed with opioid therapy[3,4]
- Considerations
  - Past hx of drug or alcohol abuse
  - Low starting dose
  - Dosing spread around the clock and not prn

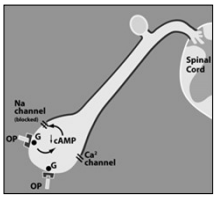
1. Brunto LL, Lazo SS, Parker KL. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 11th ed. New York, NY: McGraw Hill; 2006.
2. Kalso E, et al. *Current Medical Research and Opinions.* 2005; 21(11): 1821.
3. Galer BS. *Neurology.* 1995;45(supple 9):S22.
4. Galer B, Gammaitoni A, Alvarez N. 6. Immunology [XIV. Pain]. In: Dale DC, Federman DD, eds. *WebScientific American Medicine.* New York, NY: WebMD Corporation; 2003:2064.

139

139

Is this Patient Developing Tolerance or Is Pain Worsening?

- Opioid tolerance is a "shift to the right" in the dose-response curve
  - Higher dose required over time to maintain the same level of analgesia
- Tolerance can be pharmacokinetic…
  - Drug or concomitant medications upregulate metabolic pathways that remove opioids from the body
- …or pharmacodynamic
  - Desensitization
    - Physiological changes to the opioid receptors
  - Downregulation
    - Internalization of opioid receptors by endocytosis, reducing their numbers



DuPen A. *Pain Manag Nurs.* 2007;8:113-121.

140

140

Is Depression Worsening? Psychological Factors?

- Prolonged back pain may be associated with a psychological disturbance, manifesting as[1-3]
  - Behavioral
  - Cognitive
  - Affective
  - Somatoform (psychophysiological)
- Psychological factors that may contribute to or be caused by chronic LBP include[1,2]
  - Depression
  - Anxiety
  - Somatization
  - Posttraumatic stress disorder
  - Preexisting bipolar or other disorders

1. Andersson GBJ. *Lancet.* 1999;354:581-585.
2. Anderson GBJ. The epidemiolodgy of spinal disorders. In: Frymoyer JW, ed. *The Adult Spine: Principles and Practice.* 2nd ed. 1997.
3. Polatin PB, et al. *Spine.* 1993;18:66-71.

141

141

Social Issues May Contribute to CLBP

- Job dissatisfaction/loss of ability to work
- Pursuit of disability compensation
- Substance abuse
- Family dynamics
- Financial issues
- Loss of social identity or context
- Loss of ability to participate in recreational activities

Wheeler AH, Stubbart JR. Pathophysiology of chronic back pain. http://emedicine.com/neuro/topic516.htm.

142

142

Could this Patient have Opioid-induced Hyperalgesia (OIH)?

- Increased sensitivity to pain resulting from opiate administration[1]
- Opioids, in addition to providing analgesia, set in motion anti-analgesic or hyperalgesic processes[2]
- Pain-free animals made tolerant to morphine have significantly decreased tolerance to pain[2]
- Opioid "tolerance" may not be a downregulation of analgesic systems, but an upregulation of hyperalgesic systems[3]

1. Compton, P. The OIH paradox: Can opioids make pain worse? Pain treatment topics. http://pain-topics.org/pdf/Compton-OIH-Paradox.pdf. August 20, 2008. Accessed July 14, 2009.
2. Compton MA. *Pain Symptom Manage.* 1994; 9:462-473.
3. Laulin JP, et al. *Neuroscience.* 1999;89:631-636.

143

143

Differentiating OIH from Other Conditions

Condition	Nature of Pain	Presentation or Onset of Pain	Response to Opioid
Opioid Induced Hyperalgesia	Increased sensitivity to pain; diffuse pain, extending beyond the distribution of pre-existing pain; allodynia may be present	Abrupt onset with rapid opioid escalation or high-dose opioid administration	Pain worsens
Worsening Pain Pathology	Localized to site of pre-existing pain or new site of pathology	Variable, depending on source of pain	Pain improves
Opioid Tolerance	Localized to site of pre-existing pain	Gradual onset	Pain improves
Opioid Withdrawal	Increased sensitivity to pain; diffuse, extending beyond the distribution of pre-existing pain	Abrupt with short-acting opioids or antagonist administration; gradual with long-acting opioids	Pain improves
Opioid Addictive Disease	Increased sensitivity to pain; diffuse, may extend beyond the distribution of pre-existing pain.	Gradual onset	Pain may improve but functionality may worsen
Pseudoaddiction	Localized to site or pre-existing pain.	Variable, depending on source of pain	Pain improves

Table adapted from Mitra 2008.

Compton, P. The OIH paradox: Can opioids make pain worse? Pain treatment topics. http://pain-topics.org/pdf/Compton-OIH-Paradox.pdf. August 20, 2008. Accessed July 14, 2009.
Mitra S. *J Opioid Manage.* 2008;4:123-130.

144

144

Differential Assessment

- General principles
  - Presence of worsening pathology or psychological influences can contribute to reports of increased pain, but are not related to opioid administration
  - Tolerance, withdrawal-related symptoms, pseudoaddiction, or addiction can be differentiated by increasing opioid dose and/or frequency
  - If reports of pain increase with upward opioid titration, OIH should be considered

Compton, P. The OIH paradox: Can opioids make pain worse? Pain treatment topics. http://pain-topics.org/pdf/Compton-OIH-Paradox.pdf. August 20, 2008. Accessed July 14, 2009. 145

145

Clinical Case: CLBP
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b) Opioid tolerance
c) Worsening depression
d) Opioid hyperalgesia
e) Aberrant drug-seeking behaviors

146

Designing an Effective Treatment Plan for Mr. L

- Initial Treatment Plan
  - Continue current opioid regimen (avoid escalating doses)
  - Complete opioid treatment agreement
  - Initiate NSAID while monitoring renal function
  - Initiate acetaminophen on a schedule
  - Initiate topical analgesic
  - Provide patient education (body mechanics, maintaining activity)
  - Schedule physical therapy

147

WAFHC Policy, per CDC 2016....

- For ALL Pain Patients (Acute and Chronic)
  - Document history and physical examination
  - Complete opioid risk assessment tool
  - Document treatment plan with nonpharmacologic/pharmacologic treatments
  - Document opioid prescription and rationale
  - Consent form signed for opioids
  - Query the NH PDMP and print for electronic health record

148

WAFHC Policy, per CDC 2016....

- Acute Pain Patients (in addition to items in I)
  - Discuss: side effects, addiction, overdose risks
  - Discuss: risks of keeping unused medications in household
  - Discuss: options for safely securing and disposing of unused medications
  - Discuss: risks of operating heavy machinery and driving
  - Amounts: **3 days or less**; maximum 7 days if warranted and documented rationale why 7 days is needed
  - If pain persists for more than treated time, can renew up to 30 days. However, after thirty days, must be seen for reevaluation.

149

WAFHC Policy, per CDC 2016....

- Chronic Pain Patients (in addition to items in I)
  - Written Treatment Agreement (Provider Patient Agreement) must be signed
  - Refer to specialty for high risk of abuse/addiction
  - Refer to specialty for co-morbid psych disorder
  - Query PDMP at least two times per year (ideally before every visit)
  - Random drug screening
  - In general, we are not treating chronic pain in office (refer to subspecialty)

150

When Should Patients Be Referred to a Pain Management Specialist?

- Complex pain syndromes
- Unsuccessful outcomes
- Multimodal therapy
- History or pre-existing substance abuse
- Problems with adherence
- Interventional procedures
- Behavioral or cognitive therapy

Chou R, et al. *The Journal of Pain*. 2009; 10:113-130.

151

Drug-related Behaviors That Need to be Evaluated

Probably less predictive
- Aggressive complaining
- Medication hoarding when symptoms milder
- Requesting specific medications
- Acquisition of medications from other medical sources
- Unsanctioned dose escalation once or twice
- Unapproved use of the medication to treat another symptom
- Reporting psychic effects not intended by the clinician
- Occasional impairment

Probably more predictive
- Selling prescription medications
- Prescription forgery
- Stealing or "borrowing" medications from another person
- Injecting oral formulation
- Obtaining prescription medications from nonmedical source
- Multiple episodes of prescription "loss"
- Concurrent abuse of related illicit drugs
- Multiple dose escalations despite warnings
- Repeated episodes of gross impairment or dishevelment

Passik SD, et al. *Oncology* (Williston Park). 1998; 12(4):517-521, 524.

152

Thank you!
I would be happy to entertain any questions or comments

153

Thank you for your time and attention.

Wendy L. Wright,
DNP, ANP-BC, FNP-BC, FAANP, FAAN, FNAP
WendyARNP@aol.com

154