THE MANAGEMENT OF CHRONIC PAIN AND THE ROLE OF THE PHARMACIST

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Topic Overview

Pharmacists practicing in all settings can play important roles in the management of chronic pain. In many cases, the pharmacist is the most accessible member of a patient's medical team. When a pharmacist is involved in determining safe and effective therapies, monitoring therapies, and providing patient education, patient outcomes related to chronic pain management improve. Expanded roles for pharmacists in chronic pain management have also shown better outcomes for patients.

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Credits: 1.5 hours of continuing education credit

Type of Activity: Continuing education

Media: Internet

Fee Information: \$5.99

Estimated time to complete activity: 1.5 hours, including Course Test and course evaluation

Release Date: September 5, 2022 **Expiration Date:** September 5, 2025

Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From September 5, 2022, through September 5, 2025, participants must:

- 1) Read the "learning objectives" and "author and planning team disclosures;"
- 2) Study the section entitled "educational activity;" and
- 3) Complete the Post-test and Evaluation form. The Post-test will be graded automatically. Following successful completion of the Post-test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

Learning Objectives: Upon completion of this educational activity, participants should be able to:

- 1. **Identify** the types and classifications of pain
- 2. **Describe** the pain assessment process
- 3. **Compare** pharmacologic and nonpharmacologic pain management options
- 4. **Describe** the role of the pharmacist in chronic pain management and their contribution to improving patient outcomes

Disclosures

The following individuals were involved in the development of this activity: Marilyn Lajoie, MD, DC, CCSP, Susan DePasquale, MSN, PMHNP-BC, and Mary Elizabeth Fredrickson, PharmD, BCPS. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

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Introduction

Pain is a subjective experience, which means patients will experience pain in diverse ways. This also means that there is no objective, physical methodology to measure pain. Pharmacists practicing in all settings have important roles to play in pain management, including determining safe and effective regimens, mitigating adverse effects, identifying medication-related problems, and providing patient education. Pharmacists can be more effective in helping patients manage chronic pain when they utilize their knowledge of the physiology of pain and pain assessment. This knowledge is crucial for pharmacists to help improve outcomes for patients who have persistent pain. Positive outcomes have been found when pharmacists are involved in managing their patient's chronic pain.

Defining and Classifying Pain

Pain is a protective, physiological response to an event that has the potential to damage body tissue, or that may damage body tissue. This event is known as a "noxious stimulus."¹ Noxious stimuli are detected by nociceptors through transduction in their peripheral terminals, which causes the sensation called pain.² Nociceptive pain occurs from a "pin prick, touching something too hot or any potentially tissue damaging chemical, thermal or mechanical stimulus."²

The International Association for Study of Pain has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage."¹ Although pain is unpleasant, it is intended to cause a reaction in the person that will limit or avoid tissue damage.^{1,2}

A person experiences pain when three events occur: the person's nociceptive receptors are activated through transduction (as described above); a message is then transmitted through the central nervous system; and, a pain response results.¹ When this system is functioning optimally, it serves the intended protective purposes of limiting further injury; however, this system can malfunction, resulting in sustained pain, pain resulting in spite

of the absence of stimuli, and an amplification of pain signals, which are referred to as "central sensitization."¹

Pain is a personal, subjective experience.^{2,3} Only the person experiencing pain can fully describe it. Because every person has a distinctive tolerance threshold, each person may measure pain differently. Factors that affect the experience of pain are multifactorial, and these will influence an individual's tolerance to pain. These factors may be biological, psychological, or social.⁴ As a consequence, pain is complex, and it can be difficult to manage.⁴

Categorizing Pain

Pain can be classified into three categories: 1) nociceptive pain, which includes somatic pain (pain stemming from skin, bones, muscles, and joints) and visceral pain (stemming from the internal organs); (2) neuropathic pain, which is triggered by pathological changes in the central and peripheral nervous systems and 3) psychological pain.⁹

Nociceptive Pain

Nociceptive pain results from the stimulation of pain receptors through either tissue injury or inflammatory mechanisms.

Somatic Pain

Somatic pain symptoms tend to be a more localized, aching pain.²¹ Nociceptive receptors are stimulated, and this can evoke somatic pain when these nerve endings send pain messages to the brain because of cell injury to body areas containing connective tissue.⁶ Somatic pain is pain that occurs in areas such as the bones, joints, muscles, or the skin. It may be further classified as *cutaneous* somatic pain and *deep* somatic pain. Somatic pain is the most prevalent pain present in cancer patients.⁹ In cases of bone metastases, nociceptors are sensitized by prostaglandins and osteoclastactivating factors, which result in hyperalgesia and pain. Drugs are selected that inhibit nociceptor sensitization and bone pain and may possibly inhibit tumor growth. 6

Cutaneous somatic pain often develops in superficial tissues from injuries that are less traumatic to the body. The patient may describe this sensation as sharp or burning.²² Examples of injuries that can cause cutaneous pain include skin abrasions. Deep somatic pain is described as occurring beneath the cutaneous level and is often caused by trauma to bones or muscles, resulting in more intense pain. Deeper, somatic pain injuries may manifest as bone fractures or torn ligaments.²³

Visceral Pain

Visceral pain is that which is affected by internal organs and tissues, such as the heart, gastrointestinal system, or the kidneys, and signals nociceptors within them to respond to painful stimuli. The pain may develop as part of a disease process, which results in cramping or tissue spasms, or in ischemia development at the site. Visceral pain may also occur as a result of injury, or through some type of medical procedure, during which the organs and tissues are moved, stretched, or manipulated, resulting in pain.²¹

Visceral pain may be difficult to localize because the pain may be initiated at one site in the body and radiate to another area. With radicular pain, it may be difficult to determine the initial location of the pain and whether an injury has occurred. More than 20% of the population suffers from chronic visceral pain.²⁴ Visceral pain is sometimes described as cramping, squeezing, or a feeling of pressure. The intensity of the pain may also vary from mild and intermittent discomfort to severe and agonizing pain.¹⁰

Neuropathic Pain

Neuropathic pain occurs when a person experiences pain related to changes in nerve fibers or their conductivity, usually resulting from a type of injury, lesion or disease of the somatosensory system.^{10,11} The somatosensory system has many receptor types throughout the body, such as

thermoreceptors, mechanoreceptors, and chemoreceptors, which send signals to the spinal cord and subsequently to the brain. Lesions within this system can cause altered or aberrant signaling to pain centers throughout the body, resulting in neuropathic pain.¹²

Neuropathic pain may be categorized by the presence or absence of coexisting conditions and how the pain developed. Traumatic neuropathic pain causes the injured nerves to send incorrect pain signals to the brain, whether the injury to the body healed. An example of traumatic neuropathic pain is phantom limb pain, in which a person who has had an amputated limb continues to feel pain in the missing extremity.^{8,12}

Metabolic neuropathic pain occurs when a person experiences sensory pain as a result of complex medical disorders that affect the metabolic system, such as malnutrition or diabetes.¹³ One of the most common conditions causing metabolic neuropathic pain is diabetes mellitus. The patient with diabetes may suffer from nerve damage because of uncontrolled blood glucose levels, resulting in pain, numbness, burning, or tingling in the distal extremities. This type of pain is mechanistically dissimilar to other categories of pain syndromes, such as those which result from inflammation. In an inflammatory cause of neurogenic pain, the etiology of pain is an alteration of chemical events where the inflammation occurs and is diagnosed and treated differently.¹⁴

Infectious neuropathic pain develops from an infection in the body that causes nerve damage and, subsequently, chronic pain that may be constant or intermittent. Examples of infections that can lead to neuropathic pain include the varicella-zoster virus, which causes chickenpox and shingles. These infections can lead to post-herpetic neuralgia. Infection with Lyme disease, or human immunodeficiency virus (HIV) may also lead to neuropathic pain. The treatment of several of these disorders may cause pain that is indistinguishable from the disease itself, such as in HIV-induced neuropathy and toxic antiretroviral neuropathy.¹⁵

Immune-mediated neuropathies can cause autoimmune neuropathic pain. Chronic inflammatory demyelinating polyneuropathy occurs when the myelin sheath of the nerve fibers becomes damaged, resulting in pain in the extremities. A multicenter study conducted by Pazzaglia, *et al.* (2011) reported that over 50% of patients with immune-mediated neuropathies had symptoms of neuropathic pain.¹⁶ Common descriptors of this type of neuropathic pain were paresthesias and spontaneous superficial pain. They also reported that conditions thought to be painless, as in multifocal motor neuropathy, exhibited pain ranging from mild discomfort to overtly painful symptoms.¹⁶

Compression pain, also known as neuroma, is another type of neuropathic pain that occurs from many causes, such as swelling, inflammation, and muscle imbalance.¹ Carpal tunnel syndrome and compartment syndrome are examples of this type of pain.¹ Musculoskeletal conditions often accompany nerve injuries, and medical conditions such as tendinitis, bursitis, or arthritis are caused by the same disorders associated with neuropathic pain.¹

Toxic substance exposure can result in neuropathic pain.¹⁷ Chemicals such as lead, mercury, arsenic, thallium, lithium, chemotherapy drugs, antibiotics, such as isoniazid and metronidazole, and some cardiovascular medications, including amiodarone and statins, can all cause neuropathic pain with exposure.¹⁸⁻²⁰

Psychological Pain

Psychological pain is also known as emotional pain. This pain state may result from psychological factors or disease states that elicit a perception of pain. Practitioners should consider that the emotional context of pain can change the experience of pain for patients.

Types of Pain

There are distinct types of pain, and they each involve different treatment methods. Pain can be classified according to time course, pathophysiology, location, and etiology. Pain can be categorized as acute pain, chronic pain, cancer pain, and chronic noncancer pain.^{21,22}

Acute pain occurs for a shorter duration and is classified as lasting for less than three months or as pain restricting daily living activities for one month or less.²³ Acute pain can be very brief, lasting for a few seconds or minutes before resolving. Subacute pain has been defined as pain persisting from six to twelve weeks. The definition of chronic pain varies but is likely best defined as pain lasting beyond the expected period of healing. Chronic pain was previously defined as lasting more than three months.⁵ Cancer pain is pain associated with cancer and can be a result of the disease itself or treatment of the disease, such as adverse effects from chemotherapy. Cancer pain can be acute or chronic. Chronic noncancer pain is utilized as a category among experts who view cancer pain as a separate category of pain. However, cancer pain and chronic non-cancer pain can be categorized together under chronic pain.²¹⁻²³

Acute pain may be severe when the pain begins but often resolves completely with time and treatment. Acute pain causes a stress response, such as tachycardia and tachypnea, but this response typically ends when the pain is resolved and the tissue has healed.⁶ Examples of situations where a patient may experience acute pain include surgery, burns, or skin lacerations.

Chronic pain lasts for a much longer period of time, and it may not be more tolerable than acute pain sensations. Longer-lasting pain is not necessarily less debilitating than acute pain.⁷ Chronic pain that results from an injury can continue long after the precipitating condition has been treated. Favorable outcomes are sometimes judged by factors other than the resolution of pain; for example, a patent may be considered recovered because the patient returned to work, even though the patient's pain persists.⁵ Chronic pain can desensitize the person experiencing it so that the pain no longer triggers a stress response.⁷ A patient may be admitted for treatment that causes acute pain yet may already be suffering from chronic pain as well. A physiologic stress response may be developed due to acute pain from procedures or surgery; however, as the body's response to chronic pain continues concurrently, the patient may begin to adapt to it. In other cases, chronic pain can be very debilitating, resulting in comorbid conditions such as depression, irritability, and difficulties with sleeping.⁸ Examples of conditions that may result in chronic pain in addition to injury include autoimmune disorders (such as arthritis), certain types of cancer, or musculoskeletal dysfunction.^{2,6}

Assessing Pain

Health providers should assess a patient's pain by reviewing a patient's medical history, description of pain, and past successes in pain relief. A pharmacist's involvement in assessing a patient's pain management plan has improved a patient's health outcomes.⁴

Pain assessment includes evaluating a patient's total needs, considering the patient's physical, psychological, and emotional matters. A patient in pain may have other complications and issues that need to be managed as part of care, such as difficulties with eating, problems with concentration, impaired mobility, and constipation due to pain medications. The location and source of the pain can significantly impact a patient's ability to perform tasks, including activities of daily living.^{8,24}

In a clinical setting, assessing pain may be just as important as assessing blood pressure, heart rate, and other vital signs. Some experts view pain assessment as "the 5th vital sign."²⁵ Other experts disagree but regardless of a clinician's opinion on this subject, pain assessment is crucial enough for a patient's well-being that it should be given the same priority as other vital sign measurements. Pain assessment should occur at regular intervals to ensure that there is adequate pain management.

Patients in pain are in a vulnerable state, and they often do not voice the presence of pain or its severity. Reasons for this include not wanting to be labeled as drug-seeking, or as a complainer, and still, others do not want to disturb their healthcare providers. They may believe that pain is normal during hospitalization and may not feel the need to vocalize it. Some people think that expressing pain is too personal, and they do not wish to share that part of themselves, remaining stoic. Finally, some patients do not notify their health clinicians that they are having pain because they fear a diagnostic outcome, such as a new condition requiring narcotics, or an examination precipitating additional tests. Because there are so many reasons why patients may not disclose their symptoms, health clinicians need to assess pain so that it can be appropriately managed.

The perception of pain is affected by several factors unique to each patient. A patient's pain threshold, cultural background, expectations for pain management, and previous experiences with pain all impact the patient's responses to a current pain syndrome. These factors should also be recognized as impactful to a patient's response. Psychosocial factors should also be identified. Pain catastrophizing can be defined as "an exaggerated negative mental set brought to bear during actual or anticipated painful experience."¹⁹ Increased fear of pain is also associated with higher levels of self-reported experimentally induced pain intensity. Both may be an influence on pain assessments.¹⁹ Two of the most common causes of unrelieved pain among patients are inadequate pain assessment measures and failure to act on a patient's report of pain.

Adequate pain assessment involves determining the location, intensity, and duration of the patient's pain based on verbal or observed responses. Providing adequate pain control means acting on those responses to provide effective relief and continuing to monitor therapy to determine if additional measures are needed.^{8,24}

Location

Pain location is the site as described by the patient, which may or may not be the actual origin of the symptom. If the patient is experiencing radicular pain, it may be experienced at both the site of origin as well as the region to which the pain is emanating.^{8,24} When a patient experiences an injury such as an upper extremity fracture, pain may be felt at the fracture's site and throughout the entirety of the limb. Alternatively, referred pain occurs when the source of the pain is in one part of the body, but the patient feels pain in a completely different area. An example of referred pain is a myocardial infarction that does not produce chest pain; instead, pain is felt in the left arm and neck. Referred pain most commonly occurs in situations where a patient is experiencing visceral pain.²⁶

To determine where the patient is feeling pain, the clinician should ask the patient to point to the site of pain, rather than only asking the patient for a description. A body diagram may also be useful for some patients to point to affected areas. It can be particularly helpful if a patient is experiencing pain in more than one location and to alert a clinician to the possibility of widespread chronic pain, a sign of increased pain sensitization.²⁷ If the patient has an apparent injury, such as a wound or contusion at a specific site on the body, it would seem logical that this point is the location of the patient's pain. Despite having an obvious injury, the patient still needs to specify where the pain is located. There may be more than one location of pain, which could indicate another injury or the patient may feel the pain associated with a different condition unrelated to the obvious injury.²⁶

Duration

Duration of pain as a classification seems self-explanatory; however, it is a consideration not only of the current pain episode but also of any precipitating factors. A patient may have been participating in certain activities that initially caused the pain; for example, developing chest pain while jogging, which stops when exercise concludes. The differential diagnosis could be anginal symptoms or costochondritis, or even gastric reflux. The fact that it starts and stops with a specific activity is important to the diagnostic workup.

A patient may know the exact time when the pain started and be able to relate precisely how long the occurrence lasted. A description of pain duration also includes whether the pain is constant or intermittent; in the latter, the patient should try to describe the intervals and the length of time between episodes of pain. If the patient is currently between pain intervals, it is helpful to learn how long it has been since a painful episode last occurred.

Description

Careful attention must be paid to the type of words the patient uses to describe the pain. At times, it may be difficult for the patient to come up with words or an appropriate description of the pain type, intensity, or location. There are some tools available that clinicians may use to help the patient use the right words to describe the pain.

The OLD CARTS mnemonic can be used to help a patient to describe the location and intensity of pain. The mnemonic is used as follows:²⁸

- Onset: when did the pain start, or how long has it been going on?
- Localized: where is the pain?
- Description: explain how the pain feels: burning, aching, sharp, stabbing, throbbing
- Characteristics: describe how the pain feels (*i.e.*, aching, burning)
- Alleviating/Aggravating: is there anything that makes the pain better or worse?
- Radiation: does the pain spread anywhere else:
- Time: how long have you had the pain and has it been constant or intermittent?
- Symptoms: has the pain had an impact on any other of your daily activities, such as eating, sleeping, or mood?

A simpler method of describing pain intensity would be for the clinician to assess whether the patient is having pain and if the pain could be described as *mild, moderate, or severe*.²⁹ This pain assessment tool may need to be used in conjunction with the assessment of nonverbal signs that indicate pain severity, *e.g.*, grimacing.³⁰ Pain can also cause sleep disturbances, decreased self-esteem, diminished social interactions, irritability, a lack of interest in eating, and confusion or impaired thinking.³¹

In addition to assessing pain severity, location, and duration, part of the pain assessment process is asking patients about their perception of pain.³⁰ A patient may have a complete understanding of why pain is occurring, such as post-operatively. However, some lack an understanding of the cause of the pain they are experiencing. They may believe that they are experiencing pain because they did something wrong, or if they have referred pain, they may not understand why the pain is not located at the source of the injury or illness. Asking patients what is known about their pain provides an opportunity for education about how the body processes injuries or illness and may better explain why some procedures or treatments are necessary.

Clinicians should also be aware that a patient's pain perception may go beyond an obviously related disorder or physiologic process. Exploring what pain means to the patient by incorporating physiological and psychological issues, such as depression and anxiety, will allow for a fuller understanding of the cause of pain and the appropriate therapy needed. Of the general population, about 5% are affected by depression, but this percentage is greatly increased by those suffering from chronic pain. Estimates are that up to 60% of chronic pain patients also have depression.³² There are studies explaining the relationship between pain and depression to be bidirectionality. Depression is a positive predictor of the development of chronic pain, and chronic pain increases the risk of developing depression.^{32,33} This points to the importance of distinguishing the varied perceptions people have of pain. The psychological components of how suffering, loss of function, decreased ambulation and the fear of death impact a patient need to be included in a comprehensive pain assessment.

Methods for Assessing Pain

There are numerous methods for assessing pain. They include the numerical rating scale and the Wong-Baker FACES pain rating scale.

Numerical Rating Scale

The numerical rating scale is one of the more commonly used methods for assessing a patient's pain.³⁴ Because pain cannot be objectively measured but instead relies on a patient's admission of pain level, this type of scale can adequately explain the level of intensity the patient is experiencing in a method that is easy to understand.

The numerical rating scale is appropriate for most adults who are cognitively aware and able to respond. The numerical rating scale asks the patient to rate pain on a scale of 0 to 10.³⁴ A score of 0 means the patient has no pain, while a score of 10 is the worst pain imaginable. The patient gives a number somewhere on the scale to describe the current level of pain.³⁴

A patient's pain tolerance can also be assessed by explaining the numeric rating scale and asking what the patient's current level of pain is and what number would be an acceptable level of discomfort. For example, a patient may rate pain felt at a '7' on the numeric rating scale but may also say that the pain can be tolerated as a '2.'³⁴ For this patient, a level of pain described as a '2' may be quite tolerable, while some other patients may tolerate pain classified as a '6' and others may only be comfortable at a level of '0.' Understanding the patient's *tolerable* level of pain can guide clinicians to know whether pain management measures are working and whether the patient is being kept comfortable.

It is helpful to relate pain tolerability in relation to functional ability. Approximately 1/3rd of post-operative older patients reported pain that was "painful but bearable" with a numeric rating of 5/10, while over 50% of older adults reported it as merely "bothersome pain." It may be stated by the

patient that "I can stand the pain, it's not that bad," followed by a refusal of pain medication. 35

FACES Rating Scale

Other assessment measures are available for some patients who cannot speak but who are cognitively aware. The Wong-Baker FACES pain rating scale has a series of faces with different expressions that may explain how much pain a person has.³⁵ At one end of the scale, the equivalent of a '0' on the numeric rating scale, the face is smiling and appears happy, indicating no pain. Moving down the scale, the expressions of the faces become progressively sadder or appear to have more pain. At the opposite end of the scale, in the position of '10' on the numeric rating scale, the face is crying and appears to be in significant pain. The patient who cannot talk can use this type of pain scale to point to which face most closely resembles their level of pain. The Wong-Baker FACES scale may also be used for children ages 3 and older; however, this scale is not recommended for older adults due to its original intent to be a scale for children. There are happy faces rather than neutral expressions, and some show tears on faces, which has been stated to be problematic in getting some adults, such as stoic men and women, to use the full scale. The "animated cartoonish faces are said to be less appealing to adults."35

Assessing Pain in Cognitively Impaired Patients

Pain may be difficult to assess among patients who are cognitively impaired and who have difficulty expressing their level of pain on a numerical scale. A study by Jones, *et al.* (2019) was undertaken to quantify the impact of cognitive impairment on pain assessment and management practices in the emergency department.³⁶ They determined that those patients with cognitive impairment were less likely to have their pain assessed using a standardized tool and 9.4% more likely to be assessed using ad hoc methods only (95% confidence interval 4.6-19.1) They determined that pain is inadequately and inappropriately assessed for elderly patients with a cognitive impairment in the emergency department, which resulted in delays initiating pain

management.³⁶ If patients cannot express their pain effectively, it is important to assess for visual signs of pain in the patient and to provide pain relief measures if the patient is showing nonverbal cues indicative of pain. These cues might include fidgeting, grimacing, crying, moaning, being aggressive or disruptive, rocking, or pacing. Additionally, physiological changes may also be present, even if the patient is unable to describe being in pain. Signs include an increased heart rate, increased respiratory rate, increased blood pressure, dilated pupils, or sweating.

Assessing Pain in Children and Adolescents

Walco, Kopecky, Weisman, *et al.* (2018) reported that there are over "35 self-report pain intensity measures designed for children and adolescents;"³⁷ however, the reliability and validity of most of these tools are not adequately supported by evidence.³⁷ These tools vary when it comes to responsiveness and what may be interpreted from the assessment. Reliability and validity also vary across pediatric age groups. An in-depth discussion on pediatric, self-report, and pain measurement tools is beyond the scope of this course, but Walco, Kopecky, Weisman, *et al.*, provide a useful overview of the effectiveness of some of the scales as applied to different age groups.³⁷

Assessment Based on Cultural Considerations

A healthcare provider should consider the role cultural or ethnic backgrounds may play in a patient's sensitivity to pain or a patient's willingness to discuss pain with his or her provider. For example, Rhudy, *et al.* (2020) found that Native Americans may be more pain sensitive based on their finding that Native Americans had lower cold pain thresholds or tolerances than non-Hispanic Whites.³⁸ This suggests possible pain risk differences between Native Americans and other U.S., minority groups.³⁸ Awareness of possible cultural or ethnic differences can improve patient outcomes from pain management treatments.

Managing Pain

Beyond performing adequate pain assessments, it is important to provide appropriate treatment based on the patient's description of their level of pain. It is never enough just to assess and document a patient's pain; essential components of clinical pain care and pain relief must be afforded to the patient through appropriate pharmacologic and nonpharmacologic treatment options.

Pain management centers on providing appropriate treatment for a patient's pain to eliminate the pain or reduce it to a tolerable level. This may involve using pharmacologic and/or nonpharmacologic treatment options. Clinicians will need to use evidenced-based decisions and clinical judgment to select therapies that will appropriately manage pain while minimizing adverse effects. In some cases, when a medication is to be given on an as-needed basis instead of on a set schedule, clinical judgment must be used to determine the appropriate medication schedule, as well as when to hold back from administering medication, depending on the patient's condition.

Treatment of chronic pain should involve a multi-pronged approach that targets the cause of the pain (nociceptive vs. neuropathic vs. psychological). Patient education is crucial in setting expectations, as it is unlikely that chronic pain will be completely eliminated for many patients.

Nonpharmacologic Therapies

Many patients with chronic pain will benefit from nonpharmacological therapies. These methods may impact the body through physical means or may use cognitive or behavioral therapy to help the patient manage pain through psychological measures.^{39,40} Nonpharmacologic measures that may be used for pain control may include psychotherapy, massage, heat or cold (thermal) therapy, and transcutaneous electrical nerve stimulation.

Massage Therapy

Massage involves kneading or manipulating the muscles and tissues under the skin to promote relaxation and stress relief.⁴¹ Pain can cause the muscles to contract and tighten, causing additional pain and muscular tension. The massage practitioner rubs and manipulates the musculature, most commonly in the back, shoulders, arms, and legs. This results in improved circulation to the tissues and greater relaxation and tension release.⁴¹

Thermal Therapy

Thermal therapy involves the application of warm or cold packs to various sites on the body and may be used in areas where a patient is feeling pain.⁴¹ This process may also include warm baths, heating pads, or ice massage. Application of these measures can help with pain relief by assisting the body with tissue repair.⁴¹ Heat therapy increases circulation to the affected site, which can increase the range of motion, improve joint stiffness, and relax the muscles. Alternatively, cold therapy reduces the amount of blood flow to a site and may reduce the swelling of injured tissues. By decreasing circulation to an affected area, cold therapy can also reduce inflammation.⁴¹

Transcutaneous Electrical Nerve Stimulation (TENS)

Transcutaneous electrical nerve stimulation (TENS) activates a complex neuronal network to reduce pain by "activating descending inhibitory systems in the central nervous system to reduce hyperalgesia."⁴² A TENS unit is a physical therapy modality that delivers alternating electric current through the application of cutaneous pads (electrodes) placed over the area where the patient is experiencing pain. It activates large-diameter afferent nerve fibers that can reduce pain when sent to the central nervous system and if applied at the strongest intensity possible while the patient remains comfortable. This is critical for the success of the treatment, as lower intensities are ineffective.⁴² The modality delivers an electrical current through the electrode, stimulating the muscle fibers to regulate nociceptive impulses responsible for sending pain messages. TENS may also cause an increase in release of endorphins, which can also help the patient to feel better.⁴² Effective analgesia for chronic pain conditions may be limited due to developing tolerance to TENS. This is expected if there are daily repeated applications at the same frequency, intensity, and pulse duration.⁴²

Psychotherapy and Mind-body Exercises

Psychotherapies, such as cognitive-behavioral therapy, may improve patient outcomes for resolving chronic pain. These therapies may be done as monotherapies or in combination with physiotherapy.⁴⁰ There are mind-body exercises that can be taught to a patient, which can change responsiveness to pain. If there is any intervention that causes a change in a patient's mental or emotional response, which correspondingly makes changes in the body, it can be called a "mind-body" intervention.⁴³ This methodology is used to alter the patient's perception of the pain experience. The measures do not always relieve pain, but rather assist the patient in the ability to form new adaptations when pain is felt. Pain can cause the affected person to experience stress, depression, or anxiety, which may further compound the feelings of pain. Utilizing mind-body techniques may help to regulate the emotional responses that the patient has become accustomed to the feeling when pain is experienced.^{43,44}

Mind-body techniques cause an alteration of a maladaptive neurophysiologic pathway, leading to a more positive reaction to pain, interrupting the tendency to experience depression and anxiety secondarily. A study of veterans was undertaken by Cosio and Swaroop in 2016 to determine the differential impact that mind-body medical interventions have on psychological distress among veterans with chronic pain, not caused by cancer.⁴³ They primarily used Cognitive Behavioral Therapy and Acceptance and Commitment Therapy. The conclusion of the study was that both mind-body medical interventions for chronic pain showed a decrease in anxiety reported by the veterans and provided evidence of the treatment effectiveness of both interventions for chronic pain.⁴³

Distraction is a psychological intervention in which a patient who is in pain focuses on something other than the pain. When concentrating on something else, a distracted patient may become unaware of the pain.⁴⁵ Distraction can be through visual methods, such as watching television or reading a book; auditory measures, such as listening to music, or a physical distraction, such as massage or deep breathing techniques.⁴⁵

Other examples of mind-body methodologies to help with pain control include relaxation, mindfulness, biofeedback, and cognitive-behavioral therapy. Relaxation techniques help the muscles to relax, reducing tension and producing the opposite effect of the fight-or-flight response.^{44,45} Studies have shown that relief from anxiety and low baseline depression were the most important predictors of pain relief and the most strongly associated with functional improvement, so these techniques are relevant for better outcomes.⁴⁶

One relaxation technique is progressive muscle relaxation, in which the patient actively concentrates on tensing and then relaxing certain muscle groups. Laughter can be a form of relaxation therapy that can improve a patient's mood and how the individual responds to pain. These methods have also been shown to reduce inflammation and make the brain respond more to endorphins.^{44,45}

Mindfulness is a form of distraction where the patient focuses on other thoughts beyond pain. Zhang, *et al.* (2019) recited a definition of mindfulness that described it as "nonjudgmental attention to the present moment."⁴⁷ This approach can reduce the amount of emotional reaction that often goes along with pain, helping a patient focus on life and the activities around the patient's pain. Zhang, *et al.*, further reported that an eight-week mindfulness meditation training could effectively regulate mood and reduce anxiety and depression.⁴⁷ Mindfulness-related health benefits are associated with enhancements in mechanisms supporting cognitive control, emotion regulation, positive mood, and acceptance.⁴⁸

Mindfulness meditation could be such a suitable narcotic-free pain therapy as it has been repeatedly found to decrease chronic pain symptomologies. This form of meditation attenuates pain through unique psychological and neural processes, and it was recently demonstrated to be more effective in reducing pain than a placebo without engaging endogenously driven opioidergic systems to do so.⁴⁹

Biofeedback involves using thoughts to control certain body functions; for example, biofeedback might involve using thought processes to slow a racing heart rate.⁵⁰ Biofeedback requires the focus of attention on making a change in the body. A patient can utilize the measurement of certain bodily functions, such as blood pressure readings, or by using a heart rate monitor, and then relax and focus the mind to change these functions intentionally.⁵⁰ It is a relaxation process of learning to control the sympathetic nervous system, thereby reducing stress and tension that can contribute to pain.

Pharmacologic Therapies

Pharmacologic therapies can be implemented for patients with inadequately controlled pain, with nonpharmacologic therapies continued concurrently. These therapies should be selected based on the classification of chronic pain experienced by the patient. Pharmacists assisting in the management of chronic pain should also consider patient-specific factors when determining appropriate treatment regimens, including medical history, renal and hepatic function, and any medications the patient is currently taking. Details of pharmacologic therapies are discussed below. Dosing for each of the drugs discussed below is contained in the Prescriber's Digital Reference, drug summary, for each medication.

Non-Opioid Analgesics

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) work by inhibiting cyclooxygenase enzymes, COX-1 and COX-2. COX-1 is responsible for

production of prostaglandins involved in physiological functions, such as renal homeostasis and platelet aggregation.⁵¹ COX-2 is found in inflammatory cells and produces prostaglandins involved in inflammation, pain, and fever.⁵¹ Nonselective NSAIDs (such as diclofenac and ibuprofen) inhibit COX-1 and COX-2, whereas selective inhibitors (celecoxib) block COX-2. These drugs are indicated for mild to moderate pain relief, they reduce inflammation, and they can help to control high fever. They are useful in the treatment of musculoskeletal pain.^{51,52} Use of these medications may be limited by their adverse effects. NSAIDs can cause gastrointestinal side effects, including nausea, abdominal pain, and gastrointestinal (GI) irritation or bleeding. GI effects are time and dose-dependent. Additionally, the use of NSAIDs can cause hypertension and renal dysfunction.⁵¹ Topical NSAIDs such as diclofenac are effective for osteoarthritis and limit systemic side effects. Gastrointestinal effects can occur in any age group, but the risk increases with age.⁵¹ It is important for pharmacists to identify patients at risk for these side effects to determine the safest regimens for their patients.

Acetaminophen

Acetaminophen functions in the central nervous system and is effective in reducing mild to moderate pain and reducing fever.⁵³ Due to concerns for hepatotoxicity, it is not recommended as a first-line treatment for chronic back pain, and its overall use for the management of chronic pain is limited. It may be beneficial as an adjunct therapy for patients with mild to moderate musculoskeletal pain.54,55 Acetaminophen does not have the same antiinflammatory effects as NSAIDs; however, NSAIDs mav lead to gastrointestinal bleeding, which is less likely with acetaminophen.^{51,53,56,57} Acetaminophen also has few drug-drug interactions. The biggest concern with the use of this drug is hepatotoxicity. Acetaminophen is found in many products, and the maximum daily dose is 4000 mg per day. Preferably, doses over 3000 mg per day should be avoided. The maximum recommended dose per day is 2000-3000mg for older patients with hepatic impairment.⁵⁸

Co-analgesics

Other medications may be combined with analgesics to provide more effective pain control. Adjuvant medications, also called co-analgesics, are those that are not designed for analgesia when they are used as a monotherapy; however, when they are combined with opioid or non-opioid analgesic, there can be a greater effect of pain relief. The World Health Organization (WHO) has designed a pain control ladder to guide clinicians toward choosing and administering medications for pain relief.⁵⁶ The WHO recommends combining medications such as adjuvants and opioid analgesics to provide more effective relief when compared to using one type of analgesic at a time. Therefore, if possible, the patient can derive better pain relief when medications are administered in combination.⁵⁶

Antidepressants

Certain types of antidepressants have been found effective for the treatment of neuropathic pain. These include tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).^{59,60} Tricyclic antidepressants can affect how pain is perceived by interfering with the reuptake of the neurotransmitters serotonin and norepinephrine in the brain and, in doing so, interfere with the transmission of pain impulses. Examples include nortriptyline and amitriptyline. While TCAs have shown efficacy in treating neuropathic pain, they elicit numerous side effects, most notably anticholinergic effects (drowsiness, urinary retention, dry mouth), cardiovascular effects, and weight gain. When dosing TCAs, clinicians should start with low doses and increase the dose slowly as tolerated by the patient.^{59,60}

Serotonin-norepinephrine reuptake inhibitors work by inhibiting the reuptake of serotonin and norepinephrine. Venlafaxine and duloxetine have been used to manage neuropathic pain. Duloxetine is specifically approved for the treatment of diabetic neuropathy, chronic low back pain, and osteoarthritis.⁶¹ Side effects of SNRIs include weight loss, insomnia, fatigue, dizziness, and abdominal pain.

Antiseizure Medications

Two medications normally used as anticonvulsants (gabapentin and pregabalin) are useful for the treatment of neuropathic pain.^{62,63} Gabapentin and pregabalin reduce the transmission of pain sensations via binding to voltage-gated calcium channels and decreasing excitatory neurotransmitter release.^{62,63} Side effects of these two medications include drowsiness and dizziness, and potentially peripheral edema.^{62,63} To mitigate these side effects, these medications should be started at low doses and titrated up slowly.⁶²⁻⁶⁴ Carbamazepine is an anticonvulsant that inactivates sodium channels.⁶⁴ There is less data to support its use for neuropathic pain.⁶⁵

Adjuvant Medications

In addition to analgesics, other drugs may also be used as adjuvant therapy because their effects can reduce or eliminate symptoms commonly associated with pain. Corticosteroids may be administered with analgesics to reduce swelling or inflammation and reduce pain.⁶⁶ Benzodiazepines should not be used in the management of chronic pain given their side effect profiles, which include respiratory depression, and potential for abuse and addiction.⁶⁷

Opioids

Opioids provide pain relief by binding to certain receptors (mu, kappa, and delta) in the central nervous system, which blocks the perception of and response to pain.⁶⁸ Opiates may be classified as natural, semi-synthetic, and fully synthetic. Pharmacologic activity and side effect profiles will vary depending on their affinity for and actions at these various receptors.⁶⁸

The Centers for Disease Control and Prevention provides guidelines to assist providers who prescribe opioids for chronic pain. These guidelines are not intended for prescribers treating patients with active cancer or who are receiving palliative or end-of-life care. Per these guidelines, nonpharmacologic therapy and nonopioid medications are preferred for the initial treatment of chronic pain.⁶⁹ These guidelines do not recommend opioids as first-line or routine therapy for chronic pain and suggest they only be considered when the benefits outweigh the risks.⁶⁹ Guidelines recommend that prescribers establish realistic goals of therapy before initiating treatment, and suggest opioid therapy be continued only when benefits significantly outweigh the risks. A 2018 meta-analysis found that the benefits of opioids in the treatment of chronic, non-cancer pain were similar to those of non-opioid therapies.⁷⁰

When determining an opioid regimen for their patient, clinicians should select an immediate-release formulation, starting their patient at the lowest effective dose for the shortest duration of time possible. The goal is to provide adequate pain control while minimizing negative effects, such as constipation, nausea, vomiting, sedation, respiratory depression, or confusion, that may develop with these drugs. Guidelines recommend reevaluating risks and benefits for patients and monitoring for adverse effects prior to increasing doses, and evaluations should occur 30 days or less, post-opioid initiation.⁷¹ The long-term use of these drugs can lead to tolerance. In addition, clinicians should consider a patient's potential for addiction, abuse, diversion, potential overdoses, and misuse of the drug.^{70,72}

Types of Opioids

Opioids can be categorized by their affinity for and ability to bind to receptors. Types of opioids include full agonists, agonist-antagonists (mixed agonists), and partial agonists.⁷³ The majority of opioids are mu agonists. Full agonists bind very tightly to opioid receptors. They work in a manner similar to endorphins in the body and increasing amounts of these drugs continue to increase pain control and sedation levels. Full agonists include morphine, fentanyl, codeine, oxycodone, and hydromorphone.⁷³

The activity of agonist-antagonist (mixed mechanism) opioids varies depending on the opioid receptor and the dose given to the patient. If a patient is already taking an opioid analgesic, an agonist-antagonist medication may reduce its effectiveness.³¹ They have a ceiling effect which means that giving higher or more frequent doses will not necessarily continue to produce more

pain relief. Examples of agonist-antagonist medications include butorphanol tartrate (Stadol[®]) and nalbuphine hydrochloride (Nubain[®]).^{74,75}

Partial agonist opioids cause partial receptor activation upon binding. Like agonist-antagonist medications, they also have a ceiling effect in terms of pain relief, so their use is similarly limited.⁷⁶ An example of a partial agonist is buprenorphine (Buprenex®), which is a partial agonist at the mu receptor.⁷⁶ Buprenorphine has been used as one of the drugs to treat addictions to opioid medication.⁷⁶

Opioids are highly addictive, and the prescription of long- and shortacting opioids has been regulated, increasingly so within the past five years. Limits as to the quantity prescribed have been legislatively controlled to cut down on the number of patients becoming addicted to prescription medication and to reduce the number of opioid overdoses. The use of buprenorphine, the opioid in Suboxone (brand) was developed as a safer opioid for the treatment of pain.⁷⁷ As a partial opioid agonist-antagonist, this drug has inherent abuse deterrence properties; it is used in the treatment of opioid addictions. As a long-acting, high-affinity partial agonist at the mu-opioid receptor, buprenorphine prevents withdrawal and craving and stabilizes opioid receptors. The most common formulation is buprenorphine and naloxone (Suboxone) in a 4:1 ratio.⁷⁸

Routes of Administration

The route of administration directly impacts a drug's onset and absorption.⁷⁹ For example, a drug administered orally will be exposed to firstpass metabolism as it makes its way through the gastrointestinal tract, whereas a transdermal patch avoids this exposure.⁷⁹ The route of administration also impacts the risk that a particular drug will be misused. A "drug with high bioavailability upon oral or intranasal administration will achieve higher plasma concentration and is more likely to be [misused]."⁷⁹ There are several means of delivery of opioid medications, so the selection for administration is based on a patient's condition and the ease of taking the medication.⁷⁹ The oral route is preferable among patients who must take opioid medications on a long-term basis. It is the easiest and least expensive method of administration and can be used among conscious patients, who can swallow, and who do not have gastrointestinal issues that would preclude its action.⁷⁹

Some patients who cannot take medication by mouth may receive drugs through the rectal route. Morphine and hydromorphone are available as rectal suppositories.⁸⁰ Not all patients tolerate this route, and it is not usually considered the first choice for most people. It should also not be used among patients who have diarrhea or those with breakdowns in or around the anus and rectum. However, rectal administration of medications can be effective for those with limited alternative routes for taking medication, and the drugs are usually absorbed relatively quickly through the intestinal mucosa. Fentanyl is available in the transdermal form. This method involves placing a patch on the skin, and the medication is slowly absorbed.⁸¹ It should only be used in opioid-tolerant patients. It can provide analgesia for up to 72 hours, but it may take several hours before effective analgesia levels are achieved.⁸²

Other methods of administration of more invasive opioid medications include subcutaneous, intramuscular, intravenous, and intraspinal routes.⁷⁹ Subcutaneous administration involves injecting the medication with a needle into the subcutaneous fat under the surface of the skin. The injection can only be given in certain locations, such as the abdomen or upper arm, where the patient is more likely to have fatty tissue present, as compared to other areas. The intramuscular route also involves injecting medication into the patient, but the needle must be longer, and the injection goes much deeper into muscular tissue. Common areas used are the deltoid muscle of the upper arm and the ventrogluteal muscle of the hip. Because this method of administration can be quite painful for the patient, it is often avoided in favor of other routes.⁸³

Intravenous (IV) administration involves injecting medication directly into a patient's vein. The patient must first have an IV line in place. This route can be quick and effective and can be used on patients who would otherwise have difficulty taking medications in other methods, including unconscious patients.⁷⁹ The intrathecal (intraspinal) method of administration involves injecting medication into a catheter that has been placed in the epidural space of the spine.^{86,87} This method may be used for patients who need long-term analgesia as an alternative to other routes.^{86,87}

Administering Medications Using Patient-controlled Analgesia

Patient-controlled analgesia (PCA) is a process that was developed to allow a patient to have more control over pain by self-administering doses of medication through a pump delivery system.^{53,56} The patient has an intravenous line for fluids and medication administration and is connected to the PCA pump.^{53,56} The pump contains a syringe with the prescribed medication in it, which is set to deliver a specific amount of medication to the patient when a button is pushed. Some settings offer a basal or continuous dose, and the patient can supplement the pain pump when the need for more pain relief occurs. In other situations, the PCA is set up to give occasional doses of pain medication when the patient needs pain relief.^{53,56}

A PCA intravenous pump can reduce the need for the patient to depend on the clinician to administer pain medication. At times, it may be difficult to administer pain medication in a timely manner in an acute care setting before pain becomes uncontrolled for the patient. With PCA, the patient can push a button to deliver pain medication when pain is felt, potentially stopping it before it worsens. The PCA pump is set to deliver only a certain amount per hour so that the patient does not receive too much.^{53,56} It will lock out so that even if the patient continues to push the button to deliver additional medication, more medication will not be received. This safety feature prevents accidental overdose of opioid medications.

Patients typically use the PCA for themselves, without someone else pushing the button to deliver medication for them. The safety in this feature is that if the patient becomes sedated after receiving a bolus of medication, more medication will not be received. The most common medications used with PCA include morphine, fentanyl, and hydromorphone.^{53,56} The setup of the PCA is typically a clinical duty that requires proper staff training to change the medication syringe when it becomes empty. The use of PCA does not eliminate the need for continued assessment and patient monitoring.^{53,56} The clinician must still assess the patient's level of pain to determine if the PCA is providing adequate pain relief. If the clinician sets up the PCA, the settings should be checked with another staff member to determine that they are correct and to avoid accidental opioid overuse or toxic dosing.

The Role of the Pharmacist in Chronic Pain Management

Pharmacists are well-trained, accessible members of the health care team who can ensure pain management regimens are safe and effective, provide pertinent patient education, and collaborate with other health care providers to improve patient outcomes.⁸⁸ Pharmacists are able to care for patients with chronic pain in many practice areas, including community, inpatient, long-term care, and specialty clinic settings. In the management of chronic pain, pharmacists are well-trained to determine accurate medication histories (including allergies), utilize patient-specific factors to select appropriate pharmacologic and nonpharmacologic therapies, identify potential drug interactions, and monitor therapies for adherence and side effects. Additionally, pharmacists can provide vital patient and caregiver education and suggest referrals to other healthcare providers to improve outcomes and the patient experience.^{4,88}

Pharmacists may be further involved in primary care by utilizing "population management activities."⁴ An example of population management could include a pharmacist reviewing a patient population group as a whole in order to identify if that group is at higher risk of opioid misuse or other pain management concerns.⁴ Greater involvement by pharmacists in a patient's pain management has resulted in a decreased burden on other primary care professionals and improved patient outcomes.⁴ Giannitrapani, *et al.*, concluded by stating: "Interdisciplinary collaboration and communication

between the medicine and pharmacy services will be essential to successful clinical pharmacist role expansion and shared team prioritization."⁴

In addition to providing expertise pertaining to medication therapies, pharmacists also have a role to play in providing trauma-informed, culturally responsive care. As members of interprofessional health care teams, pharmacists can work to recognize and eliminate implicit bias and collaborate to create inclusive care settings for all patients.⁸⁸ Pharmacists should recognize barriers that may interfere with proper pain management for patients. In a study by Lau, et al. (2019), pharmacists reported that the most common barrier to a pharmacist providing care was patients being nonreceptive to interacting with them.⁸⁹ A strategy proposed to overcome this barrier was for the pharmacist to show empathy for patients and build rapport through communication.⁸⁹ Other barriers may include a lack of knowledge regarding pain assessment tools, a patient's inability to communicate his or her pain, and a prescription for pain medication that has been prescribed without a full evaluation of a patient's pain score.⁹⁰ Pharmacists who review a patient's medical history and records and who interact with primary care providers, may be able to alleviate these barriers and improve a patient's outcomes for pain management.

Summary

Pain is a personal, subjective experience, and the person experiencing pain should describe it in their own terms to include intensity but also cooccurring symptoms and the impact of pain on activities of daily life. Pharmacists should utilize subjective and objective information pertaining to their patient's pain, in addition to their knowledge of medication therapies to manage chronic pain effectively and safely.

Types of pain and their treatments have been presented in the above sections. A challenging aspect of managing pain is when it becomes chronic due to tissue and nerve damage. The perception of pain becomes influenced by many factors related to physiological and psychosocial factors. Pain types and degrees of pain combined with other comorbidities and their treatments, such as in the example of chemotherapy or radiation therapy for cancer, can significantly impair a patient's quality of life.

Pain therapies specific to the patient's diagnosis aimed at alleviating pain involve medications, pain management procedures, and alternative type treatments such as massage and mindfulness. It is strongly recommended that the best approach is to utilize the resources of an interdisciplinary team that may include medical, rehabilitation, and psychiatric services working together to promote safe and appropriate pain management treatment and patient recovery.

Pharmacists are important members of the health care team and provide vital expertise in choosing pharmacological and non-pharmacological treatment options for pain. In many cases, the pharmacist is the most accessible member of a patient's medical team. Patient outcomes related to chronic pain management improve when a pharmacist is involved in medication review, patient education, and medication therapy management. Expanded roles for pharmacists in a patient's treatment options for chronic pain have also shown better outcomes for patients.

<u>Course Test</u>

1. _____ pain is the most prevalent pain present in cancer patients

- a. Psychosomatic
- b. Visceral
- c. Cutaneous
- d. Somatic

2. A patient is diagnosed with an acute myocardial infarction with pain felt only in the patient's jaw (no chest pain). This is an example of

- a. referred pain.
- b. receptive pain.
- c. radiating pain.
- d. random pain.

3. Which of the following drugs is a full agonist opioid?

- a. Morphine
- b. Buprenorphine
- c. Amitriptyline
- d. Nalbuphine

4. Which of the following is an example of a "population management activity" a pharmacist may implement at the pharmacy?

- a. Reviewing patient records to determine if the pharmacy is treating all population groups equally
- b. Engaging in interdisciplinary collaboration and communication
- c. Reviewing a patient population group to determine if that group is at higher risk of opioid misuse
- d. Engaging in continuing education in the area of pain management

5. _____ is a psychological intervention in which a patient who is in pain focuses on something other than the pain.

- a. Referral
- b. Biofeedback
- c. Distraction
- d. Relaxation

- 6. True or False: Pharmacists have reported that a common barrier they face to providing care to patients is their patients' non-receptive attitude to interacting with them.
 - a. True
 - b. False

7. The numerical rating scale explains which of the following in a way that is easy for patients to understand.

- a. The type of pain
- b. The intensity level of pain
- c. The complexity of pain
- d. The duration of pain

8. Acetaminophen is a non-opioid analgesic that is

- a. preferred in patients with hepatic impairment.
- b. recommended as a first-line treatment for chronic back pain.
- c. recommended for reducing mild to moderate pain.
- d. safe at any dose.

9. True or False: Because of its adverse effects profile, fentanyl is not used in patient-controlled analgesia drug delivery systems.

- a. True
- b. False

10. Which of the following is true regarding adjuvant medications used to manage chronic pain?

- a. They are contraindicated for use with analgesics
- b. They can be used as an alternative pain reliever to opioids
- c. They should be given prior to administering analgesic medications
- d. They are not designed for analgesia as a monotherapy but can enhance pain relief when combined with an analgesic.

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