AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Describe the three major categories of pain
- Discuss the elements of a comprehensive pain assessment
- Identify appropriate pharmacologic and non-pharmacologic treatment options for pain
- Distinguish factors that create challenges for individual pain management

After completing the continuing education activity, pharmacy technicians will be able to

- Describe the three major categories of pain
- Explain why patients who have pain need a comprehensive pain assessment
- Identify pharmacologic and non-pharmacologic treatment options for pain
- Classify symptoms that a patient with pain may share that require referral to a pharmacist

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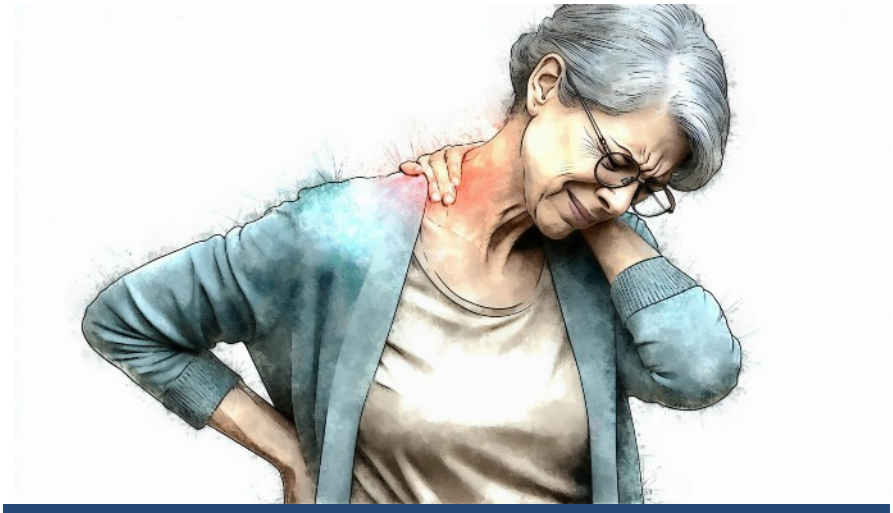

Pain Points: A Comprehensive Approach to Pain Management

TARGET AUDIENCE: Pharmacists and pharmacy technicians interested in the classifications of pain and their role in the multidisciplinary treatment approach.

ABSTRACT: The universal understanding of pain persists as one of the fundamental challenges of medicine. Since the 1950s, the definition of pain has evolved from a consequence of disease to a disease state itself. The International Association for the Study of Pain has developed the three major categories of pain (nociceptive, neuropathic, and nociplastic) to illustrate the physiologic differences of the complex pain pathways in the body. Greater understanding of pain types paves the way to a comprehensive pain assessment. Matching pathogenesis with medication selection ensures adequate analgesia. Not all pain is the same and must be considered on case-by-case basis. A more holistic approach to pain allows providers to develop a more descriptive picture of the entire condition. Applying the biopsychosocial model to pain provides insight into the many other factors that can affect the development of a pain state negatively or positively. The advances in pain medicine are significant, but numerous shortcomings remain. Most pain cases are complex and involve multiple pain types and overlapping conditions. Appropriate pain management becomes increasingly difficult the more nuanced a case is. To continue pushing pain management forward, all healthcare providers must adopt a multimodal individualized approach considering all the contributing factors of pain.

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FACULTY DISCLOSURE: Dr. Vinciguerra has no financial relationships with an ineligible company.

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INTRODUCTION

Pharmacy teams understand pain is on the nation's radar, and the nuances of pain management can be challenging for the clinical team and the patient. Pain is among the most common reasons why people seek medical care. Conditions like osteoarthritis, back pain, and headaches consistently land in the top ten reasons someone would see a doctor.[1] Statisticians estimate that more than 30% of peo-

ple worldwide are affected by some variation of chronic pain. It exerts a substantial personal and economic burden; three of the four leading causes of years lost to disability are chronic pain conditions (back pain, neck pain, musculoskeletal disorders).[2] A 2010 Institute of Medicine review estimated that chronic pain afflicts one in three Americans, costing between $560 billion and $635 billion annually in medical costs and lost productivity. It is worth noting that this estimation did not include institutionalized individuals (i.e., prisoners, nursing home patients), military personnel, or children.[3]

A few fun facts are planted along the way in this activity, so watch for interesting information about redheads, snakes, and social anxiety. Pain is the appropriate response of an intact nervous system, serving as a protective mechanism crucial to function. It is an adaptive tool that grants insight to the nature of a disease state and the healing process, until it doesn't. In 1953, John J. Bonica, the "father of pain medicine," described pain's complexity, stating that when pain is intractable (not able to be managed or controlled), it no longer serves a useful purpose. Through both mental and physical effects, it becomes destructive.[4] While the general consensus on pain has graduated from being considered a mere symptom of disease, most practitioners still fail to recognize the condition as its own distinct disease state.

Pain can range widely in intensity, quality, and duration and has diverse pathophysiologic mechanisms and meanings, making it difficult to define concisely.[5] In 2020, the International Association for the Study of Pain (IASP) produced a revised definition of pain supplemented with additional clarifications. The list below outlines the major takeaways:[6]

- Pain, an unpleasant sensory and emotional experience, is associated with or resembles actual or potential tissue damage.
- Biologic, psychologic, and social factors influence pain perception, making it a highly personal experience.
- Respecting a person's narrative of his or her pain experience is a healthcare team responsibility.
- Pain and nociception are different, so clinicians shouldn't infer that a patient is having pain exactly where the patient reports the pain.
- Although pain is usually adaptive, it may adversely affect a patient's functioning and social and psychologic well-being.
- Each individual's life experiences develop their own notion of pain.
- Patients use several behaviors to express pain, not just their words; people who cannot communicate (i.e., have dementia or cognitive compromise) can and do experience pain.

The recent modifications propose a more individualized and holistic comprehension of pain and further solidify the case for pain as a disease state.[6]

PAUSE AND PONDER: A patient walks up to your pharmacy counter and asks for help picking out an over-the-counter medication for his chest pain. What questions might you ask before recommending a product?

NOCICEPTIVE PAIN

Pain specialists define nociceptive pain as normal neural activity in response to noxious (harmful) stimuli damaging tissue.[7] Physical or chemical assaults such as trauma, surgery, or chemical burns stimulate nociceptors (pain receptors) found in the skin, organs, joints, bones, and muscles. The presence of a noxious stimuli triggers the basic pain mechanism, which can be broken down into three stages: transduction, transmission, and modulation. Transduction begins with the conversion of the inciting stimulus to chemical tissue and synaptic cleft events. Neurons propagate these events as electrical signals to be transduced as chemical events at the synapses. Transmission conveys the peripheral nociceptor activation to the central nervous system (CNS) using electrical impulses and neurotransmitter release along the neurons in the spinal cord.[7] Once the signal reaches the somatosensory cortex of the brain, the individual perceives pain. In other words, once an event occurs, a chemical process starts and travels through the tissue and synapses. Next, an electrical system takes over and eventually conveys the message that the patient needs to feel pain to the CNS.

Perception of pain also plays a role in the brain's ability to generate alerts for future avoidance behaviors.[8] The sensation of nociceptive pain continues as long as the offending stimuli remains present. Pain modulation occurs at every level of the nociceptive pathway. The body's ability to alter pain signaling partially explains why the same noxious stimulus may elicit different individual responses.[9]

The two subtypes of nociceptive pain are somatic and visceral. Somatic pain occurs due to injury to the skin, bones, joints, or soft tissue.[10] This pain is localized, often manifesting as an ache, a dull discomfort, or a sensation of soreness. Visceral pain arises from damage to visceral organs (e.g., heart, kidney, liver, lungs). Direct stimulation of afferent nerves (nerves that relay sensory information from the organ to the CNS) due to tumor, distention (swelling), or ischemia (restricted blood supply) of viscera results in this cramping/squeezing pain sensation. Visceral pain often presents as diffuse and poorly localized in space and time.[10]

The lack of sensory nerves in organs and blood vessels often results in referred pain (discussed below).[10] Pain signals from viscera are transmitted over common nerve pathways used in somatic pain responses. For example, during a heart attack, pain may initially present in the neck, jaw, shoulder, or medial arm

before the patient feels it in the chest. Visceral pain is also commonly associated with nausea/vomiting, tachycardia, and other vital sign changes due to its non-specific involvement of the autonomic system.[10]

NEUROPATHIC PAIN

Neuropathic pain can be defined as a process occurring after a primary lesion or disease of the somatosensory system (the body's system for sensing touch, pain, and temperature). The injury results in improper excitatory and inhibitory somatosensory signaling, maladaptive changes to ion channels, and increased variability of pain modulation across the CNS.[11] Prolonged exposure to a neuropathic event often results in sensitization (increased sensitivity to stimuli in the peripheral or central nervous system). When involving a noxious stimulus, sensitization is a normal response. Due to some outside force, the body becomes hyperaware of potential future damage. Sensitization, however, becomes a significant issue in chronic pain cases because it eventually produces painful stimuli even if no apparent harm is present.[12]

Peripheral sensitization describes a reduction in action potential threshold causing an amplified response of nociceptors.[12] A stimulus of a lower magnitude creates more pain than one would expect. This occurs when primary sensory neurons' peripheral terminals are exposed to inflammatory mediators and damaged tissue, localizing the dysfunction to the site of tissue injury. Nociceptors still initiate this pain response, but these nociceptors now require much less input to trigger pain signals. Central sensitization results from changes in the neurons' properties in the CNS. The result: the nociceptive system becomes abnormally responsive and overexerts itself. These CNS changes alter response to sensory inputs, no longer requiring the presence of peripheral noxious stimuli. Pain experts describe the process as sensory illusion, where pain sensation occurs even in the absence of noxious stimuli or peripheral pathologies.[12]

Common signs and symptoms associated with neuropathic pain include:[13]

- allodynia (pain due to a stimulus that does not normally provoke pain)
- hyperalgesia (increased sensitivity to feeling pain and an extreme response to pain)
- paresthesia (abnormal touch sensation, such as burning or prickling)

While nociceptive pain is understood best by its inherent "detect and protect" mechanism, neuropathy has no benefit or protective function.[14] This condition's pathology can originate from a number of different mechanisms best described by anatomic location or etiology.[15] Neuropathy's variable etiology makes it more difficult to treat than nociceptive pain. Neuropathic pain syndromes are divided into those representing a peripheral or central lesion or disease. Peripheral nerve damage may stem

from a number of potential causes including mechanical, chemical, or infectious offenders. Metabolic dysfunction, medications, toxins, or inflammatory mediators can change the density of fibers involved in neuronal signaling resulting in hyperexcitability. Injuries along the axon including trauma, compression, hypoxia, or chemical damage can result in fiber degeneration and faulty signal transmission. Some examples of common peripheral neuropathies include:[15]

- carpal tunnel syndrome
- chemotherapy-induced peripheral neuropathy
- diabetic neuropathy
- post-herpetic neuralgia

Central neuropathy is associated with traumatic injury to the brain or the spinal cord, a stroke, or multiple sclerosis. In some cases, patients may not experience the total manifestation of central neuropathy until months after a CNS injury.[15]

NOCIPLASTIC PAIN

In 2017, the IASP introduced nociplastic pain as the third mechanistic pain descriptor, indicating significant differentiation from well-established nociceptive and neuropathic pain.[16] Nociplastic pain arises from altered nociception despite no clear evidence of actual or threatened damage to tissue or the somatosensory system. Before establishing nociplastic pain as its own entity, the IASP referred to this class as predominant central sensitization (CS) pain. CS is understood as an amplification of neural signaling within the CNS that results in various forms of dysfunction that induce pain hypersensitivity. Examples of dysfunction include[16]:

- altered sensory processing in the brain in resting state
- increased brain activity in areas involved in acute pain sensation (e.g., prefrontal cortex)
- altered activity in brain-orchestrated nociceptive facilitatory pathways
- decreased or improper endogenous analgesia activity

In 2021, the IASP developed clinical criteria and a grading scale for nociplastic pain. **Table 1** (on the next page) lists nociplastic pain's criteria components.[16]

Table 1. IASP Criteria for a Nociplastic Pain Diagnosis[16]
Pain lasting at least 3 months in duration (chronic)*
Regional rather than discrete pain distribution*
Pain cannot be explained entirely by nociceptive or neuropathic mechanisms*
Patient must display clinical signs of pain hypersensitivity (e.g., thermal or mechanical allodynia) at least in the reported region of pain*
History of pain hypersensitivity in the region of pain
Patient presents with at least 1 of the defined comorbidities: increased sensitivity to light/sound/color, sleep disturbance with frequent nocturnal awakenings, fatigue, or cognitive problems with attention or memory

*Mandatory for "possible nociplastic pain" diagnosis

This criteria's establishment by a worldwide scientific organization helps recognize nociplastic pain as the third mechanistic pain descriptor along with nociceptive and neuropathic pain. The stressed importance of assessing comorbidities with non-pain symptoms and sensory hypersensitivity highlights the notion that CS, a key underlying mechanism of nociplastic pain, goes beyond the nociceptive system.[16]

Some common disease states recognized as nociplastic include fibromyalgia, irritable bowel syndrome, and chronic headache.[17] These conditions highlight the nuance required to assess chronic pain thoroughly. Typically, an individual with a chronic condition will either have mixed pain clearly involving all three pain types or a nociplastic condition disguised as neuropathy or visceral pain. Pain categorization guides its pharmacologic treatment approach and jumpstarts the pain assessment triage.[17]

PAUSE AND PONDER: Now that a third type of pain has been globally defined, how has your overall perception of pain changed?

PAIN ASSESSMENT

As recently clarified by the IASP, healthcare providers should recognize and treat pain as a unique, individual experience.[1] Chronic pain does not impact all people equally. According to the Centers for Disease Control and Prevention (CDC), the highest prevalence rates of chronic pain are seen in women, military veterans, individuals from lower socioeconomic backgrounds, and people residing in rural areas. With regard to race and ethnicity, studies are mixed; however, most have reported higher incidence in racial and ethnic minorities (e.g., African American, indigenous people). Research attributes these differences to enhanced physiologic pain sensitivity, cultural differences, and reduced access to care.[1]

To create a more holistic approach to patient assessment, healthcare providers must first categorize and classify pain, then cross-reference these factors against personal lifestyle factors. Upon determining which of the three major pain types a person is experiencing, the pain management team must consider other more general features of the pain before making a specific diagnosis. The other components of the classification system include duration, actual or perceived location, and intensity.[18]

DURATION AND LOCATION OF PAIN

Providers typically describe pain as acute or chronic. According to the IASP, acute pain is commonly associated with actual or threatened tissue damage that lasts from a few seconds to three months. Chronic pain persists or recurs for more than three months. It is sometimes further differentiated by considering if the chronic condition is cancer-related, non-cancerous, or episodic.[6]

Over the last few years, the IASP has fought alongside the World Health Organization (WHO) to change the way the healthcare system recognizes chronic pain conditions.[6] They advocate a shift to considering chronic pain as a disease in its own right rather than an underlying consequence of another affliction. In 2015, the IASP Task Force proposed updated categorization of pathologic pain conditions for the 11th Revision of the International Classification of Diseases (ICD-11). The revamped definition supported with adequate coding would grant pain sufferers greater access to proper care. This in turn improves epidemiological data regarding chronic pain and helps address some of the shortcomings that have plagued pain management.[6]

The actual or perceived location of pain can help with treatment selection and/or prognosis in an emergent situation. For example, if a patient has left arm pain, it would be vital to differentiate a fractured humerus bone from referred cardiac pain sometimes associated with a heart attack. Although etiology may not always match with sensory information, perceived location of pain helps initiate the diagnostic process and establishes a patients' baseline pain pattern.[18]

Pain intensity is a subjective but valuable diagnostic element. Unidimensional pain assessment tools such as verbal rating scales (VRS), numerical rating scales (NRS), and visual analog scales (VAS) provide a baseline pain score dictating the level of analgesia necessary to achieve an optimal pain response.[19] Providers combine these rating scales with multi-dimensional pain assessment tools (e.g., Brief Pain Inventory, McGill Pain Ques-

tionnaire) to capture comprehensive understanding of the complaint and guide treatment.[20]

THE BIOPSYCHOSOCIAL MODEL

The biopsychosocial model of pain demonstrates the dynamic interaction of physical symptoms combined with biologic, psychologic, and social factors. Some contributing biologic factors considered include age, sex, genetics, and other predisposing conditions (i.e., hormone abnormalities, nervous system sensitization).[21]

Psychologic factors corresponding to chronic pain include depression, anxiety, post-traumatic stress, diminished coping skills, and somatization (expression of psychologic or emotional factors as physical symptoms), among others.[21] If a disease state significantly impairs a patient's ability to work, a state of helplessness often follows. A chronic pain condition can rapidly diminish self-esteem, which in turn can negatively impact interpersonal relationships. Higher rates of divorce, substance abuse, and suicide are often seen in those battling chronic pain conditions.[21]

Sociocultural factors linked to chronic pain include low education status, job dissatisfaction, lack of social support, and fundamental cultural differences.[21]

ELEMENTS OF A MULTIDIMENSIONAL ASSESSMENT

Chronic pain can detrimentally affect a number of social conditions in one's life.[22] Providers must be cognizant of the evolving picture of health to provide well rounded care. They should acknowledge that the cause-and-effect relationship between pain and lifestyle is bidirectional. A patient's sub-optimal living condition may increase the likelihood of a condition developing into a chronic problem. Underlying depression, anxiety, or poor sleep habits may exacerbate an injury's severity or even predispose individuals to pain. Health care providers should increase efforts to promote each pain patient's resiliency. Two ways of doing this are strengthening emotional support systems and promoting positive health practices. Both interventions can expedite restoration and hinder chronification.[22]

Table 2. The PQRSTU Mnemonic for Pain Assessment

P	**P**recipitating or **P**rovocative Factors "What brings on the pain? What makes it worse?" Changes in position, bowel movements, and even eating habits can sometimes alter the level of pain.
	Palliative Factors "What relieves the pain? What makes it better?" This is strictly in reference to non-pharmacologic aids, including ice or heat application, sleeping, or any distraction strategies.
	Previous Therapy "What have you used for pain control in the past? How well did the medication work? Did you experience any side effects?" Consider all prescription, over-the-counter, and homeopathic remedies.
Q	**Q**uality of Pain "What does the pain feel like?" It is best practice to ask patients to try and describe it in their own words and only prompt with suggestions if they are struggling to explain the sensation (e.g., aching, stabbing, burning).
R	**R**egion/**R**adiation of Pain "Where do you feel the pain? Does it spread to other areas or remain in the same place?" Always try and have patients show you where they perceive the pain. This may provide greater context as to the pain being referred or localized.
S	**S**everity of Pain "How bad is the pain?" The use of a VRS is crucial for establishing a baseline and indicating if specific interventions should be implemented for pain control.
T	**T**emporal Aspects of Pain "When did the pain start? Is the pain constant or intermittent? How long does the pain last or how frequently does it occur?" Duration of pain and time since pain onset are crucial to differentiating an acute or chronic pain condition.
U	Yo**U**-Associated Symptoms of Pain "How does the pain affect your everyday life? What do you want to be doing right now that you cannot because of your pain?" Consider how significantly quality of life might be decreased if the patient is now unable to work or exercise because of their condition.

VRS, verbal rating scale

In addition to the unidimensional scales and questionnaires, healthcare practitioners use multidimensional assessment to address the eight elements of a pain complaint. Practitioners often use the mnemonic PQRSTU, described in **Table 2** (on previous page), to help guide this systematic approach.[23]

PAUSE AND PONDER: What is the pharmacist's role in the multidisciplinary approach to pain management?

GOALS OF PAIN MANAGEMENT

The three basic goals of a successful pain management plan are:

1. To relieve pain! Identify and treat the cause of pain (when possible) by matching the analgesic with the pathogenesis.
2. To restore function. Improve the patient's ability to perform every day activities without exceeding limits of pain and discomfort.
3. To prevent pain from becoming chronic. If pain becomes chronic, optimize therapies by titrating to the lowest dose that improves pain without unacceptable side effects.

To achieve these goals, a well-constructed pain team monitors the situation from all angles. A multidisciplinary approach is a standard of care; nurses, pharmacists, physicians, social workers, and therapists all pool their expertise with the common objective of pain control. The pain team does not just include healthcare professionals. Family members or caregivers can also significantly contribute on the road to recovery. The unique support that they provide can add a familiar layer of comfort for patients in an unfamiliar situation.[24]

In 1986, WHO designed an analgesic ladder (see **Figure 1** below) as a tool to aid in the development of cancer pain treatment plans. The simple, stepwise approach to addressing pain severity while considering adverse effects of pharmacologic agents revolutionized pain management. It was immediately clear that this conservative protocol was not limited to cancer pain and could be applied to most acute or chronic conditions.

In 2020, clinicians from the Mayo Clinic considered updates from the CDC Guideline for Prescribing Opioids for Chronic Pain and the American Society of Interventional Pain Physicians to modernize the analgesic ladder. The three modifications are as follows:[25]

- Attempt to employ integrative medical treatments at each step of the ladder. Therapies including yoga, acupuncture, tai chi, and spinal manipulation have demonstrated a positive effect on patient outcomes. Acupuncture as a complementary treatment for chronic pain displays evidence of decreasing required opioid analgesic dosages and, in some cases, eliminating the need for opioids all together.
- Consider minimally invasive interventions at step 3 when non-opioids or weak opioids have failed to control the pain. Procedures such as nerve blocks, epidural or subarachnoid administration of local anesthetics, and spinal cord stimulation may slow the progression to the need for strong opioid medications.
- Prescribe strong opioid medications at step 4 only as a last resort after all other modalities fail.

Figure 1: WHO Analgesic Ladder

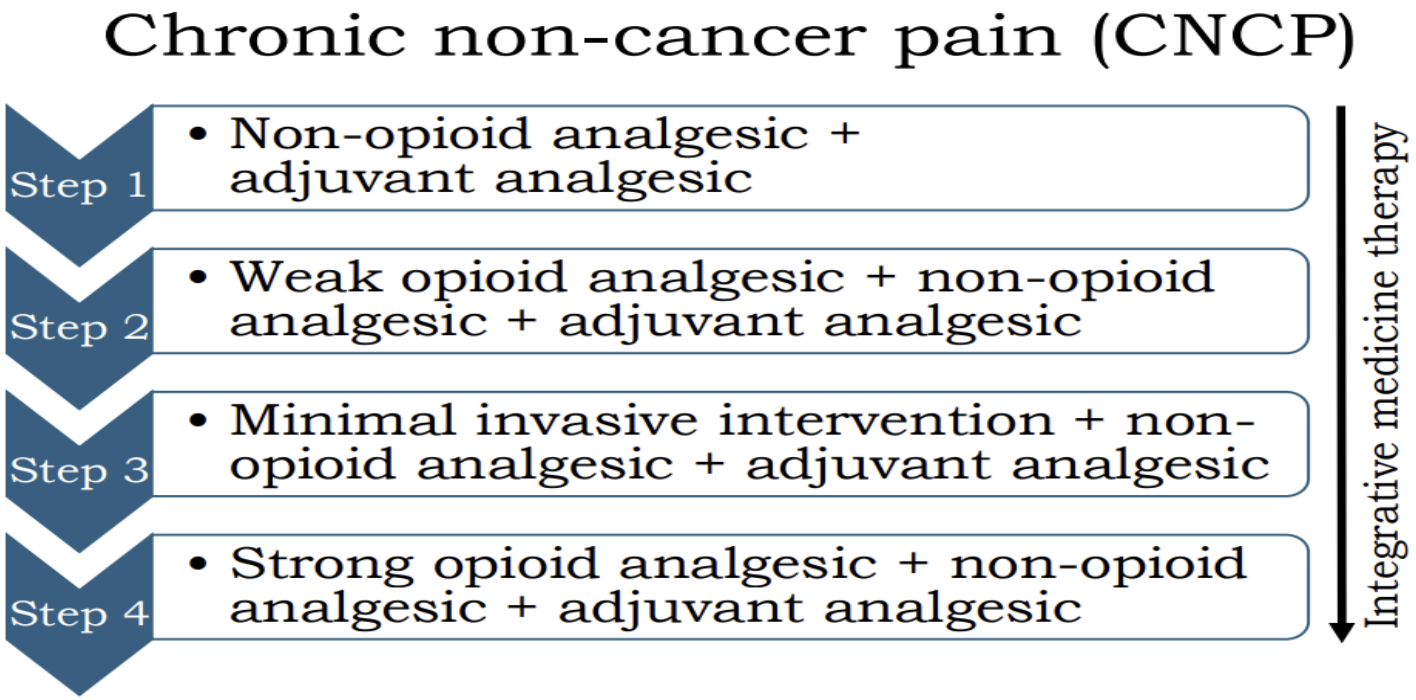


Table 3. Opioid Receptor Subtypes[33,34]		
RECEPTOR	**UNIQUE FUNCTIONS**	**LOCATIONS**
μ	• Sedation • Inhibition of respiration • Decreased intestinal transit rate • Regulation of hormone and neurotransmitter secretion	• Brain (thalamus, caudate, amygdala, raphe nuclei, gray matter, hippocampus) • Dorsal horn • Peripheral terminals • Small intestine
δ	• Regulation of hormone and neurotransmitter secretion	• Brain (cortex, amygdala, hypothalamus, midbrain) • Spinal cord
κ	• Psychotomimetic effects • Decreased gastrointestinal transit	• Brain (cortex, thalamus, hypothalamus, gray matter, black matter, caudate, and putamen)

PAUSE AND PONDER: Consider a time when a patient has told you that they do not even know what the medication they are taking is for. Or maybe they asked why they take an anti-seizure medication and have never had a seizure in their life. How can you bridge the knowledge gap?

TREATMENT OPTIONS FOR NOCICEPTIVE PAIN

First line treatments for somatic or visceral nociceptive pain include non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (aspirin; ASA), acetaminophen (APAP), and steroids.

Providers prescribe NSAIDs (e.g., celecoxib, diclofenac, ibuprofen, indomethacin, naproxen) largely due to their analgesic properties, anti-inflammatory mechanism, and antipyretic (fever reducing) effect.[26] This class of drugs exerts its effects by inhibiting the enzyme cyclooxygenase (COX). COX is responsible for the conversion of arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. Thromboxanes are involved in platelet adhesion following tissue injury. Prostaglandins and prostacyclins cause vasodilation and play a role in anti-nociception.[26]

The two isoenzymes of COX (COX-1 and COX-2) exert different effects that help explain the class's adverse effect profile.[26] COX-1 is the prime mediator for maintaining gastrointestinal tract lining. Inflammatory conditions induce COX-2 expression. Due to most NSAIDs' nonselective nature, gastric distress is a common adverse effect of these drugs. COX inhibitors with selectivity to COX-2 (e.g., celecoxib) significantly limit damage to the digestive tract. Other significant adverse drug reactions (ADRs) include renal damage and antiplatelet function.[26]

Although ASA is considered an NSAID, its unique mechanism of action is worth noting. The drug simultaneously modifies both COX-1 and COX-2. The interaction with COX-2 is believed to turn off prostaglandin production but triggers the creation of novel protective lipid mediators.[26]

It is important to recognize that while APAP has analgesic and antipyretic properties, it is considered to be at best a weak anti-inflammatory agent. A study showed that daily doses of APAP may reduce neural activity related to the emotional pain associated with social rejection. Participants' brain activity were measured and found that APAP decreased neural response in areas associated with distress caused by social pain.[27] Despite its long history of use, APAP's mechanisms are still not completely understood. It is widely accepted that its metabolite, N-acylphenolamine, works on receptors in the brain and the dorsal horn. The ADR of highest concern associated with APAP is liver damage. Healthy adults should not take more than 4 grams of APAP daily and should avoid extended exposures to high dose therapy.[28] Older patients and individuals with liver disease or chronic alcohol use should limit APAP use to 3 grams daily.

An adjuvant therapy is a drug that is not primarily recognized as an analgesic based on its pharmacologic class but has been shown in clinical practice to either demonstrate some independent analgesic effect or provide a synergistic effect when combined with opioids.[29] The adjuvant will act on excitatory neurotransmitters (e.g., glutamate, substance P), inhibitory transmitters (e.g., GABA), or neurotransmitters that modulate the experience of pain (e.g., serotonin, norepinephrine). Drug classes commonly used as adjuvant therapies for pain management include:[30]

- Skeletal muscle relaxants (e.g., carisoprodol, baclofen)
- Tricyclic antidepressants (TCAs; e.g., amitriptyline)
- Serotonin norepinephrine reuptake inhibitors (SNRI; e.g., venlafaxine, duloxetine)
- Anti-epileptics (e.g., carbamazepine)

Opioids' (e.g., codeine, hydrocodone, methadone, morphine, oxycodone, tramadol) role in pain management is paradoxical. Opioids are a mainstay in perioperative and palliative care settings. However, their use and effectiveness in chronic pain cases becomes increasingly controversial over time due to their prob-

lematic set of short-term and long-term adverse effects.[31] A solution may be on the way in the form of snake venom. Researchers reported that the isolation of a specific class of peptides from the African black mamba snake were found to have analgesic effects comparable to morphine in mice.[32]

Opioids exhibit their effects by binding to the three categories of opioid receptor subtypes: mu (μ), delta (δ), and kappa (K) found across the CNS and other tissues. Each subtype (see **Table 3** on the previous page) is capable of producing spinal or supra-spinal analgesia, but their specific localizations provide insight into the adverse effect profile of this drug class. For example, μ receptors are found in the small intestine and function to decrease intestinal transit rate, which often results in the commonly seen adverse effect of constipation.

Opioids may be classified as agonists (full or partial receptor activators), antagonists (receptor blockers), partial agonists (submaximal receptor activators), or mixed agonist-antagonists (activate one receptor subtype while blocking another).[33] The varying potency at which different opioids act at one or more of their receptors also contributes to their wide array of pharmacologic effects.[34] **Table 4** (below) provides examples of each opioid classification relative to its receptor affinity.

Opioids' common adverse effects include constipation, dependence and tolerance, CNS impairment, and respiratory depression. Counseling patients on what to watch for and how to mitigate these adverse effects when they occur improves their quality of life. Recommendations when discussing potential drawbacks of opioid therapies include:[11,36,37,38]

- Confirm a bowel regimen is in place that includes both drug and nondrug treatments. Using a stool softener, stimulant and/or osmotic laxative combined with increased physical activity, fluid intake, and dietary fiber intake can minimize constipation.
- Establish a baseline cognitive level. Sedation and decreased cognition can occur with initiation of opioid therapy or when increasing the dose. Pharmacists should perform a thorough medication review to modify or eliminate unnecessary medications that synergize CNS effects (e.g., antihistamines, antidepressants).
- Differentiate between dependence and tolerance. Physical dependence is the result of an altered physiologic state due to chronic drug exposure. Tolerance describes the need for a dose increase to achieve desired analgesic effect. Clinicians should also recognize the lack of complete cross tolerance with opioids. Tolerance with one opioid does not mean tolerance to all, and titrating a new opioid to the target equianalgesic dose is crucial in the prevention of an overdose.
- Identify risk factors for opioid-induced respiratory depression. Advanced age, female sex, and comorbidities (e.g., diabetes, sleep apnea) increase the likelihood of this potentially fatal adverse effect. The simultaneous use of multiple opioid drugs or modified-release opioid formulations can also put patients at higher risk.

Opioid use in patients with hepatic or renal insufficiency must be closely monitored. Opioids undergo phase 1 metabolism via the cytochrome P450 (CYP) pathway and/or phase 2 glucuronidation in the liver.[39] Primary metabolic enzymes include CYP3A4 and CYP2D6, resulting in substantial interaction potential with a number of commonly used drugs (e.g., cardiovascular agents, antibiotics, statins). Moderate to severe liver disease can result in

Table 4. Opioid Affinity and Activity[35]

	RECEPTOR SUBTYPE		
	μ	**δ**	**K**
Morphine (agonist)	Affinity: +++ Activity: ***	Affinity: + Activity: *	Affinity: + Activity: *
Buprenorphine (partial/mixed agonist)	Affinity: ++ Activity: (***)	Affinity: - Activity: -	Affinity: + Activity: XX
Naltrexone (antagonist)	Affinity: +++ Activity: XXX	Affinity: ++ Activity: X	Affinity: ++ Activity: XXX

+, low affinity; ++, moderate affinity; +++, high affinity; -, negligible affinity/activity; *, agonist activity; ( ), partial agonist activity; X, antagonist activity.

higher peak plasma levels of opioids and their metabolites, which is associated with an increased incidence of adverse events. Primary elimination of opioids through urine necessitates dose adjustment in the renally impaired population. The impact of kidney dysfunction on opioid excretion is not uniform. For example, while morphine only sees its clearance decrease slightly, the clearance of morphine's active metabolites decreases significantly. Accumulation of these metabolites correlates with serious CNS adverse effects and respiratory depression. Hepatic or renal impairment impact fentanyl and methadone, two commonly used opioids, least. Clinicians should consider low and slow dose titration, dose reduction, and extension of dosing intervals when treating people with hepatic or renal impairment.[39]

Designation of opioids based on potency is of limited practical use and often can perpetuate misperception among prescribers. The notion that a "weak" opioid (e.g., tramadol, codeine) is less likely to result in dependence or withdrawal symptoms compared to a "strong" opioid is false. Prescribers need to consider the potential harm of opioid use and misuse regardless of the drug's classified potency.[40]

In the United States, the number of patients taking opioids regularly is equal to the number of patients diagnosed with psoriatic arthritis, epilepsy, and obsessive-compulsive disorder combined. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) defines opioid use disorder (OUD) as repeated opioid use within 12 months resulting in problems or distress including two or more of the following:[41]

- Continued opioid use despite worsening physical or psychological health
- Continued opioid use despite social and interpersonal consequences
- Decreased social or recreational activities
- Difficulty fulfilling professional duties at school or work
- Excessive time spent obtaining or recovering from taking opioids
- Taking more opioids than intended
- Experiencing opioid cravings
- Inability to decrease the amount of opioids used
- Development of opioid tolerance
- Continued opioid despite the dangers it poses to the user
- Experiencing withdrawal or continuing to take opioids to avoid withdrawal

Congress enacted the Drug Addiction Treatment Act of 2000 (DATA 2000) to allow qualified practitioners to prescribe buprenorphine outside of opioid treatment programs in an effort to increase access to medication-assisted treatment.[42] Interested prescribers needed to obtain the DATA-Waiver (a document to allow prescribing of opioid treatment products outside of parameters established by existing law. As of December 2022, the DATA-Waiver previously necessary to prescribe medications for OUD treatment no longer exists, and any provider with a standard DEA number may prescribe buprenorphine products. Pharmacists play a versatile role in combatting the opioid epidemic by using prescription drug monitoring programs, providing education, dispensing naloxone, and referring patients or loved ones to resources and treatment services.[42]

PAUSE AND PONDER: You have noticed that a patient is asking for a refill on their opioid prescription a week early for the third consecutive month. What questions might you have for the patient? The prescriber?

NEUROPATHIC PAIN TREATMENT OPTIONS

When considering neuropathic pain treatment, guidelines recommend first considering the patient's report of negative (e.g., reduced sensation to touch, vibration, pin prick, and temperature) or positive sensory symptoms (e.g., spontaneous or evoked pain). Spontaneous pain includes dysesthesia (abnormal sensation), paresthesia, or superficial burning pain. Evoked pain symptoms include touch-induced hyperalgesia, thermal hyperalgesia, or a prolonged sensation of pain after the stimuli is removed (aftersensation).[43]

First line treatments for neuropathic pain include sSNRIs, gabapentinoids, TCAs, and topical medications.

Duloxetine and venlafaxine are the most common SNRIs used to treat pain.[43] These drugs exhibit some staying power when considering neuropathic pain first line options. The class has demonstrated effectiveness in both peripheral and central neuropathies, including peripheral diabetic neuropathy, painful peripheral neuropathy, and central neuropathic pain secondary to multiple sclerosis. Compared to TCAs and selective serotonin reuptake inhibitors, patients tolerate SNRIs better, with the most common adverse effects including nausea, headache, and drowsiness. Beyond neuropathic pain, SNRIs have also provided benefit in a number of potentially concurrent chronic pain conditions including osteoarthritis, chronic low back pain, and fibromyalgia.[43]

Long recognized as the cornerstone of nerve pain treatment are gabapentinoids: gabapentin and pregabalin. This notion has recently fallen under a heightened scrutiny due to a lack of strong data. A recent study found around 50% of patients treated with gabapentin will not derive meaningful pain relief but will likely experience adverse events.[44] While sometimes mistaken as benign drugs, gabapentinoids carry significant risks and have been moved onto the controlled substance schedule (drugs that carry the potential risk for addiction/use disorder) in many states. CNS effects such as dizziness, sedation, and gait instability occur in roughly every third patient, even when taken at a therapeutic dosage. This creates additional concern when prescribers use them with opioids. Concomitant gabapentinoid and opioid use increases risk of hospitalization and opioid-related death compared to gabapentinoid or opioid monotherapy. The updated Beers criteria list cautions against the use of this dual therapy regimen in older adults.[45]

TCAs impact pain through multiples mechanisms of action. Serotonin and norepinephrine reuptake inhibition serves as the primary pain-relieving effect.[43] In addition, drugs like amitriptyline and nortriptyline block other neurotransmitters and neuromodulators involved in the pain response, including histamine, acetylcholine, and epinephrine. This wide-spread, non-specific activity also contributes to TCAs' broad adverse effect profile. Significant incidence of anticholinergic effects (e.g., dry mouth, constipation, urinary retention) combined with cardiotoxic potential create legitimate concern when using these drugs in older adults.[46] The fact that only 20% to 30% of the dose normally used in effective anti-depressant treatment is necessary for pain relief may mitigate these concerns slightly.[43]

Topical lidocaine or capsaicin circumvent the cautious dosing regimens of previously discussed classes.[43] Although lidocaine is considered first or second line therapy only in post herpetic neuralgia, its safety and tolerability establish the drug as a viable adjunct option for other neuropathic pain causes. A three-week trial period may provide the patient with modest pain relief while using a non-systemic mechanism of action, so long as that person does not have red hair. Studies show that redheads are more sensitive to thermal pain and more resistant to the effects of topical anesthetics like lidocaine.[47] Success of capsaicin is dependent on consistent use, however, pharmacists should caution patients against overuse due to nerve desensitization risk.[43]

NOCIPLASTIC PAIN TREATMENT OPTIONS

Non-pharmacologic interventions are first line for nociplastic pain. The pain management plan should include[48]:

- routine, aerobic and mind-body exercises
- cognitive behavioral therapy and/or acceptance commitment therapy
- strict sleep hygiene practices
- physical/occupational therapy
- keeping a pain journal to track goals and identify potential barriers

A positive patient-provider relationship is crucial due to the complex nature of the disease states that cause nociplastic pain. Providers must communicate to patients that pain may not be a true representation of underlying inflammation and/or joint damage. Explanation and identification of nociplastic pain may validate the patient experience and improve the withdrawn and dismissive affect associated with this population.[48]

Data on effective pharmacologic treatment options for nociplastic pain is limited. The main objectives of treatment are to reduce symptoms and improve quality of life. Most first line and adjuvant drugs used in nociceptive pain are considered marginally effective at best. Codeine provides weak analgesia in regards to fibromyalgia but not without the increased risk of prescription opioid misuse seen in nociplastic pain patients. TCAs, SNRIs, and gabapentinoids have shown some efficacy in nociplastic pain, but are not without concern due to the high incidence of adverse effects linked to these drug classes.[17]

It is worth mentioning that ketamine has shown promise in complex regional pain syndrome (CRPS), making a case for trial in other nociplastic pain conditions. CRPS occurs after a stroke, heart attack, or injury that presents as severe extremity pain disproportionate to the inciting event. Ketamine primarily works in the CNS to decrease neuronal activity, and secondarily through other pathways that affect pain and mood regulation.[49]

CONCLUSION

Successful pain management demands collaboration. Consider the work that you do every day. Whether pain is the chief complaint or a secondary issue, odds are that it will be a factor in your clinical decision making. A comprehensive pain assessment starts this process. Understanding the different pain classifications enables the assessment to guide next steps in care. Healthcare providers formulate and modify a treatment plan as more information rolls in. Pain does not follow an algorithm; it is an individual experience that requires nuance and balance. How can you make an impact? **Figure 1** lists ways to improve your practice.

Figure 1. Safety and Counseling Related to Types of Pain

Best

❶ **Be COMMUNITY CHAMPIONS** and be a readily available resource to your patient and a key facilitator of their diverse pain management team

❷ **Be a pillar of your local health community** by attending opioid overdose trainings and participating in the local opioid task force

❸ **Conduct meticulous medication reconciliation** to identify and/or consider potential adjuvant therapies

Better

❶ **Encourage patients to take part in their own pain management** through physical and social activity

❷ **Increase awareness of naloxone** using pharmacy displays and patient-friendly literature

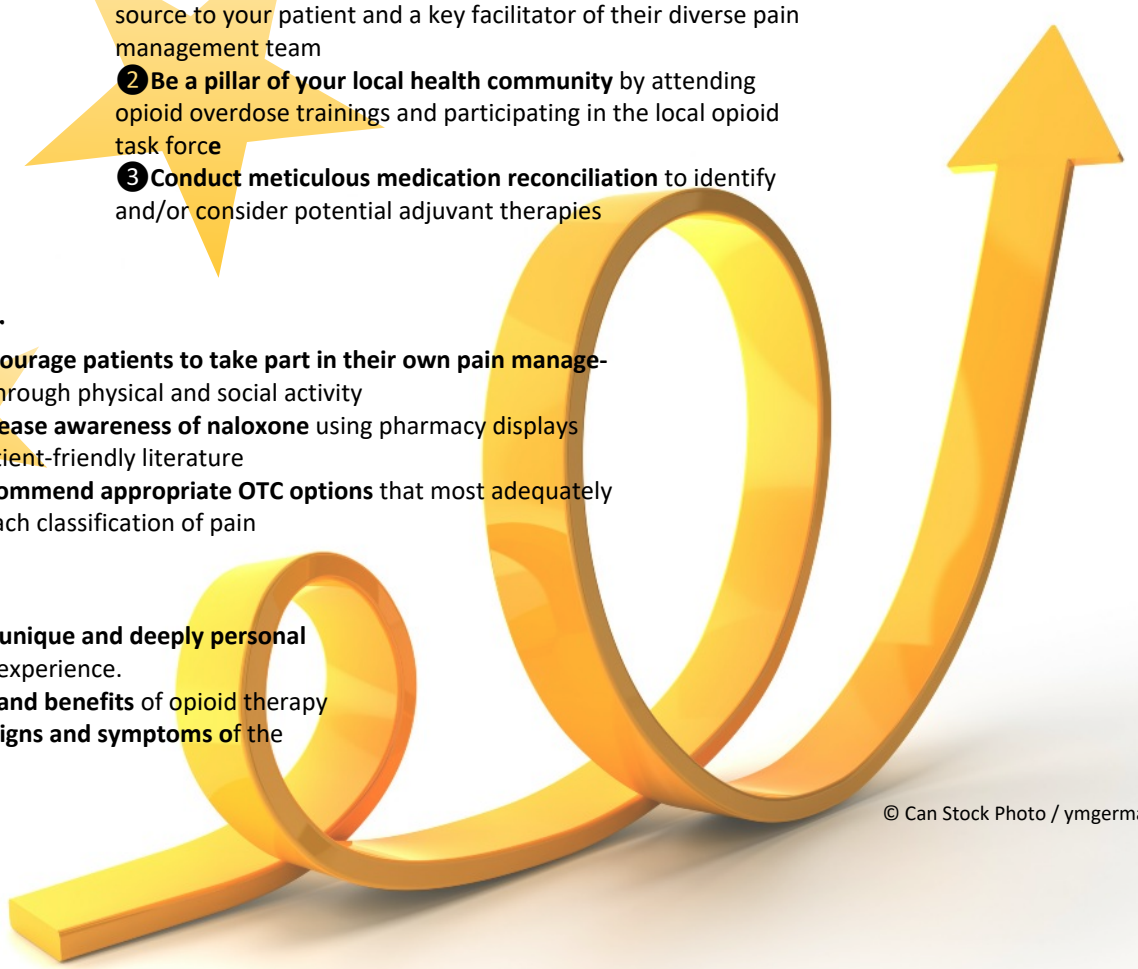
❸ **Recommend appropriate OTC options** that most adequately treat each classification of pain

Good

❶ **Appreciate the unique and deeply personal nature** of the pain experience.

❷ **Know the risks and benefits** of opioid therapy

❸ **Recognize the signs and symptoms of** the three types of pain



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