Case Studies in Managing Pain: A multimodal approach

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Disclosures

- Speaker Bureau:
  - Sanofi-Pasteur, Merck, Pfizer, Moderna and Seqirus: Vaccines
  - AbbVie and Biohaven: Migraines
  - Idorsia: Insomnia
  - Exact Sciences: Colorectal Cancer
  - AstraZeneca: Asthma
- Consultant:
  - Pfizer, Sanofi, Merck, GlaxoSmithKline, Idorsia, Bayer, Moderna, Seqirus, Shield Therapeutics

All relevant financial disclosures have been mitigated.

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Objectives

- At the end of this presentation, the participant will be able to:

1. Describe the pathophysiology of pain as it relates to the concepts of pain management.
2. Identify evidence-based non-opioid options for the treatment of pain.
3. Discuss the risks and benefits of opioid therapy.
4. Manage ongoing opioid therapy and recognize behaviors that may be associated with opioid use disorder.

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Tips

- References
  - Listed throughout and at the end of the presentation

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Pathophysiology of Pain

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Acute and Chronic Pain[1]

	Acute Pain	Chronic Pain
Temporal Features	Recent, well-defined onset; expected to end in days of weeks	Remote, ill-defined onset; duration unpredictable
Biologic Function	Essential warning; impels rest and avoidance of further harm	None apparent
Intensity	Variable	Variable
Associated Affect	Anxiety common when severe or cause is unknown	Irritability or depression
Associate pain-related behaviors	Pain behaviors common when severe or cause is unknown (i.e., rubbing, splinting)	May or may not give an indication of pain
Associated features	May have signs of sympathetic hyperactivity when severe	May have vegetative signs (i.e., weight loss, loss of appetite, insomnia)
Types and examples	Post-operative trauma, burns, headache, IBS	AIDS, cancer, osteoarthritis, neuropathic pains, osteoarthritis

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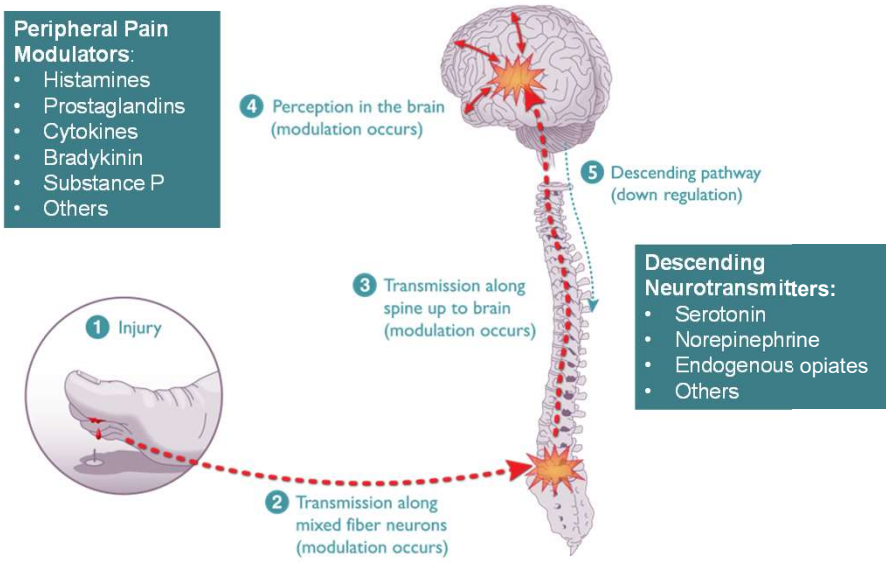
THE NEUROMECHANISMS OF PAIN



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Physiology of Pain – Neurochemical Mediators

- A large number of neurotransmitters and other chemical mediators play a role in pain processing and modulation.
- Mediators act in a complex and interrelated process.

Excitatory (Promotes or intensifies the pain process)	**Inhibitory** (Blocks or dampens the pain process)
Key mediators	**Key mediators**
• Glutamate • Substance P • Prostaglandins	• Opioids • Norepinephrine • Serotonin • Gamma-aminobutyric acid (GABA)

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Physiology of Pain – Pathways and Effects on Pain Perception[2]

- Pain is a complex process mediated by multiple pathways and mechanisms both in the periphery and central nervous system (PNS and CNS [spinal cord and brain]).
- Fundamental characterization of pain
  - Nociceptive/inflammatory
    - Activation of pain-sensitive afferent neural pathways in response to injury
  - Neuropathic
    - Abnormal pain processing due to lesion of peripheral or central nervous system or both

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Nociceptive Pain – Somatic[2]

- Somatic pain
  - Pain resulting from activation of nociceptors in the cutaneous (skin and underlying tissues) or deep tissues such as bone, blood vessels, muscles, and other supporting structures
  - **Superficial somatic pain**

Pain syndrome examples
- Traumatic bone fractures
- Muscle sprains
- Post-op incision pain

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Nociceptive Pain – Visceral[2]

- Visceral pain
  - Activation of nociceptors in the organs and linings of the body cavities capable of responding to stimuli caused by stretching, inflammation, or ischemia to visceral structures

Pain syndrome examples
- Pancreatitis
- Hepatic metastases
- Irritable bowel syndrome

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Neuropathic Pain[3]

- Pain believed to be sustained by aberrant somatosensory processing in the peripheral nervous system (PNS) or CNS
  - "Centrally mediated"
    - Deafferentation pain (e.g., phantom pain)
    - Sympathetically maintained pain (e.g., Complex Regional Pain Syndrome - CRPS)
  - "Peripherally mediated"
    - Originate in the nerve root, plexus, or nerve
    - Polyneuropathies and mononeuropathies

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Prevalence of Neuropathic Pain

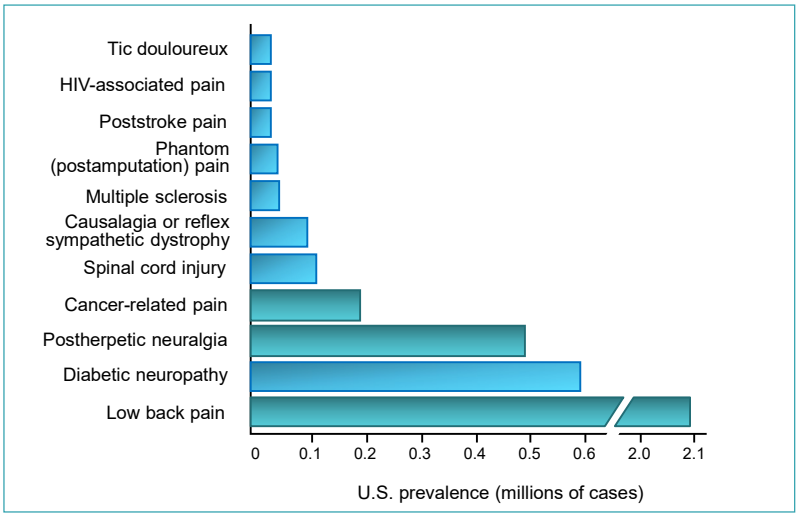

Image source: Adapted from Bennett, G.J. (1998). Neuropathic pain: new insights, new interventions. *Hosp Pract* (1995), 33(10):95-8, 101-4, 107-10 passim. https://pubmed.ncbi.nlm.nih.gov/9793544/

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Possible Descriptions of Neuropathic Pain

Sensations[4]

- Numbness
- Tingling
- Hot-burning
- Paresthetic
- Paroxysmal
- Lancinating
- Electric-like
- Raw skin
- Shooting
- Deep, dull, bone-like ache

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Possible Descriptions of Neuropathic Pain (continued)

Signs/Symptoms[4]

- Allodynia: Pain from a stimulus that does not normally evoke pain
  - Thermal
  - Mechanical
- Hyperalgesia: Exaggerated response to a normally painful stimulus
- Muscle and tissue spasm, tightness, and tenderness
- Muscle weakness and atrophy
- Skin color changes, rashes, swelling, and temperature abnormality

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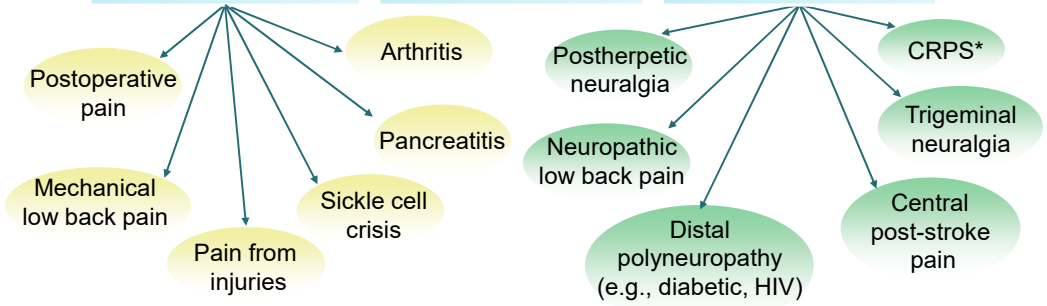
Nociceptive vs. Neuropathic Pain

Nociceptive Pain	Mixed Type	Neuropathic Pain
Caused by activity in neural pathways in response to potentially tissue-damaging stimuli[1]	Caused by a combination of both primary injury and secondary effects	Initiated or caused by primary lesion or dysfunction in the nervous system[3]



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TYPES OF PAIN

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

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What is mixed pain?

Which of the following pain combinations are possible representations of mixed pain?

A. Somatic and visceral pain
B. Somatic and neuropathic pain
C. Visceral and neuropathic pain
D. Somatic, visceral and neuropathic pain
E. All of the above

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Mixed Pain

- Mixed pain includes[5,6]:
  - Specific pain syndrome such as fibromyalgia, headache syndromes, and low back pain
  - Specific disease states such as cancer or AIDS
  - Presentations of pain caused by multiple etiologies (e.g., cancer-related pain and post-herpetic neuralgia)
  - Mixed neuropathic pain is characterized by both peripherally and centrally mediated pain (e.g., stump pain from amputation and phantom limb pain).

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What is multimodal therapy?

Which statement is true in regard to multimodal drug therapy?

1. Combines drugs and techniques that target more than one pain mechanism
2. Provides balanced and safer pain therapy
3. Incorporates into major pain management guidelines

A. Option #1
B. Option #2
C. Option #3
D. All of the above
E. None of the above

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Multimodal Therapy

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HOW IS PAIN MANAGED?

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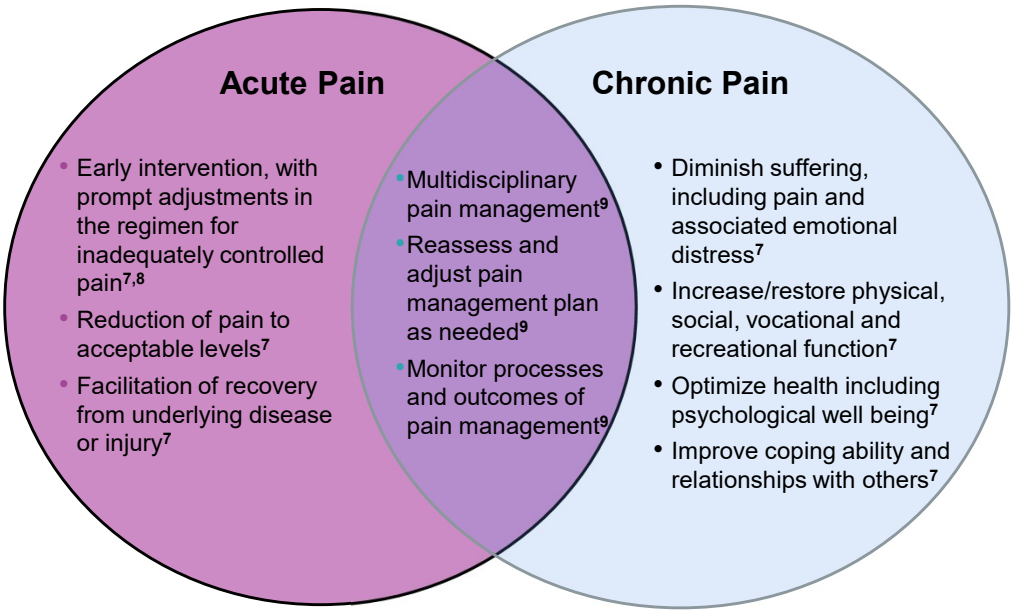
Treatment Goals for Acute and Chronic Pain



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Drug Therapy of Acute Pain – An Evolving Understanding

- Recognizing the need for a multimodal approach to drug therapy
  - Combinations of drugs and techniques that target more than 1 pain mechanism, not 2 drugs that target the same[10]
  - Not a new concept, but one that is gaining increasing attention as a therapeutic framework[8]
  - Strong evidence to support the utility of this approach; incorporated into major pain management guidelines
    - American Society of Regional Anesthesia and Pain (ASRA)[10]
    - American Pain Society (APS)[8]
    - American Society of Anesthesiology (ASA)[11]

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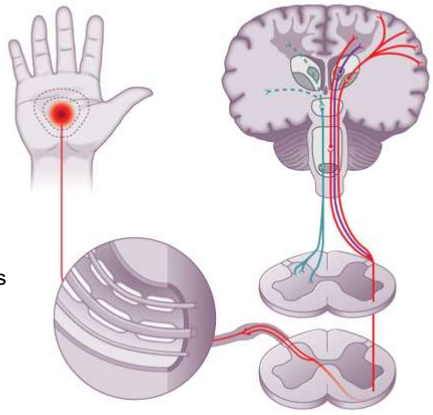
POTENTIAL SITES OF ACTION FOR ANALGESIC AGENTS

Peripherally Mediated Pain:

- Acetaminophen
- 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

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Drug Therapy for Acute Pain – Moving to a Multimodal Strategy

- Multimodal therapy: Combining classes of agents
  - Opioids ***plus*** NSAIDs reduced postoperative morphine use by approximately 50%, with associated decrease in opioid-induced adverse effects and increase in patient satisfaction[12-14]
  - Opioid ***plus*** gabapentin or pregabalin reduced opioid requirements, pain, and opioid-induced adverse effects.[15, 16]
  - Combining 2 classes of agents with opioids extends the multimodal model.

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Case-based Learning
Acute Pain from End-stage OA

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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.

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Clinical Case: End-stage Osteoarthritis (OA) (continued)

- 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.

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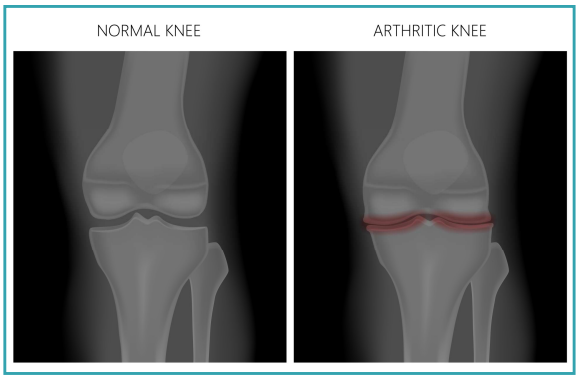
Osteoarthritis (OA)

- 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



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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

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Pain Management Best Practices: 2019 Report[21]

- Patient-centered care in the diagnosis and treatment of acute and chronic pain
- A multimodal approach that includes medications, nerve blocks, physical therapy, and other modalities should be considered for acute pain conditions.
  - Acetaminophen can be effective for mild to moderate pain.
  - NSAIDs such as aspirin, ibuprofen, and naproxen can provide significant pain relief for inflammation, such as from arthritis, bone fractures or tumors, muscle pains, headache, and acute pain caused by injury or surgery.

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OTC Analgesics: Where do they fit in pain management?

Multiple guidelines recommend OTC analgesics for the management of acute and chronic pain.

Numerous products, formulations, and delivery options are available.

Consumers can self-manage pain with OTC analgesics but are often also directed by healthcare providers to use OTC analgesics.

OTC analgesics are often more cost-effective for the consumer given the trend of higher deductibles and copays.

May be used individually or as an adjunct to RX medications

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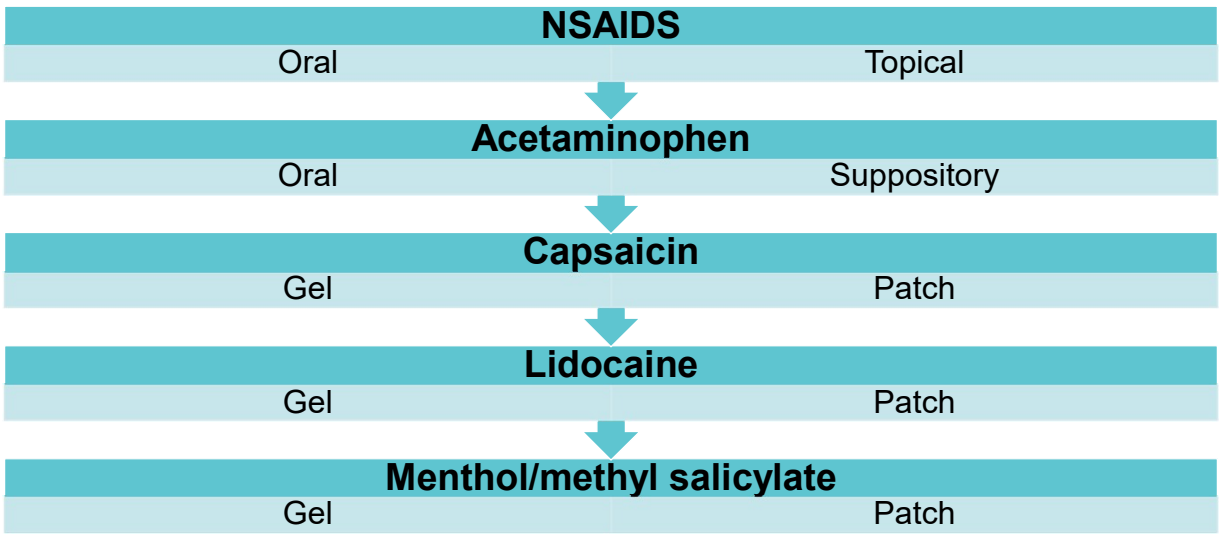
OTC Analgesics – Numerous Options



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What's coming soon?

- Nerve growth factor inhibitors
  - Fasinumab
  - Tanezumab (Rejected by FDA)

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How do you want to treat this patient?

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Case-based Learning

Postherpetic Neuralgia

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

- Mrs. M is a 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.

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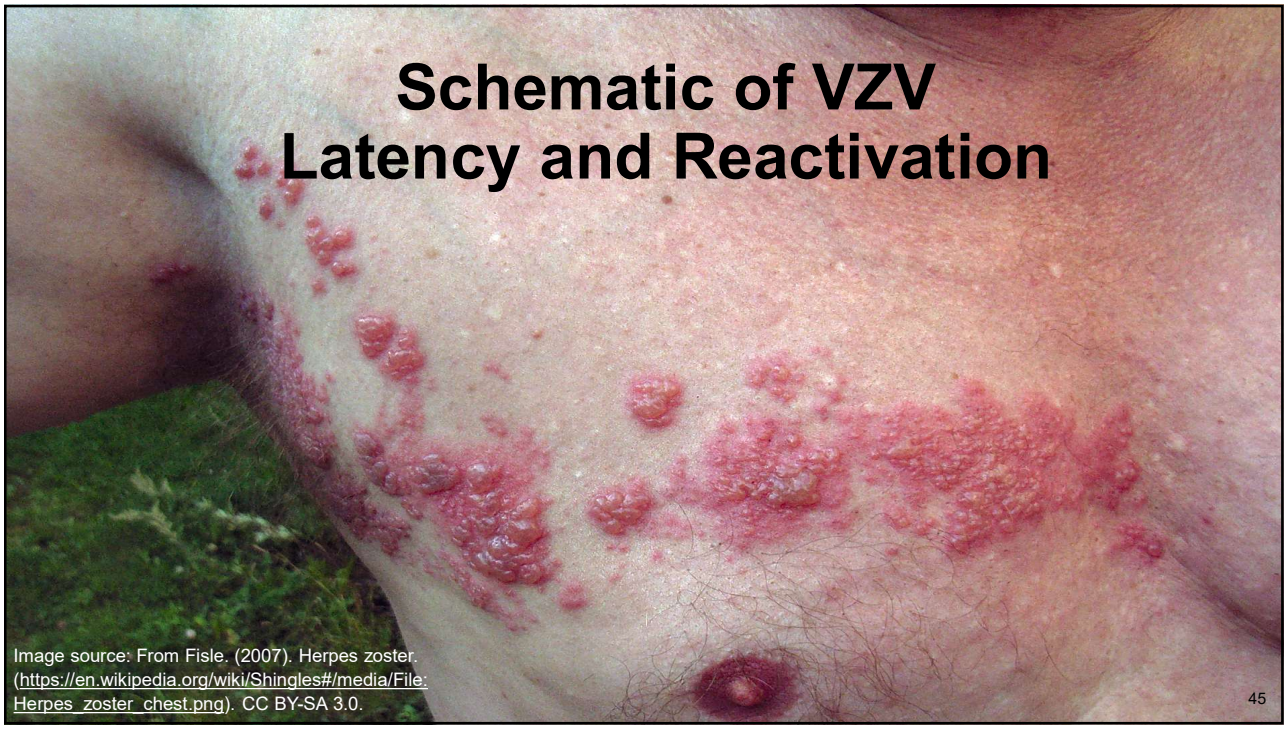
Clinical Case: Cancer-related Pain and Post-herpetic Neuralgia (continued)

- At her medical oncologist's office, she reports 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.
  - 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

Clinical Case: Breast Cancer History

- 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



Clinical Case: Breast Cancer Initial Assessment

- Patient reports excruciating pain in her torso and upper arms.
  - What type of pain is she experiencing?
    - Chronic cancer pain (somatic and visceral in origin)
    - Postherpetic neuralgia (PHN)
    - Cutaneous hypersensitivity (allodynia and hyperalgesia)
    - All of the above

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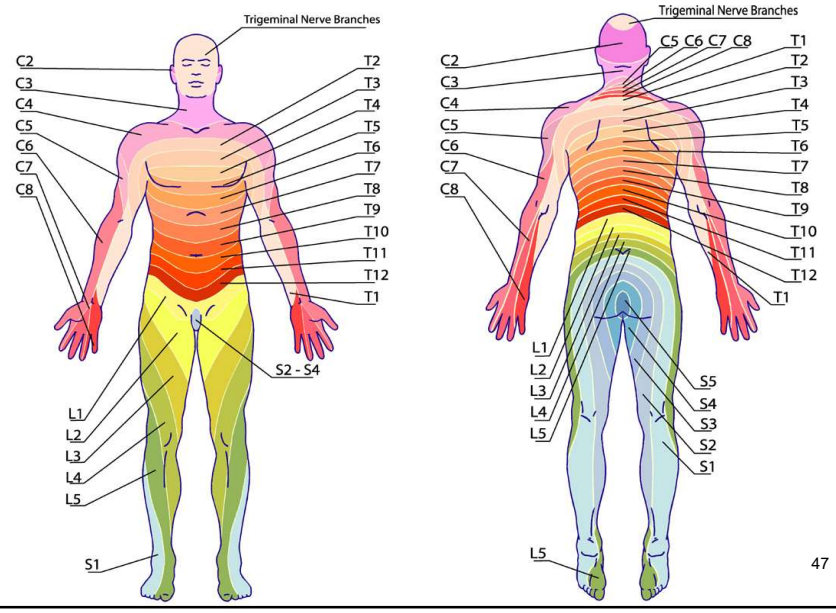
Typical Locations of Herpes Zoster

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



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Characterization of Pain Associated With PHN

- Dysesthesia
  - An unpleasant abnormal sensation, spontaneous or evoked[23,24]
- Hyperalgesia
  - Pain of exaggerated severity in response to normally painful stimulation[23,24]
- Allodynia
  - Pain evoked by a normally innocuous stimulus[23, 24]
    - 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.[25]

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PHN – Risk Factors

- Age[26-28]
- Severity of acute pain[26-28]
- Severity of acute rash[26-28]
- Painful prodrome[26]
- Gender – Female[26]

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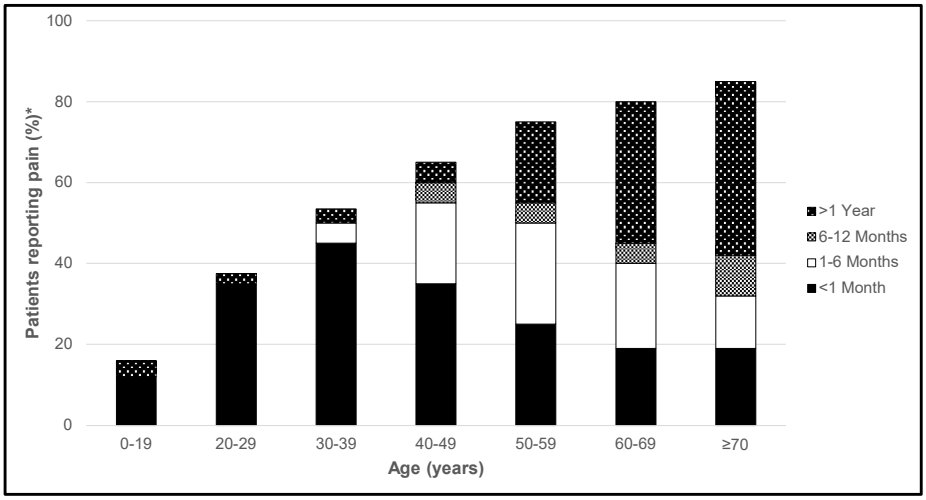
Duration of Pain Associated with PHN and Increased Age[29]



*Population represents those referred to a pain clinic.

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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

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Management Strategies for PHN[29]

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

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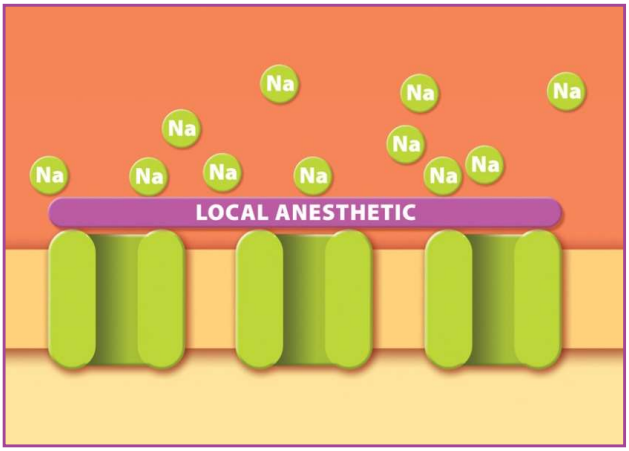
Classes of Pain Medications – Local Anesthetics[22]

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.



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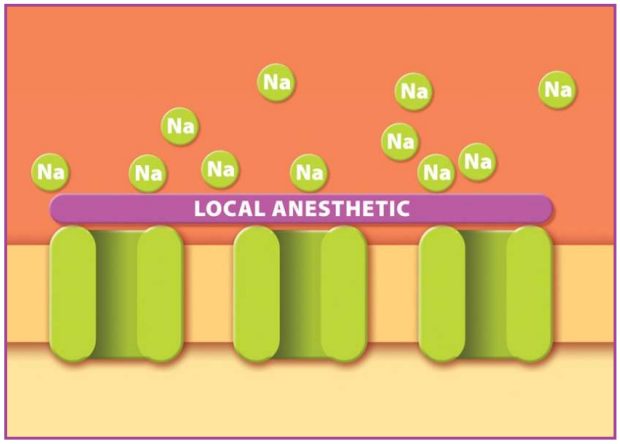
Classes of Pain Medications – Local Anesthetics[22] (continued)

Examples: Lidocaine, bupivacaine (cont.)

- Interrupts pain input at the nerve roots
- Associated with few adverse effects



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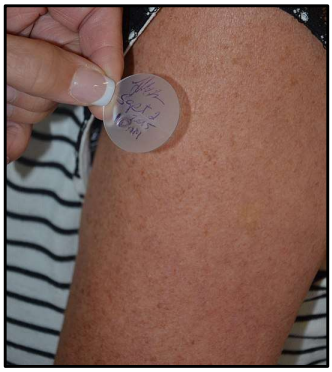
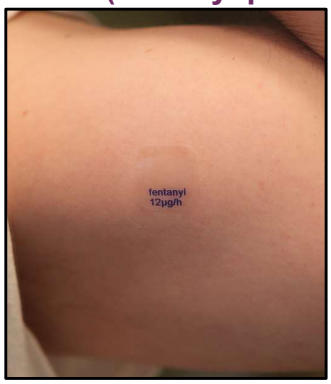
Topical vs. Transdermal Medication Delivery Systems

Topical (lidocaine patch 5%)[3, 32-34]



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

Transdermal (fentanyl patch)[34, 35]



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

Lidocaine Patch 5%

- Lidocaine 5% in pliable patch[36]
- Up to 3 patches applied once daily directly over painful site[37, 39]
  - 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[32, 38, 39]
- Drug interactions and systemic adverse effects unlikely.[3, 32, 40]
  - Most common adverse effect: Application-site sensitivity
- Clinically insignificant serum lidocaine levels[3]
- Mechanical barrier decreases allodynia[39]

Classes of Pain Medications – Antidepressants[22]

- Tricyclics
  - Examples: Amitriptyline, nortriptyline, desipramine
  - Inhibit both norepinephrine (NE) and serotonin reuptake to varying degrees
  - Possesses other properties (e.g., local anesthetic-like activity)

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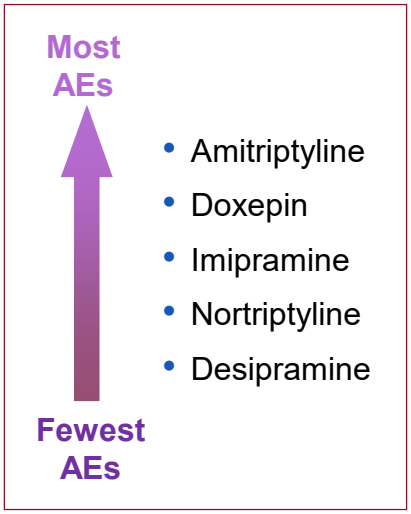
Tricyclic Antidepressants – Adverse Effects[22]

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



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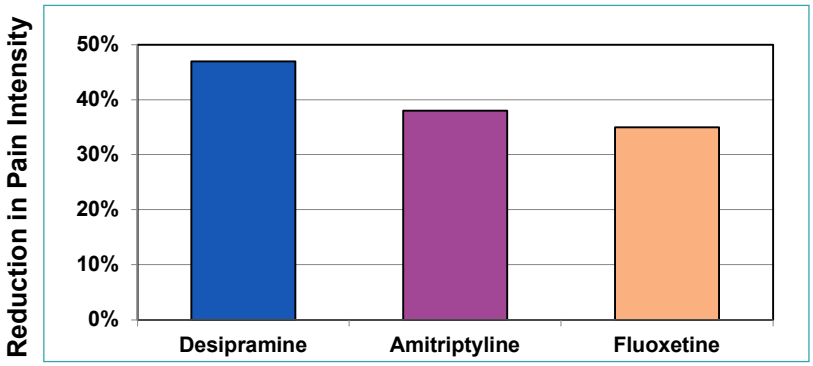
Antidepressant Use for PHN

2005 study revealed that TCAs and SSRIs reduced PHN pain, with desipramine providing satisfactory relief in 80% of those treated.

A Comparison of Pain Intensity Reduction with 3 Antidepressants



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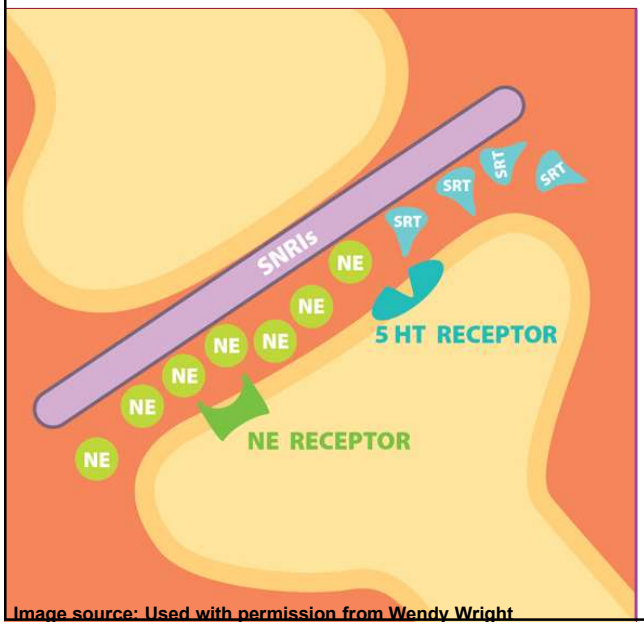
Classes of Pain Medications – Antidepressants[22] (continued)



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- Serotonin norepinephrine reuptake inhibitors (SNRIs)
  - Examples: Venlafaxine, duloxetine
  - 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

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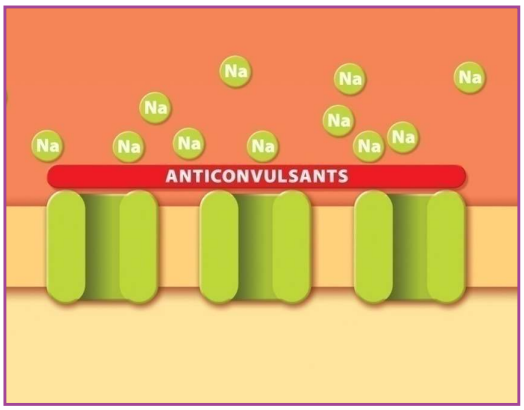
Classes of Pain Medications – Local Anesthetics[22]

Examples: Gabapentin, pregabalin, lamotrigine, topiramate

- Decrease excitability of neurons by modulating sodium channels; does 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.



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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.

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Case-based Learning

Chronic Low Back Pain

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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 kg/m^2
- History of depression (currently taking sertraline)

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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

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Clinical Case – CLBP History (continued)

- 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

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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.

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Clinical Case – CLBP Initial Assessment (continued)

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

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Does this patient have opioid nonresponsive neuropathic pain?

Examples: Morphine, oxycodone, fentanyl

- Remains therapeutic mainstay for moderate to severe pain management[22]
- Most common agents in the class act at the mu receptor.[22]
- Agonistic effects both in peripheral nociceptors and centrally (spinal cord and descending pathway)[22]

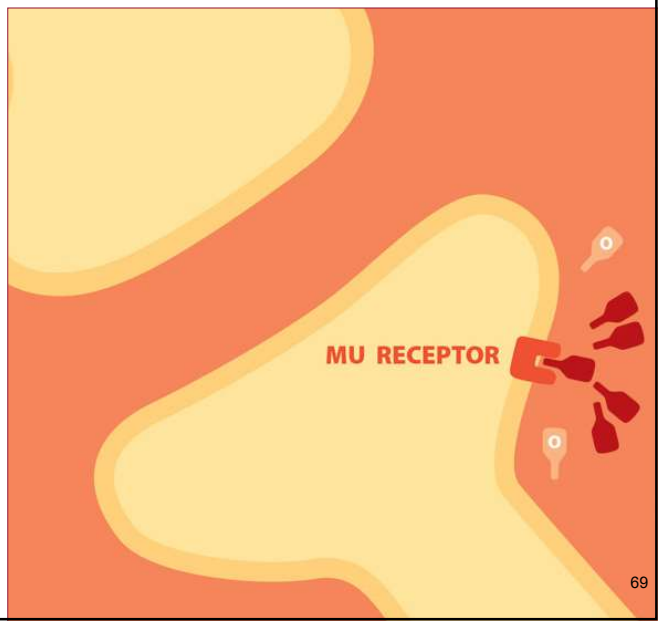
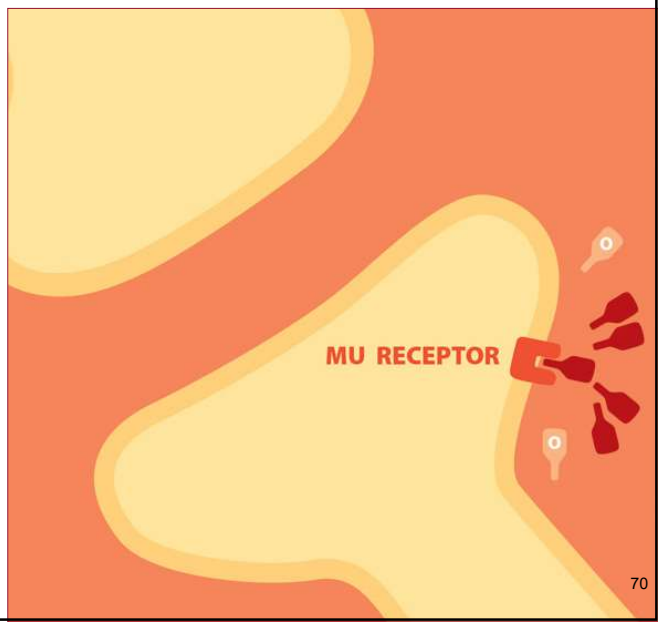


Image source: Used with permission from Wendy Wright

Does this patient have opioid nonresponsive neuropathic pain? (continued)

Examples: Morphine, oxycodone, fentanyl (cont.)

- Considerations
  - Past hx of drug or alcohol abuse
  - Low starting dose
  - Dosing spread around the clock and not PRN



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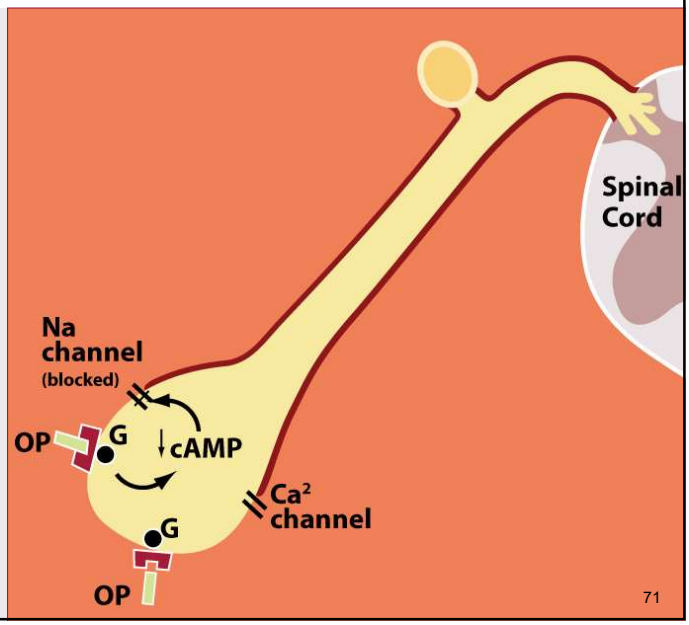
Is this patient developing tolerance or is pain worsening?

- 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



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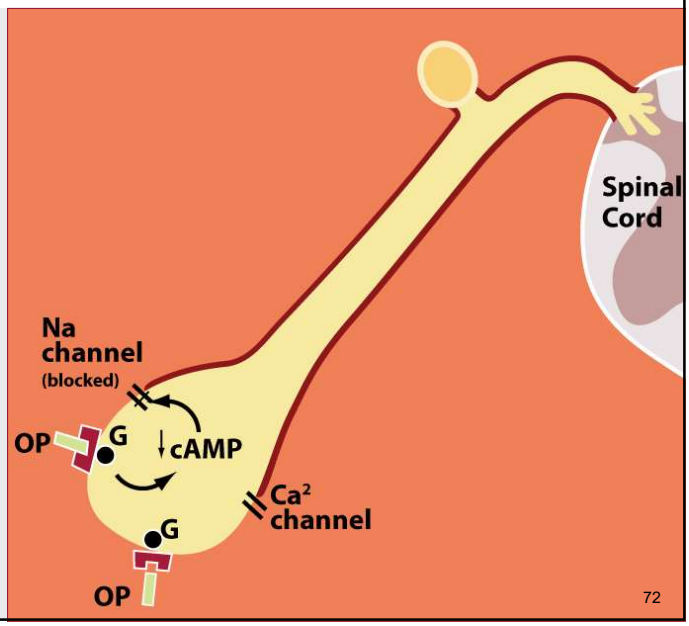
Is this patient developing tolerance or is pain worsening? (continued)

- …or pharmacodynamic
  - Desensitization
    - Physiological changes to the opioid receptors
  - Downregulation
    - Internalization of opioid receptors by endocytosis, reducing their numbers



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Is depression worsening? Psychological factors?

- Prolonged back pain may be associated with a psychological disturbance, manifesting as…[42-44]
  - Behavioral
  - Cognitive
  - Affective
  - Somatoform (psychophysiological)

- Psychological factors that may contribute to or be caused by chronic LBP include…[42, 43]
  - Depression
  - Anxiety
  - Somatization
  - Posttraumatic stress disorder
  - Pre-existing bipolar or other disorders

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Social issues may contribute to chronic lower back pain (CLBP).[45]

- 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

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Could this patient have opioid-induced hyperalgesia (OIH)?

- Increased sensitivity to pain resulting from opiate administration[46]
- Opioids, in addition to providing analgesia, set in motion anti-analgesic or hyperalgesic processes[47]
- Pain-free animals made tolerant to morphine have significantly decreased tolerance to pain.[47]
- Opioid "tolerance" may not be a downregulation of analgesic systems, but an upregulation of hyperalgesic systems.[48]

Differential Assessment[46]

- 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, pseudo-addiction, 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.

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

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Designing an Effective Treatment Plan for Mr. L

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

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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.

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WAFHC Policy, per CDC 2016…(continued)

- **Acute** pain patients (in addition to items in I)
  - Discuss adverse 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.

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WAFHC Policy, per CDC 2016… (continued)

- **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 comorbid psych disorder.
  - Query PDMP at least two times per year (ideally before every visit).
  - Random drug screening
  - In general, do not treat chronic pain in office. (Refer to subspecialty.)

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2022: New CDC Guidance[49]

- Removes restrictions on dosing
- Encourages providers to use best judgment
- Nonopioids first-line; but opioids when appropriate
  - Pendulum is swinging back to the middle.
- Now available
  - CDC Clinical Practice Guideline for Prescribing Opioids for Pain – United States, 2022

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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.

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Initiating Opioids (continued)

- 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.

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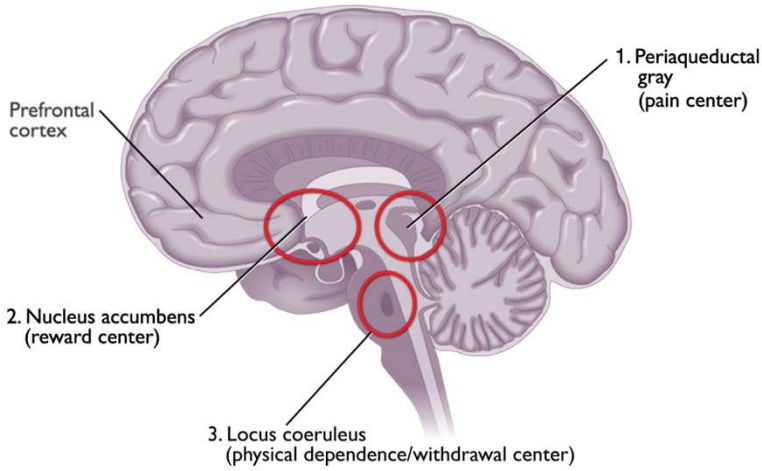
OPIOID RECEPTORS IN THE BRAIN: RELATIONSHIP TO ANALGESIA, OUD, AND WITHDRAWAL



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Opioid Adverse Effects

- Respiratory depression – Most serious
- Opioid-induced constipation (OIC) – Most common
- Sedation, cognitive impairment
- Falls and fractures
- Sweating, miosis, urinary retention
- Hypogonadism
- Tolerance, physical dependence, hyperalgesia
- Addiction in vulnerable patients

Prescribers should report serious AEs to the FDA: www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf or 1-800-FDA-1088

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Opioid-induced Respiratory Depression[50, 51]

- Chief hazard of opioid agonists, including ER/LA opioids
  - If not immediately recognized and treated, may lead to respiratory arrest and death
  - Greatest risk: Initiation of therapy or after dose increase

- Manifested by reduced urge to breathe and decreased respiration rate
  - Shallow breathing
  - CO2 retention can exacerbate opioid sedating effects

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Opioid

More Likely to Occur	Reduce Risk

• In elderly, cachectic, or debilitated patients
  ▪ Contraindicated in patients with respiratory depression or conditions that increase risk
• If given concomitantly with other drugs that depress respiration
• Patients who are opioid-naïve or have just had a dose increase
	• Proper dosing and titration are essential.
	• 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

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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

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Considerations for Change from IR to ER/LA Opioids[50–53]

Drug and dose selection is critical.

- Some ER/LA opioids or dosage forms are only recommended for opioid-tolerant patient.
  - **Any** strength of transdermal fentanyl or hydromorphone ER
  - Certain strengths/ doses of other ER/LA products (check drug prescribing information)

Monitor patients closely for respiratory depression.

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

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Considerations for Change from IR to ER/LA Opioids[50–53] (continued)

Individualize Dosage by Titration Based on Efficacy, Tolerability, and Presence of AEs

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

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

IMPORTANT

FOR 1 WEEK OR LONGER

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/products.html

START WITH AN EDT FOR ADULTS

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

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GUIDELINES FOR OPIOID ROTATION

Calculate equianalgesic dose of new opioid from EDT

REDUCE CALCULATED EQUIANALGESIC DOSE BY 25%–50%*

SELECT % REDUCTION BASED ON CLINICAL JUDGMENT

CLOSER TO 50% REDUCTION

IF PATIENT…

- Is receiving a relatively high dose of current opioid regimen
- Is elderly or medically frail

CLOSER TO 25% REDUCTION

IF PATIENT…

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

*75%–90% reduction for methadone

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GUIDELINES FOR OPIOID ROTATION *(continued)*

IF SWITCHING TO METHADONE:

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

IF SWITCHING TO TRANSDERMAL:

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

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Informed Consent

Before initiating a trial of opioid analgesic therapy, confirm patient understanding of informed consent to establish:

- **Analgesic and Functional Goals of Treatment**
- **Expectations**
- **Potential Risks**
- **Alternatives to Opioids**

The potential for and how to manage

- Common opioid-related AEs (e.g., constipation, nausea, sedation)
- Other serious risks (e.g., abuse, addiction, respiratory depression, overdose)
- AEs after long-term or high-dose opioid therapy (e.g., hyperalgesia, endocrinologic or sexual dysfunction)

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Consider a patient prescriber agreement (PPA).

Reinforce expectations for appropriate and safe opioid use.

- Obtain opioids from a single prescriber.
- Fill opioid prescriptions at a designated pharmacy.

- Safeguard opioids
  - Do not store in medicine cabinet.
  - Keep locked (e.g., use a medication safe)
  - Do not share or sell medication.
- Instructions for disposal when no longer needed

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Consider a patient prescriber agreement PPA. (continued)

Reinforce expectations for appropriate and safe opioid use.

- Commitments to return for follow-up visits
- Comply w/ appropriate monitoring.
  - e.g., random UDT and pill counts

- Frequency of prescriptions
- Enumerate behaviors that may lead to opioid discontinuation.
- An exit strategy

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Patient Prescriber Agreement (PPA)

Document signed by both patient and prescriber at time an opioid is prescribed.

Clarify treatment plan and goals of treatment w/patient, patient's family, and other clinicians involved in patient's care.

Assist in patient education.

Inform patients about the risks and benefits.

Document patient and prescriber responsibilities.

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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

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SCREENING VERSUS CONFIRMATORY UDTs

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

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

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WINDOWS OF SPECIFIC DRUG DETECTION

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

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

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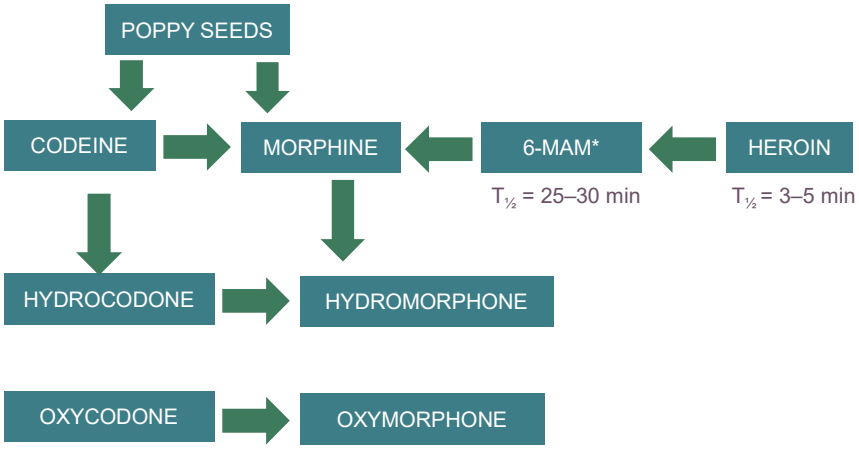
EXAMPLES OF OPIOID METABOLISM



*6-MAM = 6-Monoacetylmorphine

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Management of Acute Pain[54]

- "The implications for people taking opioids like morphine, oxycodone and methadone are great, since we show the short-term decision to take such opioids can have devastating consequences of making pain worse and longer lasting. This is a very ugly side to opioids that had not been recognized before."
- Study looked at just 5 days of morphine use; **increase in pain with 5 days of exposure**
- **Study co-leader Prof. Linda Watkins, CU-Boulder**

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Multimodal Strategy – Implications for Practice

- Effective and safe practices with multimodal strategies require that nurses
  - Understand the rationale for combining analgesics.[55, 56, 58]
  - Be knowledgeable about classes of analgesics.[55, 56, 58]
    - Mechanisms of action and pharmacodynamics
    - Synergistic and AEs
  - Ensure timely administration of all analgesics, avoiding gaps in analgesia.[56-58]

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Multimodal Strategy – Implications for Practice (continued)

- Effective and safe practices with multimodal strategies require that nurses (cont.)
  - Institute proper assessment and monitoring practices[56, 57]
  - Aggressively manage AEs of analgesics[55, 56, 58]
  - Remain informed about novel dual-mechanism analgesics and drug delivery systems[55, 56, 58]

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A CLOSER LOOK AT THE ORT-OUD

Opioid Risk Tool – OUD (ORT-OUD)

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

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

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

Scoring:

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

Naloxone[59]

- Every person using opioids should have naloxone available.
- Now sold over the counter without a prescription
- Illicit opioids may be associated with rigid chest wall syndrome requiring multiple doses.

When should patients be referred to a pain management specialist?[49]

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

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Drug-related Behaviors that Need to be Evaluated[60]

Probably Less Predictive	Probably More Predictive
• Aggressive complaining • Medication hoarding when symptoms milder • Requesting specific medications • Acquisition of medications from other medical sources • Unsanctioned dose escalation once or twice	• 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”

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Drug-related Behaviors that Need to be Evaluated[60] (continued)

Probably Less Predictive	Probably More Predictive
• Unapproved use of the medication to treat another symptom • Reporting psychic effects not intended by the clinician • Occasional impairment	• Concurrent abuse of related illicit drugs • Multiple dose escalations despite warnings • Repeated episodes of gross impairment or dishevelment

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I would be happy to entertain any questions or comments

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Thank you for your time and attention.

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References

1. Portenoy, R.K., Kanner, R.M. (1996). Definition and Assessment of Pain. In: Portenoy, R.K., Kanner, R.M., eds. *Pain Management: Theory and Practice*. Philadelphia, Pa: FA Davis Company.
2. Galer, B., Gammaitoni, A., Alvarez, N. (2003). Pain. In: Dale DC, Federman DD, eds. *WebMD Scientific American® Medicine.* New York, NY:WebMD Corporation.
3. Galer, B.S., Dworkin, R.H. (2000). *A Clinical Guide to Neuropathic Pain*. New York, NY: McGraw Hill, Healthcare Information Programs.
4. Murnion, B.P. (2018). Neuropathic pain: current definition and review of drug treatment. *Aust Prescr.*, 41(3):60-63. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6003018/
5. Portenoy, R.K., Bennett, D.S., Rauck, R., Simon, S., Taylor, D., Brennan, M., Shoemaker, S. (2006). Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain. *J Pain*, 7(8):583-91. https://pubmed.ncbi.nlm.nih.gov/16885015/
6. Webster, L.R. (2008). Breakthrough pain in the management of chronic persistent pain syndromes. *Am J Manag Care*, 14(5 Suppl 1):S116-22. https://pubmed.ncbi.nlm.nih.gov/18611099/

References (continued)

7. National Pharmaceutical Council Inc. (2001). *Pain: Current Understandin of Assessment, Management, and Treatments*. https://www.npcnow.org/sites/default/files/media/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf
8. Gordon, D.B., Dahl, J.L., Miaskowski, C., McCarberg, B., Todd, K.H., Paice, J.A., Lipman, A.G., Bookbinder, M., Sanders, S.H., Turk, D.C., Carr, D.B. (2005). American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. *Arch Intern Med*., 165(14):1574-80. https://pubmed.ncbi.nlm.nih.gov/16043674/
9. Authors unknown. (1997). Practice guidelines for chronic pain management. A report by the American Society of Anesthesiologists Task Force on Pain Management, Chronic Pain Section. *Anesthesiology*, 86(4):995-1004. https://pubmed.ncbi.nlm.nih.gov/9105246/
10. Rathmell, J.P., Wu, C.L., Sinatra, R.S., Ballantyne, J.C., Ginsberg, B., Gordon, D.B., Liu, S.S., Perkins, F.M., Reuben, S.S., Rosenquist, R.W., Viscusi, E.R. (2006). Acute post-surgical pain management: a critical appraisal of current practice, December 2-4, 2005. *Reg Anesth Pain Med*., 31(4 Suppl 1):1-42. https://pubmed.ncbi.nlm.nih.gov/16849098/

References (continued)

11. American Society of Anesthesiologists Task Force on Acute Pain Management. (2004). Practice Guidelines for Acute Pain Management in the Perioperative Setting: An Updated Report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology,* 100:1573-1581. https://pubs.asahq.org/anesthesiology/article/100/6/1573/6558/Practice-Guidelines-for-Acute-Pain-Management-in
12. Stephens, J., Laskin, B., Pashos, C., Peña, B., Wong, J. (2003). The burden of acute postoperative pain and the potential role of the COX-2-specific inhibitors. *Rheumatology* (Oxford), 42 Suppl 3:iii40-52. https://pubmed.ncbi.nlm.nih.gov/14585917/
13. Zemmel, M.H. (2006). The role of COX-2 inhibitors in the perioperative setting: efficacy and safety. A systematic review. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination (UK) https://www.ncbi.nlm.nih.gov/books/NBK73241/
14. Tiippana, E.M., Hamunen, K., Kontinen, V.K., Kalso, E. (2007). Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg*., 104(6):1545-56, table of contents. https://pubmed.ncbi.nlm.nih.gov/17513656/

References (continued)

15. Mathiesen, O., Møiniche, S., Dahl, J.B. (2007). Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. *BMC Anesthesiol*., 7:6. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1950698/
16. Elia, N., Lysakowski, C., Tramèr, M.R. (2005). Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology*, 103(6):1296-304. https://pubmed.ncbi.nlm.nih.gov/16306743/
17. Tzschentke, T.M., De Vry, J., Terlinden, R. (2006). Tapentadol hydrochloride. Analgesic, mu-opioid receptor agonist, noradrenaline reuptake inhibitor. *Drugs Future*, 31:1053–1061
18. FDA. (2010). Tapentadol (Nucynta®).Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022304s003lbl.pdf.
19. Kleinert, R. & Hallmann, Caspar & Steup, Achim. (2006). Efficacy of a single dose of tapentadol HCl for analgesia after third molar surgery. *J Pain*, 7. S44. Abstract 773

References (continued)

20. American Society of Anesthesiologists Task Force on Chronic Pain Management; American Society of Regional Anesthesia and Pain Medicine. (2010). Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology*, 112(4):810-33. https://pubs.asahq.org/anesthesiology/article/112/4/810/10691/Practice-Guidelines-for-Chronic-Pain-ManagementAn
21. U.S. Department of Health and Human Services. (2019). Pain Management Best Practices Inter-Agency.Task Force Report: Updates, Gaps, Inconsistencies, and Recommendations. https://www.hhs.gov/sites/default/files/pmtf-final-report-2019-05-23.pdf
22. Brunto, L.L., Knollman, B.C., Hilal-Dandan, R. (2017). *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, (13th ed.). McGraw Hill/ Medical.
23. Mallick-Searle T, Snodgrass B, Brant JM. (2016). Postherpetic neuralgia: epidemiology, pathophysiology, and pain management pharmacology. *J Multidiscip Healthc*., 9:447-454. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5036669/#:~:text=Postherpetic%20neuralgia%20(PHN)%20is%20a,herpes%20zoster%20(HZ)%20rash.

References (continued)

24. Rullán, M., Bulilete, O., Leiva, A., Soler, A., Roca, A., Gonzalez-Bals, M.J., Lorente, P., Llobera, J. and PHN group. (2017). Efficacy of gabapentin for prevention of postherpetic neuralgia: study protocol for a randomized controlled clinical trial. Trials 18, 24. https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-016-1729-y
25. Petersen, K. L., Fields, H. L., Brennum, J., Sandroni, P., & Rowbotham, M. C. (2000). Capsaicin evoked pain and allodynia in post-herpetic neuralgia. *Pain*, 88(2), 125-133.
26. Jung, B. F., Johnson, R. W., Griffin, D. R., & Dworkin, R. H. (2004). Risk factors for postherpetic neuralgia in patients with herpes zoster. *Neurology*, 62(9), 1545-1551.
27. Forbes, H.J., Bhaskaran, K., Thomas, S.L., Smeeth, L., Clayton, T., Mansfield, K., Minassian, C., Langan, S.M.(2016). Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: A cohort study. *Neurology*, 87(1):94-102. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932239/
28. Wei, S., Li, X., Wang, H., Liu, Q., Shao, L. (2019). Analysis of the Risk Factors for Postherpetic Neuralgia. *Dermatology,* 235 (5): 426-433. https://karger.com/drm/article-abstract/235/5/426/114198/Analysis-of-the-Risk-Factors-for-Postherpetic?redirectedFrom=fulltext

References (continued)

29. Kost, R.G., Strauss, S.E. (1996). Postherpetic neuralgia--pathogenesis, treatment, and prevention. *N Engl J Med.,* 335:32-42.
30. Oster, G., Harding, G., Dukes, E., Edelsberg, J., & Cleary, P. D. (2005). Pain, medication use, and health-related quality of life in older persons with postherpetic neuralgia: results from a population-based survey. *The Journal of pain*, 6(6), 356-363.
31. Oxman, M. N., Levin, M. J., Johnson, G. R., Schmader, K. E., Straus, S. E., Gelb, L. D., Arbeit, R.D., Simberkoff, M.S., Gershon, A.A., Davis, L.E., Weinberg, A., Boardman, K.D., Williams, H.M., Zhang. J.H., Peduzzi, P.N., Beisel, C.E., Morrison, V.A., Guatelli, J.C.,... & Silber, J. L.; Shingles Prevention Study Group. (2005). A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *New England Journal of Medicine*, 352(22), 2271-2284.
32. Argoff, C.E. (2000). New analgesics for neuropathic pain: the lidocaine patch. *Clin J Pain*, 16(2 Suppl):S62-6. https://pubmed.ncbi.nlm.nih.gov/10870742/
33. Gudin, J. and Nalamachu, S. (2020) Utility of lidocaine as a topical analgesic and improvements in patch delivery systems, *Postgraduate Medicine*, 132:1, 28-36, https://www.tandfonline.com/doi/full/10.1080/00325481.2019.1702296?scroll=top&needAccess=true&role=tab

References (continued)

34. Burch, F., Codding, C., Patel, N., Sheldon, E. (2004). Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients. A prospective, multicenter, open-label effectiveness trial. *Osteoarthritis Cartilage*, 12(3):253-5. https://www.oarsijournal.com/article/S1063-4584(03)00272-3/fulltext
35. Fentanyl transdermal system (Duragesic®). (2021). Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/019813s081lbl.pdf
36. FDA. (2015). Lidocaine patch 5% (Licoderm®).Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020612s012lbl.pdf. Endo Pharmaceuticals Inc.
37. Gammaitoni, A.R., Alvarez, N.A., Galer, B.S. (2002). Pharmacokinetics and safety of continuously applied lidocaine patches 5%. *Am J Health Syst Pharm*., 59(22):2215-20. https://pubmed.ncbi.nlm.nih.gov/12455305/

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References (continued)

38. Cheville, A.L., Sloan, J.A., Northfelt, D.W., Jillella, A.P., Wong, G.Y., Bearden Iii, J.D., Liu, H., Schaefer, P.L., Marchello, B.T., Christensen, B.J., Loprinzi, C.L. (2009). Use of a lidocaine patch in the management of postsurgical neuropathic pain in patients with cancer: a phase III double-blind crossover study (N01CB). *Support Care Cancer*, 17(4):451-60. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5653964/
39. Hines, R., Keaney, D., Moskowitz, M.H., Prakken, S. (2002). Use of Lidocaine Patch 5% for Chronic Low Back Pain: A Report of Four Cases. *Pain Medicine*, Volume 3, Issue 4, Pages 361–365. https://academic.oup.com/painmedicine/article/3/4/361/1843399
40. Gammaitoni, A. R., & Davis, M. W. (2002). Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Annals of Pharmacotherapy*, *36*(2), 236-240. https://pubmed.ncbi.nlm.nih.gov/11847940/
41. Kalso, E., Allan, L., Dobrogowski, J., Johnson, M., Krcevski-Skvarc, N., Macfarlane, G. J., Mick, S., Ortolani, S., Perrot, S. Perucho, A., Semmons, I. and Sörensen, J. (2005). Do strong opioids have a role in the early management of back pain? Recommendations from a European expert panel. *Current medical research and opinion*, 21(11), 1819-1828

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References (continued)

42. American Psychological Association. (2019) *APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts*. https://www.apa.org/depression-guideline/guideline.pdf
43. Singhal, K., Muliyala, K.P., Pakhare, A.P., Behera, P., Santoshi, J.A. (2021). Do Patients of Chronic Low Back Pain have Psychological Comorbidities? *Avicenna J Med*., 11(3):145-151. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8500070/
44. Robertson, D., Kumbhare, D., Nolet, P., Srbely, J., Newton, G. (2017). Associations between low back pain and depression and somatization in a Canadian emerging adult population. *J Can Chiropr Assoc*., 61(2):96-105. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5596967/
45. Makris, U.E., Higashi, R.T., Marks, E.G., Fraenkel, L., Gill, T.M., Friedly, J.L., Reid, M.C. (2017). Physical, Emotional, and Social Impacts of Restricting Back Pain in Older Adults: A Qualitative Study. *Pain Med*., 18(7):1225-1235. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5914385/
46. Tompkins, D.A., Campbell, C.M. (2011). Opioid-induced hyperalgesia: clinically relevant or extraneous research phenomenon? *Curr Pain Headache Rep*., 15(2):129-36. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3165032/

References (continued)

47. Compton, M.A. (1994). Cold-pressor pain tolerance in opiate and cocaine abusers: correlates of drug type and use status. *J Pain Symptom Manage*., 9(7):462-73. https://pubmed.ncbi.nlm.nih.gov/7822886/
48. Laulin, J.P., Célèrier, E., Larcher, A., Le Moal, M., Simonnet, G. (1999). Opiate tolerance to daily heroin administration: an apparent phenomenon associated with enhanced pain sensitivity. *Neuroscience*, 89(3):631-6. https://pubmed.ncbi.nlm.nih.gov/10199599/
49. CDC. (2022). CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022 *MMWR*, 71(3); 1–95. https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm
50. Chou., R., Fanciullo, G.J., Fine, P.G., Adler, J.A., Ballantyne, J.C., Davies, P., Donovan, M.I., Fishbain, D.A., Foley, K.M., Fudin, J., Gilson, A.M., Kelter, A., Mauskop, A., O'Connor, P.G., Passik, S.D., Pasternak, G.W., Portenoy, R.K., Rich, B.A., Roberts, R.G., Todd, K.H., Miaskowski, C.; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. (2009). Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*., 10(2):113-30. https://pubmed.ncbi.nlm.nih.gov/19187889/

References (continued)

51. FDA. (2018). *Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain*. https://www.fda.gov/media/99496/download
52. FDA. (2017). *Introduction for the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics*. https://www.fmda.org/2017/Blueprint%20Opioid%20LA.ER%20REMS%20as%20of%201.20.2017.pdf
53. Whiteman, H. (2016) *Opioids might worsen chronic pain, study finds*. Medical News Today website. https://www.medicalnewstoday.com/articles/310645
54. Krenzischek, D.A., Dunwoody, C.J., Polomano, R.C., Rathmell, J.P. (2008). Pharmacotherapy for acute pain: implications for practice. *Pain Manag Nurs*., 9(1 Suppl):S22-32. https://pubmed.ncbi.nlm.nih.gov/18294591/
55. Dunwoody, C. J., Krenzischek, D. A., Pasero, C., Rathmell, J. P., & Polomano, R. C. (2008). Assessment, physiological monitoring, and consequences of inadequately treated acute pain. *Pain Management Nursing*, 9(1), 11-21.
56. Polomano, R.C., Dunwoody, C.J., Krenzischek, D.A., Rathmell, J.P. (2008). Perspective on pain management in the 21st century. *Pain Manag Nurs*., 9(1 Suppl):S3-10. https://pubmed.ncbi.nlm.nih.gov/18294589/

References (continued)

57. Polomano, R.C., Rathmell, J.P., Krenzischek, D.A., Dunwoody, C.J. (2008). Emerging trends and new approaches to acute pain management. *Pain Manag Nurs*., 9(1 Suppl):S33-41. https://pubmed.ncbi.nlm.nih.gov/18294592/
58. Cheatle, M.D., Compton, P.A., Dhingra, L., Wasser, T.E., O'Brien, C.P. (2019). Development of the Revised Opioid Risk Tool to Predict Opioid Use Disorder in Patients with Chronic Nonmalignant Pain. *J Pain*, 20(7):842-851. https://pubmed.ncbi.nlm.nih.gov/30690168/
59. CDC. (2023). *When to Offer Naloxone to Patients.* https://www.cdc.gov/opioids/naloxone/factsheets/pdf/Naloxone_FactSheet_Clinicians.pdf
60. NIH on Drug Abuse (2021). *What Are the Signs of Having a Problem With Drugs?* https://nida.nih.gov/research-topics/parents-educators/conversation-starters/what-are-signs-having-problem-drugs