From: Randy Spokane
Sent: Friday, August 17, 2012 8:23 AM
To: TevaUS_TP_Sales_All
Cc: Jim Reilly; James Dailey; Nathan Ross; Jennifer Moore; Matthew Day; Bill M Smith; John C. Jacobs
Subject: 2S MBO's
Attachments: FEN-2301_PPLS Pain Physiology Assessment and Management Module_NOV 2011 _FINAL.pdf

Hello Team,

By now, all of you have received a notification from Teva LMS in regards to an assignment focused on Oncology. That assignment is part of your second semester MBO's and while the assessment is located on the LMS, the learning module can be found in **Smartlink under Sales Training and Development, FENTORA, Pain Learning System Training Modules, FEN-2301 PPLS: Pain Physiology, Assessment and Management Module. All of the questions are derived from Lesson 3, Cancer Pain, pages 28-42.** I've also attached the module for your convenience.

While the remaining components of the 2S MBO are in the final stages of being approved, please feel free to go ahead and complete the Oncology learning module and assessment.

Please feel free to direct any questions to your RM.

Thanks,

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Pain Products Learning System

PAIN PHYSIOLOGY, ASSESSMENT, AND MANAGEMENT

FEN-2301 November 2011

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FEN-2301 November 2011

Contents

LESSON 1. The Nervous System and Pain

Ralph Mortimer, a 56-year-old mail carrier and ex-Marine, has always prided himself on his high threshold for pain. Despite war and sports injuries, appendicitis, dog bites, and a tooth extraction, he has never taken anything stronger than aspirin or acetaminophen. Ralph considers pain management an exercise in mind over matter.

Learning Objective

After completing this lesson, you will be able to:

- Describe the anatomy and physiology of the nervous system as it relates to pain transduction, transmission, perception, and modulation

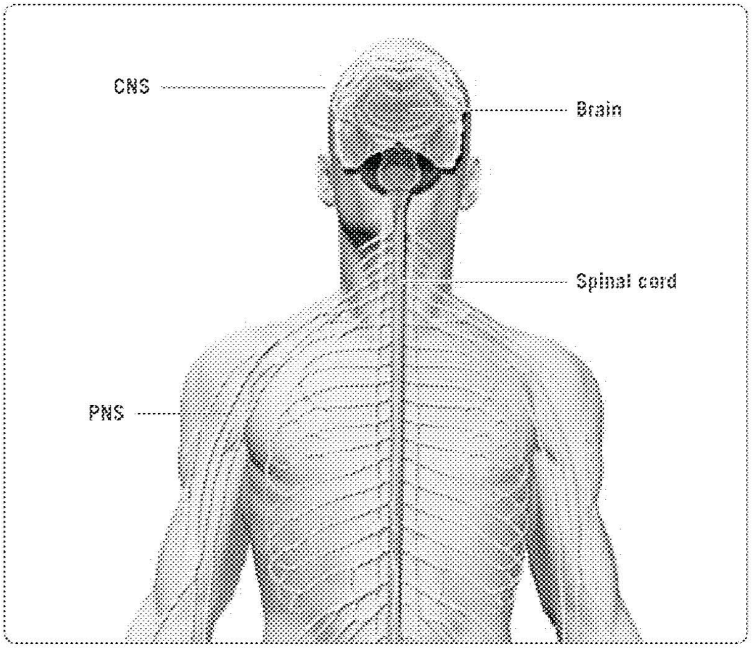
Overview of the Nervous System

neuron
the structural and functional unit of the nervous system, consisting of a cell body and its processes, an axon, and one or more dendrites

ganglia
plural for a mass of nervous tissue (ganglion) made up principally of neuron cell bodies that lies outside of the brain or spinal cord

The nervous system has two anatomically distinct components: the central nervous system (CNS), consisting of the brain and spinal cord, and the peripheral nervous system (PNS), composed of peripheral nerves and specialized clusters of **neurons** called **ganglia** (Figure 1). The nervous system contains hundreds of billions of neurons, each of which receives and gives rise to tens of thousands of connections.

Figure 1. The Nervous System



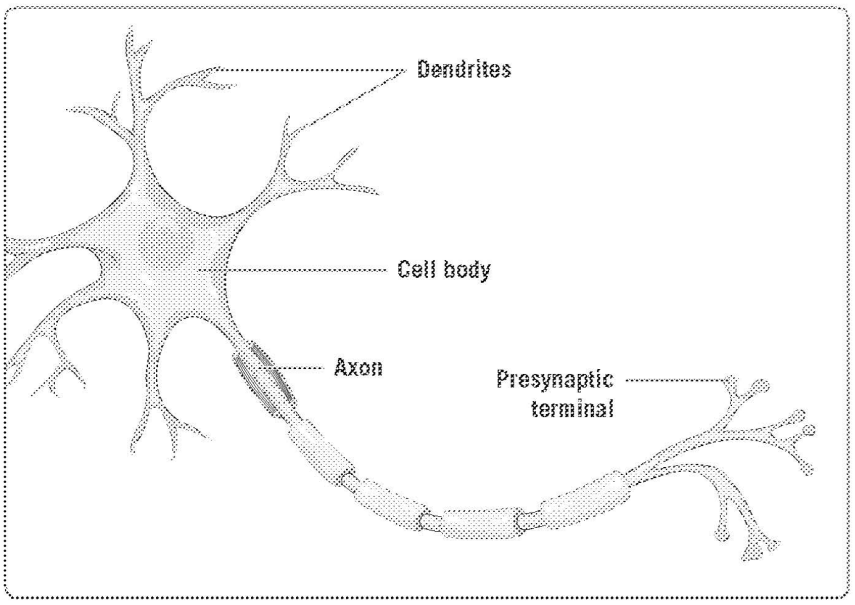
The Neuron

Nerves are made up of a series of neurons. Nerves that transmit impulses more rapidly are found in pathways that require a fast flow of sensory and motor information, such as those that control some postural reflexes. **Axons** that do not require higher speeds typically serve internal organs (such as glands, blood vessels, and organs in the gut).

Neurons are the main units of the nervous system. They typically have four main regions: cell body, dendrites, axon, and **presynaptic** (axon) **terminals** (Figure 2). Each of these regions has a specialized function.

- Cell body: the metabolic center of the neuron. It usually gives rise to two types of processes: several short dendrites and one long, tubular axon
- Dendrites: branch out from the cell body and are the main pathways for receiving electrical signals from other neurons
- Axon: extends away from the cell body and is the main unit for carrying electrical signals over distances from 0.1 mm to 3 m to other neurons. The axon is insulated and protected with **myelin**. Myelin increases the transmission speed of nerve impulses. Near its end, the axon divides into fine branches that form communication sites with other neurons. Where two neurons communicate is known as the **synapse**. The synapse will be explained in further detail later in this module
- Presynaptic terminals: the swollen ends of an axon's branches that contain secretory granules capable of releasing **neurotransmitters** into the synaptic space

Figure 2. Anatomy of a Neuron



axon
a segment of a neuron that conducts nerve impulses away from the cell body

presynaptic terminal
the terminal at the axonic end of the neuron that relays impulses via neurotransmitters to an adjacent neuron

myelin
the phospholipid-protein of the cell membranes of the CNS and PNS that forms a sheath, acting as an electrical insulator and increasing the velocity of impulse transmission in the neurons

synapse
the space between two neurons where the axon of one neuron comes into close proximity to the cell body or dendrites of another neuron and where neurotransmitters are released; synapses are susceptible to the effects of therapeutic drugs and toxic substances

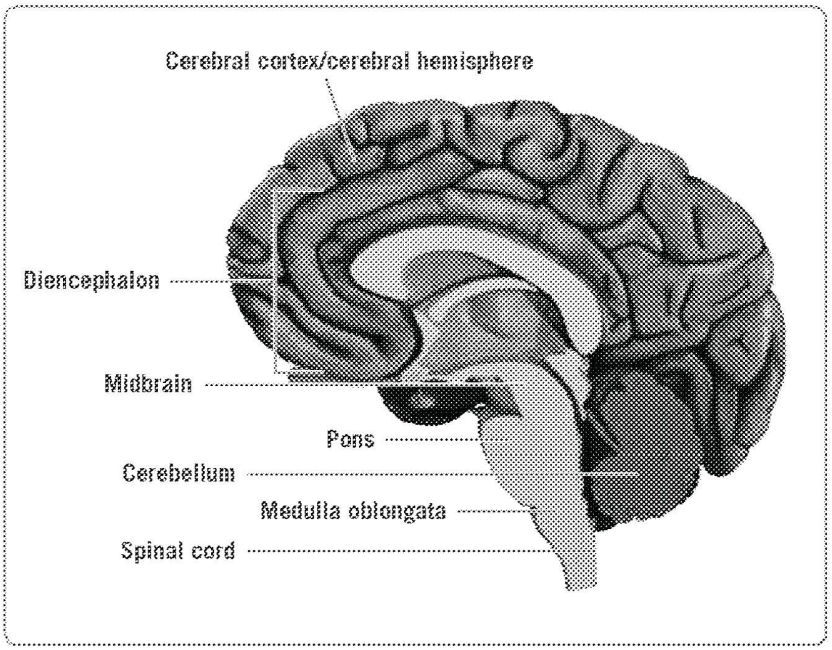
neurotransmitter
a chemical that is released when the axon of a presynaptic neuron is excited; neurotransmitters act to inhibit or excite a target cell

The Central Nervous System

The CNS receives information from sensory receptors located throughout the body. It then processes this information and sends signals that control bodily functions. Anatomically, the CNS includes the spinal cord and six areas of the brain: the medulla oblongata, pons, cerebellum, midbrain, diencephalon, and cerebral cortex (cerebral hemispheres) (Figure 3). Each area of the brain is responsible for specialized functions. The **thalamus**, which lies within the diencephalon, processes incoming pain signals, and the reaction to pain is governed by the cerebral cortex.

thalamus
the largest subdivision of the diencephalon of the brain that receives all sensory stimuli except olfactory. In the thalamus, sensory stimuli are associated, integrated, and then relayed to specific areas of the cortex. Primitive uncritical sensations of pain, crude touch, and temperature are recognized in the thalamus.

Figure 3. Cross Section of the Brain and Spinal Cord



The Peripheral Nervous System

The PNS relays information to the CNS and executes motor commands generated in the brain and spinal cord. It is divided into the autonomic (or involuntary) and somatic divisions (Figure 4). The autonomic division mediates sensation and motor control of the **viscera**, smooth muscles, and **exocrine** glands.

viscera
internal organs that are enclosed within a cavity, especially the abdominal organs

exocrine
referring to the external secretion of a gland, or to glands whose secretion reaches epithelial tissue either directly or through a duct

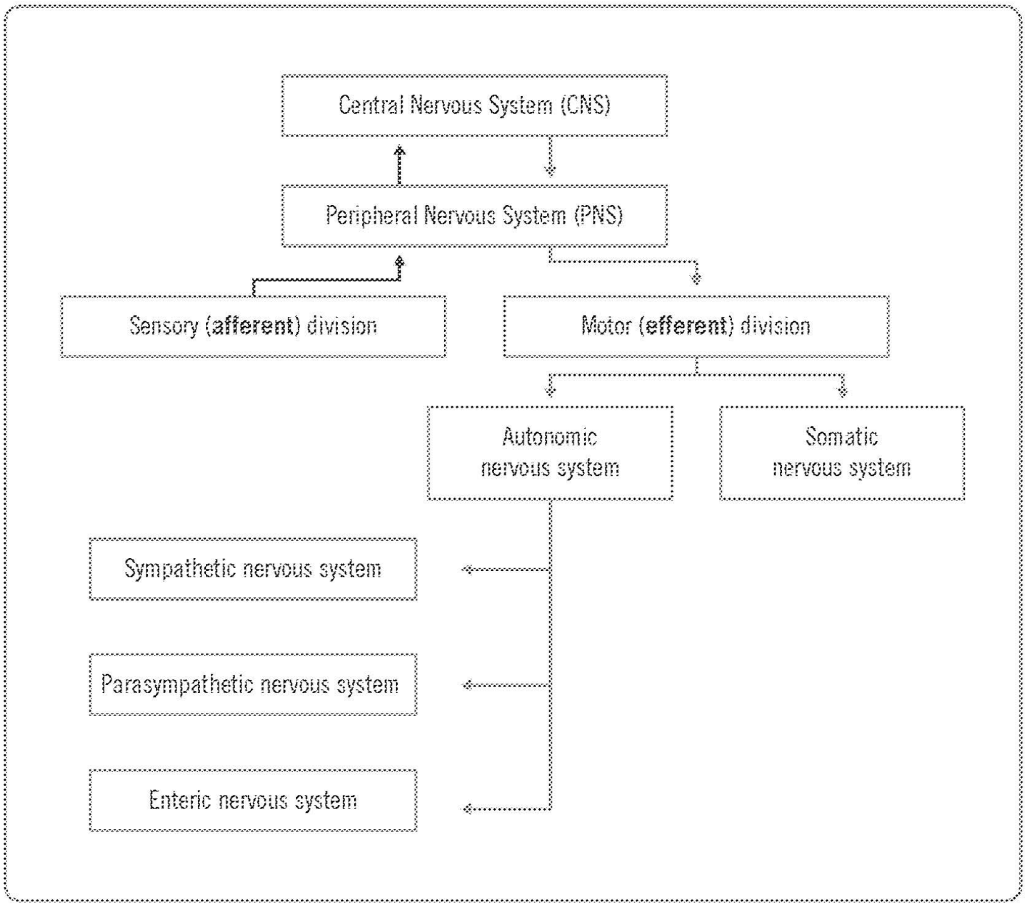
The autonomic division consists of the sympathetic, parasympathetic, and enteric systems.

- Sympathetic nervous system: increases heart rate, respiration rate, etc, in times of stress and manages the “fight or flight” reaction
- Parasympathetic nervous system: manages “rest and digest” by maintaining basal heart rate, respiration, and metabolism under normal circumstances

- Enteric nervous system: has minimal connections to the rest of the nervous system, unlike the sympathetic and parasympathetic systems. The neurons of the enteric system are located in the gastrointestinal tract and mediate digestive reflexes

The somatic division includes sensory neurons that innervate the skin, muscles, and joints. Receptors provide sensory information to the CNS about muscle and limb position, and touch and pressure at the body surface.

Figure 4. Taxonomy of the Nervous System



afferent

in neurology, the type of nerve that transports impulses toward the CNS

efferent

in neurology, the type of nerve that conducts impulses from the CNS to the periphery

Neurotransmitters and the Role of Opioid Receptors in Pain Pathways

Impulses are transmitted from one neuron to another neuron or target cell in a process called neurotransmission. Neurons do not actually touch the other neurons or target cells. Neurotransmission occurs at a synapse, which comprises the presynaptic terminal, **synaptic cleft**, and **postsynaptic terminal**.

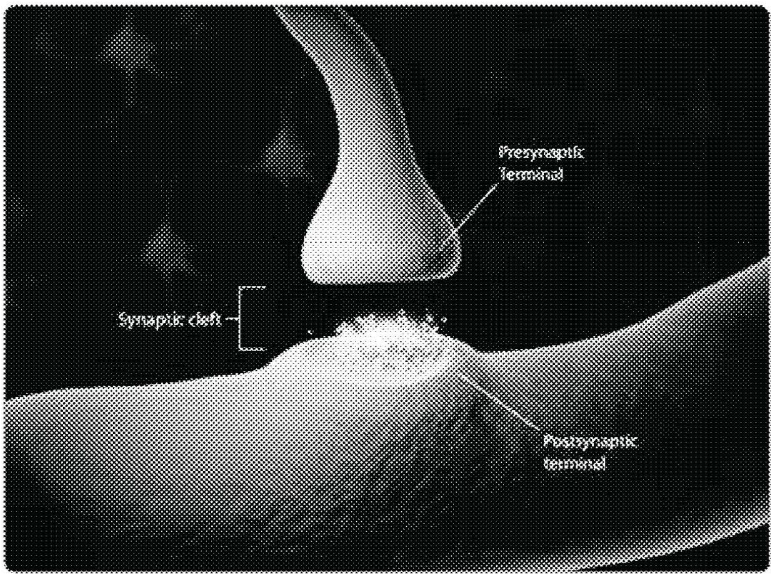
synaptic cleft
the synapse of a neuromuscular junction

postsynaptic terminal
the end of the neuron, either a dendrite or part of the cell body that receives impulses via neurotransmitters from an adjacent neuron

The neuron transmitting the signal is called the presynaptic cell. The cell receiving the signal is called the postsynaptic cell. The presynaptic cell releases neurotransmitters from the presynaptic terminals into the synaptic cleft, which is the space between the two cells.

Communication between the two cells consists of the electrical signal from the presynaptic cell triggering the release of a neurotransmitter into the synaptic cleft. The neurotransmitter then binds to the receptor on the postsynaptic cell, either exciting or inhibiting a specific action mediated by the target cell (Figure 5).

Figure 5. Neurotransmission



norepinephrine
a neurotransmitter released by most sympathetic postganglionic neurons and by some neurons of the brain

serotonin
a chemical found in platelets, the GI mucosa, mast cells, carcinoid tumors, and the CNS that acts as a neurotransmitter to produce vasoconstriction

gamma-aminobutyric acid (GABA)
the principal inhibitory neurotransmitter in the brain

endorphin
a polypeptide produced in the brain that binds to opioid receptors and produces analgesia, increasing an individual's threshold for pain

Neurotransmitters

A neurotransmitter is a substance released at a synapse by one neuron that binds to and affects a receptor in the postsynaptic cell to produce a specific action.

A number of distinct neurotransmitters have been identified, including **norepinephrine**, **serotonin**, **gamma-aminobutyric acid (GABA)**, and **endorphins**. Each neurotransmitter is associated with specific physiologic functions; however, it is the receptor—not the neurotransmitter itself—that determines whether a response is excitatory or inhibitory. Table 1 summarizes the characteristics of some of the key neurotransmitters that play a role in the transmission of pain. Understanding the functions of these neurotransmitters is integral to appreciating the mechanism of action of the various classes of analgesic agents.

Table 1. Selected Neurotransmitters in Pain Processes

Neurotransmitter	Functional Class	Sites Where Secreted	Comments
Norepinephrine	Excitatory or inhibitory, depending on receptor type bound	CNS: brain stem, **limbic system**, some areas of cerebral cortex PNS: main neurotransmitter of ganglion neurons in the CNS	A "feel good" neurotransmitter; release enhanced by amphetamines; removal from synapse blocked by **tricyclic antidepressants (TCAs)** and cocaine
Serotonin	Mainly inhibitory	CNS: brain stem, hypothalamus, limbic system, cerebellum, pineal gland, spinal cord	May play a role in sleep, appetite, nausea, migraine, and mood regulation. Drugs that block its uptake (eg, Prozac®, Cymbalta®) relieve anxiety and depression.
Adenosine triphosphate (ATP)	Excitatory or inhibitory, depending on receptor type bound	CNS: **basal nuclei** PNS: dorsal root ganglion neurons	ATP released by sensory neurons or by injured cells provokes pain sensation
GABA	Generally inhibitory	CNS: cerebral cortex, hypothalamus, cerebellum, spinal cord, others	Principal inhibitory neurotransmitter in the brain; important in presynaptic inhibition at axoaxonic synapses. Inhibitory effects augmented by alcohol, benzodiazepines, and barbiturates. Substances that block its synthesis, release, or action induce convulsions.
Enkorphins (eg, enkephalin)	Generally inhibitory	CNS: widely distributed in brain, hypothalamus, limbic system, pituitary, spinal cord	Natural **opiates**; inhibit pain by inhibiting **substance P**; effects mimicked by morphine, heroin, and methadone

limbic system

a group of brain structures that is activated by motivated behavior and arousal, influencing the endocrine glands and autonomic nervous system

tricyclic antidepressant (TCA)

a class of antidepressant whose chemical structure has three fused rings; blocks the reuptake of norepinephrine and serotonin at nerve endings

basal nuclei

also known as basal ganglia—a group of nuclei that lie deep in the cerebral hemispheres that contribute to some of the subconscious aspects of voluntary movement but do not initiate it

opiate

a drug containing or derived from opium

substance P

a peptide involved in the body's response to noxious stimuli, depression, and anxiety, as well as eliciting local tissue reactions that resemble inflammation

Table 1. Selected Neurotransmitters in Pain Processes (cont'd)

Neurotransmitter	Functional Class	Sites Where Secreted	Comments
Tachykinins: substance P, neurokinin A	Excitatory	CNS: basal nuclei, midbrain, hypothalamus, cerebral cortex PNS: certain sensory neurons of dorsal root ganglia (pain afferents)	Substance P mediates pain transmission in the PNS; involved in respiratory and cardiovascular controls in the CNS

Role of Opioid Receptors in Pain Pathways

endogenous opioids
a group of more than 15 substances found in the brain, certain endocrine glands, and the GI tract that have morphine-like activity

There are numerous sites within the CNS that can be activated by naturally occurring brain substances (collectively known as endorphins, or **endogenous opioids**) to produce analgesia. Profound pain and fear are the most powerful activators of this endogenous analgesic system, but electrical stimulation of certain areas of the brain can also produce analgesia. This led to the discovery of specific opiate receptors in the CNS and at several loci in the brain stem. Researchers have identified three separate opioid receptors—μ (mu), λ (lambda), and κ (kappa)—that are expressed in distinct but overlapping distribution.

Exogenous opiates (opioid drugs) bind with high affinity to μ-opioid receptors within specialized neurons of the ascending and descending pain pathways; binding to the λ- and κ-opioid receptors is more variable. There are two types of μ-opioid receptors, μ_1 and μ_2; the degree of binding by opiates to these receptors determines the analgesic properties and side effect profile of various opioid drugs.

- Binding to the μ_1 receptor occurs at peripheral, spinal, and supraspinal sites to:
  - Inhibit the transmission of nociceptive signals from the periphery to the spinal cord
  - Activate descending inhibitory pathways, modulating transmission in the spinal cord
  - Alter limbic system activity, thereby modulating the perception of pain
- Binding to the μ_2 receptor within certain body systems (eg, gastrointestinal and respiratory tracts) is primarily responsible for the key side effects of opioid analgesics (eg, respiratory depression, gastrointestinal effects, and sedation)

Summary

- The nervous system has two anatomically distinct components: the CNS, consisting of the brain and spinal cord, and the PNS, composed of peripheral nerves and specialized clusters of neurons called ganglia. The nervous system contains hundreds of billions of neurons, each of which receives and gives rise to tens of thousands of connections.
- Neurons are the main units of the nervous system. They typically have four main regions: cell body, dendrites, axon, and presynaptic terminals. Nerves are made up of a series of neurons.
- The CNS, which includes the spinal cord and six areas of the brain (the medulla oblongata, pons, cerebellum, midbrain, diencephalon, and cerebral cortex) receives information from sensory receptors located throughout the body. It then processes this information and sends signals that control bodily functions. Each area of the brain is responsible for specialized functions. The thalamus, which lies within the diencephalon, processes incoming pain signals, and the reaction to pain is governed by the cerebral cortex.
- The PNS relays information to the CNS and executes motor commands generated in the brain and spinal cord. It is divided into the autonomic (or involuntary) and somatic divisions. The autonomic division mediates sensation and motor control of the viscera, smooth muscles, and exocrine glands and consists of the sympathetic, parasympathetic, and enteric systems.
- The somatic division includes sensory neurons that innervate the skin, muscles, and joints. Receptors provide sensory information to the CNS about muscle and limb position, and touch and pressure at the body surface.
- Impulses are transmitted via neurotransmitters from the presynaptic neuron to a postsynaptic neuron or target cell in a process called neurotransmission. A number of neurotransmitters have been identified, including norepinephrine, serotonin, GABA, and endorphins. Each neurotransmitter is associated with specific physiologic functions; however, it is the receptor—not the neurotransmitter itself—that determines whether a response is excitatory or inhibitory.
- There are numerous sites within the CNS that can be activated by endogenous opioids (endorphins) to produce analgesia. Researchers have identified three separate opioid receptors—μ (mu), λ (lambda), and κ (kappa). Exogenous opiates (opioid drugs) bind with high affinity to μ-opioid receptors within specialized neurons of the ascending and descending pain pathways. There are two types of μ-opioid receptors, μ_1 and μ_2. Binding to the μ_1 receptor is linked to analgesia at spinal and supraspinal sites, whereas binding to the μ_2 receptor within body systems is primarily responsible for the key side effects of opioid analgesics.

Self-Check Questions

1. Complete the following sentence by filling in the blanks.

The four main regions of a neuron are the _____, _____, _____, and presynaptic terminals.

2. Which area of the brain processes incoming pain signals?

A. Pons
B. Cerebellum
C. Cerebral cortex
D. Diencephalon

3. The _____ division of the _____ nervous system includes sensory neurons that innervate the skin, muscles, and joints.

A. Sympathetic; autonomic
B. Somatic; peripheral
C. Parasympathetic; somatic
D. Sensory; central

4. Indicate the functional class of the following neurotransmitters by placing an X in the appropriate column. (HINT: Two of the neurotransmitters can be either, depending on the receptor type.)

	Excitatory	Inhibitory
Norepinephrine		
Serotonin		
ATP		
GABA		
Enkephalin		
Substance P		

5. The key side effects of opioid analgesics are thought to be due to binding to which receptor?

A. Kappa
B. Lamba
C. Mu_1
D. Mu_2

LESSON 2. What Is Pain?

Ralph worked as a mail carrier with a walking route. Often, he experienced a dull ache in his knee by lunchtime, for which he took acetaminophen. The pain wasn't bad but seemed to be coming on earlier each day. His knee didn't appear swollen, even at the end of the day, but the ache persisted through the evening and even kept him awake some nights. He switched from acetaminophen to ibuprofen, and 2 months later, he was taking two tablets every 4 to 6 hours around the clock. He decided it was time to get the knee checked out by his physician.

Learning Objectives

After completing this lesson, you will be able to:

- Differentiate chronic pain from acute pain
- Distinguish between nociceptive, neuropathic, and mixed pain, including associated processes and pain signaling
- Explain the impact of chronic pain, including impaired functional capacity and the physiological, psychological, and economic consequences of chronic pain

Definition of Pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." It is important to appreciate that pain can occur without tissue damage; the IASP asserts that a patient has the right to receive treatment for any type of pain.

One of the most significant barriers to the optimal treatment of pain is its subjective nature: individuals perceive and tolerate pain differently. Therefore, the patient's self-report is the single most reliable indicator of pain, and clinicians need to respect patients' perceptions of pain. These perceptions are the result of a complex experience that includes not only the physical processes involved but also the context in which the pain occurs, previous experience with pain, the degree of fear and anxiety associated with the underlying cause of the pain or anticipated disability, and other psychosocial factors.

The Somatosensory System and Pain

In order to appreciate the complex processes involved in the perception of pain, it is important to understand the **somatosensory** system and the different types of receptors that encode pain signals. The major groups of somatosensory receptors are mechanoreceptors, which distinguish touch and **proprioception**; thermoreceptors, which sense temperature; and **nociceptors**, which perceive pain or **noxious** stimuli.

somatosensory
pertaining to sensory activity that arises from sites other than the special sense organs (eyes, ears, nose) and conveys information about the body and its immediate surroundings

proprioception
the awareness of posture, movement, and changes in equilibrium and the knowledge of position, weight, and resistance of objects in relation to the body

nociceptor
a free nerve ending that acts as a receptor for painful stimuli

noxious
harmful; not wholesome

- Mechanoreceptors, found in hairy and nonhairy skin and in muscle, exhibit different types of adaptation, from slowly adapting receptors that respond to the intensity and duration of the stimulus, to very rapidly adapting receptors, which are capable of sensing changes in the stimulus and characteristics such as tapping or vibration.
- Thermoreceptors are slowly adapting receptors that detect cold and warmth; there are actually two classes (cold and warm) that function below and above 36°C (96°F), respectively. Warm receptors become inactive at temperatures above 45°C (113°F), when polymodal nociceptors capable of responding to a potentially damaging stimulus take over.
- Nociceptors are responsible for detecting and responding to noxious stimuli, ie, stimuli that are capable of producing tissue damage. Nociceptors may be either thermal/mechanical or polymodal; the latter respond to high-intensity mechanical or chemical stimuli as well as to hot-cold stimuli. Skin that is damaged produces an inflammatory response by releasing chemicals such as **bradykinin**, **prostaglandins**, substance P, K^+, and H^+. Mast cells near the injured site release **histamine**, which directly activates nociceptors, and the nociceptors themselves release substances that sensitize them to stimuli that were not previously noxious or painful. The nociceptors subsequently have a heightened sense of perception to stimuli (a lower threshold of pain activation), an experience known as **hyperalgesia**. In some cases, pain is perceived in response to a stimulus that does not normally provoke pain, such as brushing the skin; this phenomenon is termed allodynia.

bradykinin
a peptide that, when coupled to appropriate receptors, causes a broad spectrum of activity, including relaxation of venular smooth muscle and hypotension, stimulation of sensory neurons, release of cytokines

prostaglandins
a group of biologically active unsaturated fatty acids produced via the cyclooxygenase (COX) pathway and mediate inflammation; formation is blocked by NSAIDs

histamine
a substance released from mast cells during allergic reactions that causes vasodilation, increased secretion of stomach acid, constriction of smooth muscle, tissue swelling, and itching

hyperalgesia
increased pain sensitivity

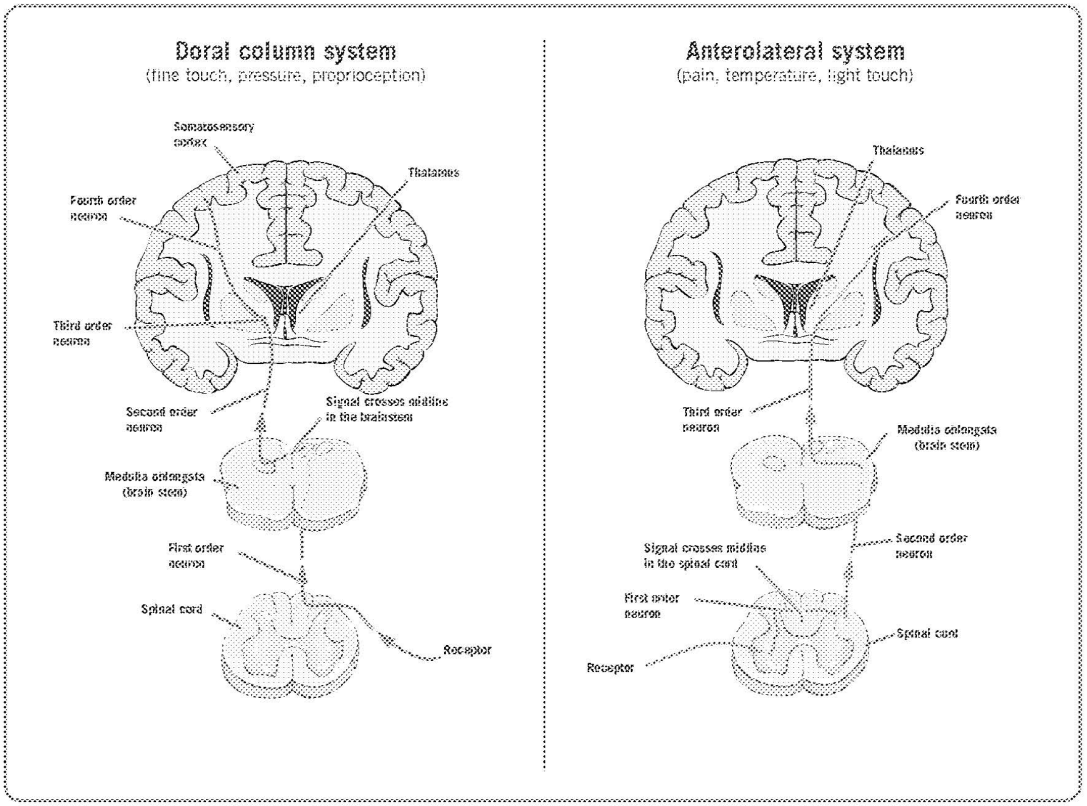
Somatosensory pathways

The somatosensory system transmits information to the CNS via one of two pathways: the dorsal column system and the anterolateral system.

- The dorsal column system processes sensations such as fine touch, pressure, two-point discrimination, vibration, and proprioception and consists mainly of larger myelinated nerve fibers with relatively fast conduction velocities.
- The anterolateral system processes the sensations of pain, temperature, and light touch. It consists of smaller and slower unmyelinated nerve fibers.

Recall that sensations are transmitted from presynaptic to postsynaptic neurons via neurotransmitters. Signals travel from the site of origin in the periphery to the spinal cord, brain stem, and the thalamus, finally reaching the cerebral cortex where the signal is processed in the appropriate sensory area. Information received on one side of the body is transmitted to the opposite (contralateral) side of the cerebral cortex. As shown in Figure 6, signals relayed by the dorsal column system cross the midline in the brain stem, whereas those transmitted via the anterolateral system cross the midline in the spinal cord.

Figure 6. Somatosensory pathways



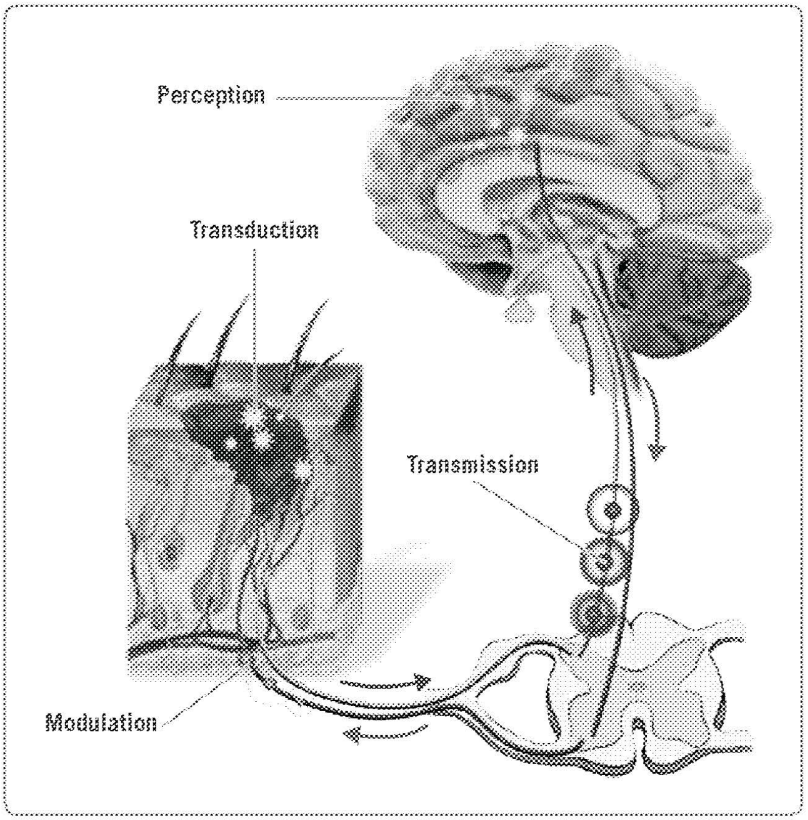
KEY CONCEPT

Nociceptors are peripheral nerve endings that act as sensory receptors. They are preferentially sensitive to noxious stimuli or to stimuli that would become noxious if prolonged. Nociceptors are capable of encoding the relevant properties of stimuli (eg, sharpness, heat intensity in the painful range, location).

An important concept in the understanding of pain is nociception, or the process by which information about tissue damage is conveyed to the CNS. Nociception comprises four processes (Figure 7).

- Transduction
- Transmission
- Perception
- Modulation

Figure 7. Nociception



Understanding how each of these processes contributes to the sensation of pain is foundational to appreciating the roles of various analgesics and other interventions in relieving pain. An explanation of each step of nociception, the important structures and mediators involved in each process, and the clinical implications for analgesia are presented in Table 2.

Table 2. The Process of Nociception

Process	Definition	Important Structures and Mediators	Clinical Implications
Transduction	Conversion of energy from a noxious thermal, mechanical, or chemical stimulus into electrical energy in the form of nerve impulses by nociceptors	• Afferent nerve fibers • Prostaglandins • Substance P • Bradykinin • Histamine • Serotonin • **Cytokines**	• **Nonsteroidal anti-inflammatory drugs (NSAIDs)** decrease synthesis of prostaglandins • Antiepileptic drugs and local anesthetics block or modulate **ion channels**, inhibiting the generation of nerve impulses
Transmission	Transmission of neural signals from the site of transduction in the periphery to the spinal cord and then from the spinal cord to the brain	• Axon • **Dorsal horn (DH)** • Excitatory amino acids (glutamate, aspartate) • **Neuropeptides** • Synapses	Opioid analgesics bind to opioid receptors on primary afferent and DH neurons, mimicking the inhibitory effects of endogenous opioids, and to opioid receptors in the brain to activate descending pathways, inhibiting DH nociceptive transmission
Perception	The awareness of signals arriving in higher structures of the CNS as pain • A complex network of brain structures, known as the pain matrix, processes and integrates sensory, executive, attentional, emotional, and motivational components of pain. Not well understood but likely responsible for the unique perception of pain between individuals.	• **Reticular (activating) system** • **Somatosensory cortex** • Limbic system	The same pathways that process nociceptive pain also process other input from the periphery, and the brain can process only a limited number of signals. Nonpharmacologic techniques such as distraction, relaxation, and imagery may competitively limit the number of pain signals that reach the cortex for processing

nonsteroidal anti-inflammatory drug (NSAID)

a drug with analgesic, anti-inflammatory, and antipyretic activity that is used to treat acute and chronic pain and to prevent the complications of sepsis

cytokines

numerous distinct proteins produced primarily by white blood cells that provide signals regulating cell growth and function during inflammatory states, each secreted by a specific cell in response to a specific stimulus

ion channel

proteins that span the lipid bilayer of the cell membrane, regulating the movement of charged particles (ions) into and out of cells

dorsal horn

the posterior (back) portion of the gray matter of the spinal cord

neuropeptides

an endogenous peptide that influences neural activity or functioning (eg, endorphin)

reticular (activating) system

the alerting system of the brain extending from the central core of the brain to all parts of the cerebral cortex

somatosensory cortex

either of two regions in the brain that receive and process somatosensory stimuli

Table 2. The Process of Nociception (cont'd.)

Process	Definition	Important Structures and Mediators	Clinical Implications
Modulation	Descending inhibitory and facilitory input from the brain that influences nociceptive transmission at the level of the spinal cord	Endogenous opioids Serotonin Norepinephrine GABA	Some antidepressants interfere with the reuptake of serotonin and norepinephrine at synapses to increase their relative concentration in the interstitial synaptic space, enhancing the activity of endogenous pain-modulating pathways

NSAID = nonsteroidal anti-inflammatory drug

Types of Pain

etiology
the cause of disease and the study of the cause of disease

There are many different classification systems for pain. Using one of the simplest systems, pain can be classified according to its duration (temporal characteristics), **etiology**, or physiology. In this section, we will explore each of these categories in detail, as classifying pain is imperative to developing an appropriate pain management treatment plan.

- Temporal characteristics
  - Acute pain
  - Chronic pain
    - Persistent pain
    - Intermittent pain
    - Breakthrough pain
- Etiology of pain
    - Cancer pain
- Physiology of pain
  - Nociceptive pain
    - Somatic pain
    - Visceral pain
  - **Neuropathic pain**

neuropathic (pain)
originating in the peripheral nerves or CNS rather than arising from damaged organs or tissues

Temporal Characteristics of Pain

Acute Pain

Acute or normal pain has a sudden onset and commonly declines over a short period of time. Acute pain typically is associated with an identifiable, localized injury or trauma to the body and generally resolves when the injury is healed. The function of normal pain is to influence our actions or behaviors to protect ourselves from injury. Acute pain episodes can interfere with day-to-day activities, such as getting dressed, eating, and traveling.

Acute pain can also be a recurrent problem, where the same underlying cause results in pain of an episodic nature interspersed with pain-free periods. Examples of acute, recurrent pain include migraine, dysmenorrhea, and sickle cell disease. Please note that some experts, such as those at the Institute of Medicine, believe that these types of intermittent pains are a subset of the acute pain category. Other experts consider these types of intermittent pains such as migraine or sickle cell disease as a subset of chronic pain given that the duration is often chronic. Some physicians, as we will discuss later, define breakthrough pain in different ways. Some clinicians believe that breakthrough pain is a type of acute pain. This is probably not ideal given that rapid-onset opioids are all contraindicated in acute pain. It is better to think of breakthrough pain as a type or component of chronic pain as we will discuss in a later section.

Chronic Pain

Chronic pain is pain that extends beyond the period of healing and is variously defined as 3 to 6 months. Chronic pain has a pathology that is inadequate in explaining the presence and/or extent of the pain. From a functional viewpoint, chronic pain is a long-term pathologic experience that outlasts its role as a protective measure and invades almost all aspects of the patient's life (eg, functional capacity, emotional state, and social/family interactions).

Chronic pain may be experienced continuously or intermittently over the course of the condition. Chronic pain also can manifest as a combination of continuous and intermittent pain. Currently, the mechanisms that lead to chronic pain syndromes are not completely understood, but **central sensitization** may play a key role in perpetuating pain signals beyond the temporal and spatial stimulus that originally provoked the pain.

central sensitization
a state in which the response to normal neuronal inputs is greatly enhanced due to increases in excitability and a reduction in inhibitory transmission, occurring with repeated peripheral noxious stimulation

Breakthrough Pain

Breakthrough pain is a type of pain that often occurs in chronic disease states. Breakthrough pain is a transitory flare of moderate to severe pain that occurs in patients with otherwise stable, controlled persistent pain. By stable persistent pain, we mean that the patient's persistent pain is controlled to a level of moderate or less with around-the-clock (ATC) opioid therapy (persistent pain level ≤ a 6 on a scale of 1 to 10). Patients who have severe or excruciating persistent pain have uncontrolled persistent pain and usually need to have further adjustments of their ATC opioid therapy.

Generally, breakthrough pain can be categorized into one of three types:

- Incident pain: pain that occurs in relationship to some activity or physical function, such as coughing, standing, changing position, or having a bowel movement
- End-of-dose pain: pain that routinely increases as the duration of scheduled analgesic medication is reaching its limit
- Spontaneous pain: pain that arises for nonspecific reasons. Spontaneous pain is always unpredictable

As mentioned before, physicians define breakthrough pain in different ways, and some clinicians believe that breakthrough pain is a type of acute pain.

Etiology of Pain

benign
not recurrent or progressive; not malignant

The classification regarding etiology of pain in past years was nonmalignant/**benign** versus malignant pain. Many pain specialists disagreed with this classification, rationalizing that all pain is malignant and should be addressed appropriately. The current classification generally is thought of as cancer and noncancer. Even this classification is not agreed upon by many pain specialists because they believe that a distinction between cancer and noncancer pain is not clinically relevant. Both cancer and noncancer pain generally have the same underlying pathophysiologic mechanisms. It could be argued that the underlying pathophysiology is the most important factor in deciding on a treatment strategy.

Cancer Pain

Pain that is associated with cancer may be caused by progression of the disease itself (a tumor invading or compressing tissue, nerves, or blood vessels) or may be due to painful diagnostic procedures and treatments (biopsies, surgery, bone marrow transplant, and toxic damage to tissue by chemotherapy or radiation treatment). Regardless of whether the pain arises from disease progression or treatment, it may be either acute or chronic and may be viewed in that context. Cancer pain will be examined in detail in Lesson 3.

Physiology of Pain

Pain can be classified according to its presumed underlying pathophysiology as either nociceptive or neuropathic, although both pain states can exist at the same time as mixed pain. Often, inadequately treated nociceptive pain results in neuronal remodeling, resulting in neuropathic pain syndromes. Following treatment for cancer, patients who undergo mastectomy or **thoracotomy** often develop neuropathic pain in the **axillary** region or along any of the **intercostal** nerves adjacent to the thoractomy scar, respectively.

thoracotomy
a surgical incision of the chest wall

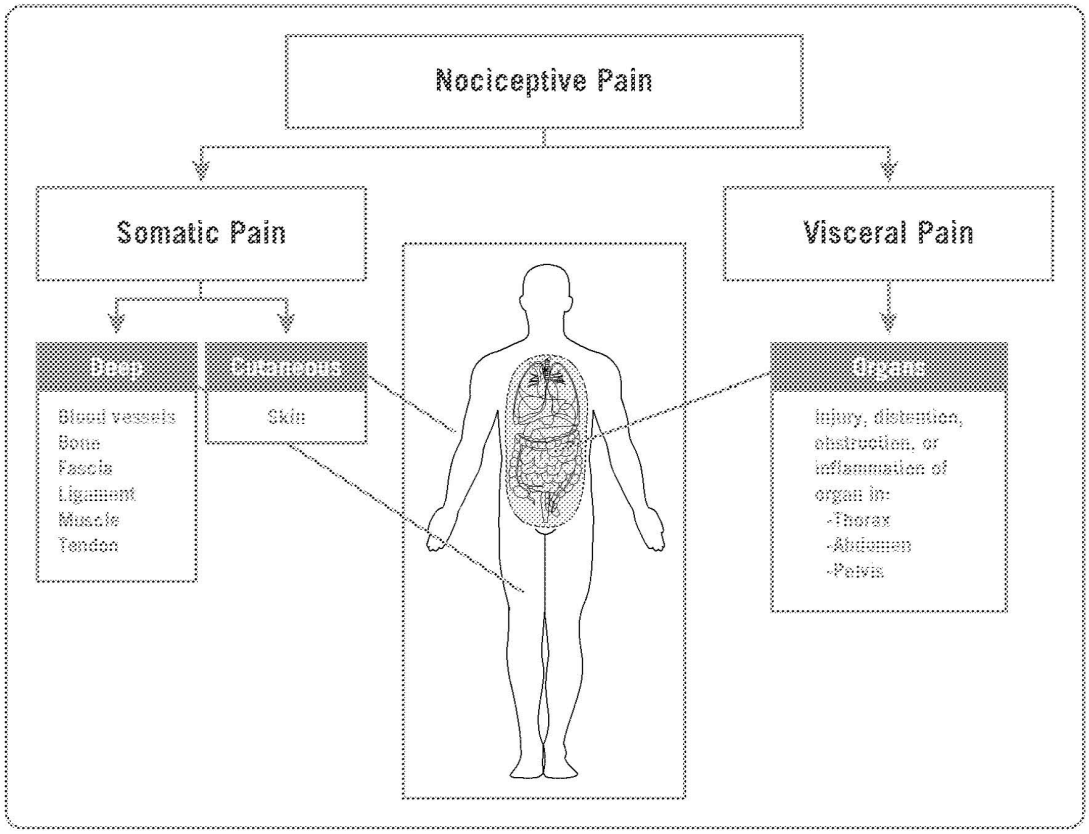
axillary
pertaining to the armpit

intercostal
between the ribs

Nociceptive Pain

Nociceptive pain is caused by the activation of nociceptors in response to injury, disease, inflammation, or some other noxious stimulus, and may be either somatic or visceral in origin (Figure 8). Generally, there is a close association between the intensity of the stimulus and the way the pain is perceived. Nociceptive pain serves to notify the CNS of real or potential tissue damage and serves a purpose: avoidance of further injury to tissue. Somatic pain emerges from tissues such as muscles, joints, bone, and skin, whereas visceral pain arises from internal organs including the heart, lungs, gastrointestinal tract, pancreas, liver, kidneys, and bladder. Visceral pain is more likely to arise from a disease process than from an external injury.

Figure 8. Nociceptive Pain



Neuropathic Pain

In contrast to nociceptive pain, which is associated with a properly functioning nervous system, neuropathic pain is caused by abnormal signal processing in the CNS or PNS, reflecting some type of injury or impairment to the nervous system itself. Neuropathic pain is often disproportionate to the stimulus or occurs when no identifiable stimulus exists. Pathophysiologic changes in nerve tissue, independent of the inciting event, result in continuous or episodic discharge of neurotransmitters and the subsequent perception of pain. Some examples of conditions associated with neuropathic pain include postherpetic neuralgia, which arises following a herpes zoster infection; diabetic, alcoholic, or postchemotherapy neuropathy (caused by agents that are toxic to the nervous system); carpal tunnel syndrome (nerve entrapment), phantom limb pain, and paraneoplastic neurological syndromes associated with certain cancers. Neuropathic pain is often described as burning, tingling, prickling, a sensation of cold, or like electric shocks.

Table 3. Comparison of Characteristics of Somatic, Visceral, and Neuropathic Pain

Characteristic	Somatic Pain	Visceral Pain	Neuropathic Pain
Origin	Stimulation of nociceptors	Stimulation of nociceptors	Nerve damage
Nerve function	Normal	Normal	Abnormal
Location of injury	Tissue (skin, muscle, tendon, bone, etc)	Abdominal, thoracic, pelvic viscera	Nerves
Descriptions	Dull, sharp, aching, gnawing	Dull, aching, colicky, referred to cutaneous sites	Burning, shooting, tingling
Abnormal sensations	None	None	Common
Response to analgesia	Tends to respond	Tends to respond	Variable response
Examples	Injury, postoperative pain, bone cancer pain	Pancreatic cancer pain, liver/lung cancer pain	Postherpetic neuralgia, phantom limb pain, tumor invasion of nerves

Nature and Character of Pain

Different types of pain do not feel the same. A headache does not feel the same as stubbing your toe or slicing your hand. In fact, the nature and character of pain may differ in several ways. The nature and character of pain includes its location and distribution, duration and periodicity, quality, and intensity. Clinicians must determine these characteristics when performing a pain assessment, as the nature and character of pain help to guide selection of appropriate treatment. Lesson 4 will provide a more comprehensive tutorial on the evaluation of pain.

The Impact of Chronic Pain

Chronic pain can impact the patient in a number of ways due to neuropsychiatric adverse effects, decreased physical functioning, and economic loss.

- Neuropsychiatric adverse effects due to inadequately controlled chronic pain include anxiety, fear, anger, depressed mood, impaired cognitive function, and sleep disturbances. These symptoms not only interfere with the patient's quality of life, but they can also impair his or her participation in the treatment of the underlying disease.
- Some of the additional physiological consequences of unrelieved pain include weight loss, fever, increased respiratory and heart rates, increased blood pressure, cardiovascular disease, deep vein thrombosis, pneumonia, delayed gastric emptying, constipation, immobility, weakness, infection, and decreased urine output.
- Chronic pain not only affects the physical and psychological health of patients; it directly hits their pocketbooks as well. This not only affects the patient but also his or her employer. In fact, the indirect costs associated with chronic pain, such as lost productivity, are significantly greater than direct medical and pharmacy costs.

A cross-sectional survey using data from the American Productivity Audit, a random telephone survey of 28,902 working adults conducted between August 1, 2001 and July 30, 2002, indicated that 13% of the total workforce experienced a loss in productive time during a 2-week period due to pain. Although headache was the most commonly reported condition resulting in lost productivity (5.4%), back pain, arthritis, and musculoskeletal pain were reported by 3.2%, 2.0%, and 2.0% of respondents, respectively. Common pain conditions resulted in lost productive times of 3.5 to 5.5 hours per week, costing an estimated $61.2 billion per year.

Chronic pain also takes a substantial toll on quality of life and productivity. The Pain in the Workplace study conducted in 2006 indicated that persistent chronic pain had increased dramatically in full-time US workers over the previous 10-year period. Responses to this survey indicated a 27% increase in the number of employees who called in sick 5 or more days during the previous 12 months due to pain. Furthermore, 89% of full-time workers living with chronic pain said they typically go to work when they have pain rather than stay home, and almost half acknowledged that their pain often or sometimes affected their ability to do their job. In another survey of 303 chronic pain sufferers taking opioids, 50% reported they had lost a job due to pain, 70% said they had trouble concentrating, 77% reported feeling depressed, and 86% said they had trouble sleeping due to their pain. These statistics reflect some of the indirect costs of uncontrolled chronic pain.

FAST FACT

Chronic pain affects more than 15% of the US population, is a leading cause of disability in middle-aged Americans, and increases in prevalence among older patients. The total annual cost of chronic pain to society in the United States is estimated at $100 billion.

Summary

- The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."
- Because individuals perceive and tolerate pain differently, the patient's self-report of pain is the single most reliable indicator of pain.
- Nociception is the process by which information about tissue damage is conveyed to the central nervous system. Nociception and pain occurs in four steps: transduction, transmission, perception, and modulation.
- The somatosensory system transmits information to the CNS via one of two pathways: the dorsal column system and the anterolateral system.
- Pain can be classified according to its duration (acute or chronic), etiology (noncancer or cancer), or physiology (nociceptive, neuropathic, or mixed).
- Chronic pain can impact the patient in a number of ways due to neuropsychiatric adverse effects, decreased physical functioning, and economic loss.

Self-Check Questions

1. Complete the following sentence by filling in the blank.

Pain can be described as an unpleasant sensory and emotional experience associated with _____, or described in terms of such damage.

2. Nociception includes four processes. Which process can be defined as "descending inhibitory and facilitory input from the brain that influences nociceptive transmission at the level of the spinal cord'?

A. Transduction

B. Transmission

C. Perception

D. Modulation

3. Select the statement that does not correctly describe acute or chronic pain.

A. Acute pain has a sudden onset and commonly declines over a short period of time

B. Acute pain typically is associated with an identifiable, localized injury or trauma to the body

C. The function of chronic pain is to influence our actions or behaviors to protect ourselves from injury

D. Chronic pain is a long-term pathologic experience that outlasts its role as a protective measure

4. Which of the following words or phrases best completes the following sentence?

_____ pain emerges from tissues such as muscles, joints, bone, and skin and can be categorized as _____.

A. Somatic; neuropathic

B. Somatic; nociceptive

C. Visceral; neuropathic

D. Visceral; nociceptive

5. Categorize the potential consequences of chronic pain by placing the appropriate letter before each of the following items.

Neuropsychiatric = N, Decreased physical functioning = P, Economic loss = E, Other = O

___ Ability to perform chores at home

___ Anxiety

___ Deep vein thrombosis

___ Depressed mood

___ Impaired cognitive function

___ Inability to complete full day's work

___ Increased blood pressure

___ Pharmacy and medical costs

___ Poor concentration

___ Sleep disturbances

___ Socialization

___ Weight loss

LESSON 3. Cancer Pain

Ralph saw his family doctor, who told him he was probably just getting arthritis in his knee after so many years of walking his mail route. Dr Layfield ordered X-rays, started Ralph on a prescription-strength NSAID, and filled out the paperwork to enable Ralph to switch to lighter duty at the post office. When the radiology report came back, Dr Layfield called him at work. The X-ray was suspicious, revealing some type of mass inside his knee joint. She wanted him to see an oncologist as soon as possible.

Learning Objectives

After completing this lesson, you will be able to:

- Identify the sources of cancer pain
- Define breakthrough cancer pain and identify its patterns and characteristics

Definition and Brief Overview of Cancer

Cancer is a term used to describe any of more than 100 types of disease in which abnormal cells divide without control and are able to invade and destroy other tissues. These abnormal cells can spread to other parts of the body through the blood and **lymph** systems.

Most cancers are named for the organ or type of cell in which they originate. For example, cancer that begins in the breast is called breast cancer; cancer that begins in **basal cells** of the skin is called basal cell carcinoma. The main categories of cancer are shown in Table 4. In the United States, the five most prevalent sites of cancer are prostate, breast, lung and bronchus, colon and rectum, and the urinary bladder.

lymph, lymphatic

an alkaline, clear, colorless tissue fluid that contains albumin, globulins, salts, urea, neutral fats, and glucose

basal cell

a type of cell found in the deepest layers of the epidermis

Table 4. Main Categories of Cancer

Category	Site of Origin
Carcinoma	Skin or in tissues that line or cover internal organs Adenocarcinomas begin in cells that make and release mucus and other body fluids
Sarcoma	Bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue
Leukemia	Blood-forming tissue such as bone marrow; causes large numbers of abnormal blood cells to be produced that are subsequently released into the general circulation
Lymphoma and **myeloma**	Immune system
CNS	Brain and spinal cord

myeloma
a tumor that originates in the portion of the bone marrow responsible for forming red blood cells

malignant
growing worse; resisting treatment, said of cancerous growths; harmful

lymphatic system
includes all of the lymph vessels that collect and return tissue fluid to the blood, including the lymph nodes and nodules, the spleen, and the thymus

metastasis
change in location of a disease or its manifestations from one part of the body to another due to the movement of body cells, especially cancer cells, from one body part to another

in situ
in the normal place; localized, not disturbing or invading surrounding tissue

Cancer Staging

In addition to categorizing a cancer by site, clinicians will also refer to it by stage. Staging is based on knowledge of the way cancer progresses (Table 5). Because cancer cells grow and divide without control or order and do not die when they should, they often form a mass of tissue called a **malignant** tumor. As the malignant tumor grows, it can invade nearby tissues and organs.* Cancer cells can also break away from the tumor and enter the bloodstream or the **lymphatic system**, spreading from the primary site to lymph nodes or other organs, where they may form new tumors. The spread of cancer in this way is called **metastasis**.

*Not all tumors are cancerous; tumors can be benign or malignant. Benign tumors aren't cancerous. They can often be removed and, in most cases, they do not come back. Cells in benign tumors do not spread to other parts of the body.

Table 5. Cancer Stages

Stage	Definition
Stage 0	Carcinoma **in situ**
Stage I, Stage II, and Stage III	Higher numbers indicate more extensive disease: Larger tumor size and/or spread of the cancer beyond the organ in which it first developed to nearby lymph nodes and/or organs adjacent to the location of the primary tumor
Stage IV	The cancer has spread to another organ(s)

Cancer is the second leading cause of death in the United States. The National Cancer Institute (NCI) estimated that there would be 1,529,560 new cases of cancer in 2010 (excluding nonmelanoma skin cancers) and 569,490 deaths. More than 4 million Americans have been diagnosed with cancer within the past 5 years, and it is estimated that over 11 million cases have been diagnosed in the past 33 years.

Most Common Types and Sources of Cancer Pain

Pain that occurs in cancer patients is generally the result of one or more of three causes.

- Direct tumor involvement (invasion of nerves, bone, and hollow organs)
- Cancer-directed therapy (surgery, chemotherapy, radiation therapy)
- Causes unrelated to the cancer or its treatment (diabetic peripheral neuropathy, migraine)

Table 6. Most Common Types of Cancer Pain

Cancer type	Pain Source	Pain Manifestation*
Skin (nonmelanoma)	Tissue damage	Localized, sharp, prickling, or burning
	Cancer treatment	Pain manifestation depends on type of treatment
Lung (including bronchus)	Skeletal metastasis	Localized pain
	Pancoast tumor (superior pulmonary sulcus tumor)	Pain in shoulder and arm Severe, unrelenting; worsening by arm movement
	Chest wall disease (especially thoracic tumor location)	Localized with cutaneous hyperalgesia (sharp, prickling, or burning)
	Cancer treatment	Pain manifestation depends on type of treatment
Prostate	Bone metastasis	Continuous, dull, aching
Breast	Bone metastasis	Continuous, dull, aching
	Cancer treatment	**Paresthesia**, **dysesthesia**, **allodynia**, hyperalgesia (related to surgery)
Colon/rectal	Pressure on bones/nerves/ organs near colon	Dull, achy, gnawing, diffuse, crampy
	Cancer treatment	Pain manifestation depends on type of treatment

*Pain manifestation will vary depending on the individual, source of pain, and, in the case of cancer treatment, type and extent of treatment.

paresthesia

an abnormal or unpleasant sensation that results from injury to one or more nerves, often described by patients as numbness or as a prickly, stinging, or burning feeling

dysesthesia

an unpleasant abnormal sensation, whether spontaneous or evoked

allodynia

pain in response to a non-nociceptive stimulus

More often, complex patterns of pain due to combinations of these categories are present, rendering diagnosis and control of pain in cancer patients a challenge. In a study of 2266 cancer patients referred to a pain center (all of whom had pain), 30% of the patients presented with one, 39% with two, and 31% with three or more distinct pain syndromes (Figure 9). Eighty-five percent of these patients reported pain caused by the cancer, while antineoplastic treatment was the primary cause of pain in 17%. The majority of this pain was nociceptive, arising from bone (35%), soft tissue (45%), or visceral structures (33%), whereas 34% of the pain complaints were categorized as neuropathic in nature.

Table 7. Sources of Pain in Cancer Patients

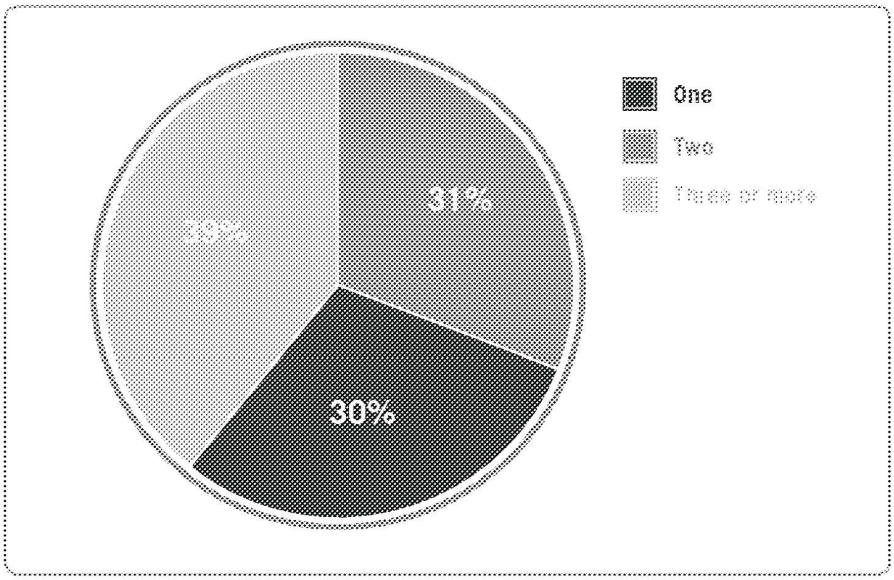
Cause of Pain	Type of Pain
Pain directly due to cancer	• Pain due to local invasion of tissues • Obstruction syndromes • Nerve compression/infiltration • Ulceration • Bone metastases
Pain indirectly related to cancer or disability	• Bed sores • Muscle spasms • Constipation • Lymphedema • Postherpetic neuralgia • Pulmonary embolism • Infections
Pain due to cancer treatment	• Postoperative pain • Stump pain, phantom limb pain • Constipation (opioid-induced) • Postradiation inflammation/fibrosis • Mucositis, stomatitis • Vinca alkaloid neurotoxicity • Bone necrosis
Pain due to other conditions	• Arthritis • Headache • Coexisting heart disease • Coexisting diabetes mellitus • (Many other coexisting conditions)

KEY CONCEPT

Pain that occurs in cancer patients is generally the result of one or more of three causes:

- Direct tumor involvement
- Cancer-directed therapy
- Causes unrelated to the cancer or its treatment

Figure 9. Percentage of Cancer Patients Referred to a Pain Center With One or More Pain Syndromes



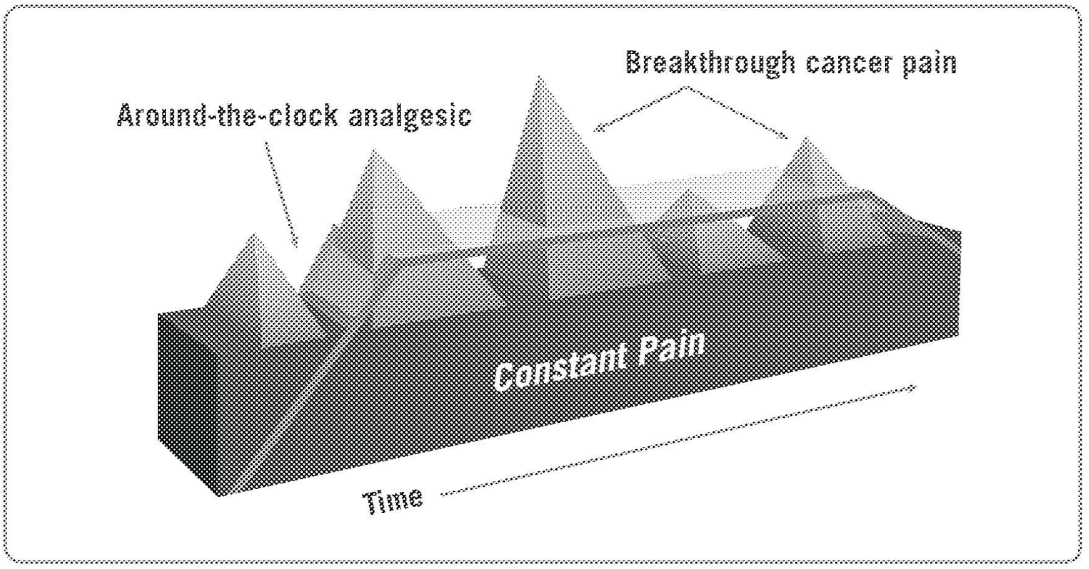
Severe pain is most often reported by patients with prostate cancer (41%), followed by esophageal (38%), gynecologic (33%), colorectal (32%), and lympho-**hematologic** cancers (32%). The site of cancer origin is a key factor in the location, but not the duration, intensity, or etiology of pain. Generally, there is an association between the number of metastases and the presence and severity of pain, although the relationship between the severity of pain and the extent of disease is not linear and is heavily influenced by psychological factors.

hematologic
pertaining to the blood and blood-forming tissues

Breakthrough Cancer Pain

Chronic pain often contains two components: persistent (baseline) pain and breakthrough pain. It is important to understand that not all chronic pain patients have persistent pain; rather, they may have intermittent pain. The overall depiction of the mountain graph (Figure 10) is very useful to educate on breakthrough pain. You may get questions from physicians on whether all the increases above the persistent pain require treatment. It is also important to note that in many patients, the persistent pain generally will not be constant but, rather, will vary over time during the day. Breakthrough cancer pain is a type of intermittent pain. Breakthrough cancer pain typically has a rapid onset (3–5 minutes to peak severity), short duration (about 30 minutes), and extreme intensity. The cause and site of breakthrough cancer pain are often the same as that of the baseline persistent pain. Breakthrough cancer pain is usually associated with tumor, although in one study, 14% of the cases of breakthrough cancer pain were related to therapy, and 4% were unrelated to either the cancer or its treatment.

Figure 10. Depiction of Breakthrough Cancer Pain



While an ATC analgesic can manage constant pain, flares of breakthrough cancer pain can appear despite regular analgesic dosing.

CLINICAL CONTROVERSY

There are several definitions of breakthrough cancer pain currently in use in the United States and Europe. For instance, in Europe, end-of-dose failure is not considered a subtype of breakthrough cancer pain. Some physicians define breakthrough pain as requiring that patients need to be on ATC opioid therapy, while others define breakthrough pain more broadly to include any therapy for persistent pain. Finally, a minority of physicians do not believe that breakthrough pain exists outside of cancer. It is important to realize that each of your physicians may have a different definition of breakthrough cancer pain, so you should strive to determine exactly what a physician means when he or she uses this term. The definition that we use in our promotional material is "a transitory flare of moderate to severe pain that occurs in patients with otherwise stable, controlled persistent pain. 'Stable persistent pain' means that the patient's persistent pain is controlled to a level moderate or less with around-the-clock opioid therapy (persistent pain level ≤ a 6 on a scale of 1 to 10). Patients that have severe or excruciating persistent pain have uncontrolled persistent pain and need to have further adjustments of their around-the-clock opioid therapy."

Breakthrough cancer pain episodes can be characterized as incident pain, idiopathic or spontaneous pain, and end-of-dose failure. Increasing the dose of the background pain regimen could result in increased side effects or tolerance, so breakthrough cancer pain requires individualized management. There have been no well-controlled studies comparing the risks and benefits of long-acting opioids alone to short-acting opioids and long-acting opioids as a treatment option for persistent and breakthrough cancer pain. Breakthrough cancer pain has been shown in the various cancer surveys to be quite prevalent and have a significant impact on patient function. Given that many episodes of breakthrough cancer pain reach peak intensity quickly and are unpredictable, there is a great need for agents that will work quickly to relieve the patient's pain.

In addition, breakthrough cancer pain can have a profound negative impact on patients and can increase their utilization of healthcare resources. Therefore, managing breakthrough pain, as well as baseline cancer pain, is an important aspect of the treatment plan for patients with cancer.

KEY CONCEPT

- Incident pain is directly related to an event or activity, eg, position change, bearing of weight, a bowel movement, swallowing food, coughing, often well-defined and predictable
- Idiopathic/spontaneous pain occurs without relationship to particular events or procedures; always unpredictable and fleeting and often requires **adjuvant** or rapid-acting analgesics
- End-of-dose failure emerges because of too much time between doses of pain medication; can generally be prevented by monitoring and modifying time-contingent dosing schedules to appropriate intervals

adjuvant

a word meaning to aid; may be used to describe a drug that is added to a prescription to hasten or increase the effect of a main ingredient

Breakthrough Cancer Pain as a Discrete Phenomenon

Three sentinel studies have been published that led to the recognition and characterization of breakthrough cancer pain as a separate, quantifiable, and treatable pain state. Review the summaries of these three studies to strengthen your dialog with physicians regarding the unique characteristics of breakthrough cancer pain.

Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain*. 1990;41(3):273-281.

The prevalence and characteristics of breakthrough cancer pain were not well defined prior to 1990, when Russell Portenoy and Neil Hagen published the results of a prospective survey of 90 inpatients referred for evaluation and treatment by the Pain Service at Memorial Sloan-Kettering Cancer Center during a 3-month period. Using an operational definition of breakthrough (cancer) pain developed during a previous study, patients were asked "Do you ever have flares of pain or pain attacks in between doses of the medication that is taken on a set schedule throughout the day?" Patients who answered this question affirmatively and who met predefined criteria (63 patients) were then queried about the following aspects of their breakthrough cancer pain episodes.

- Temporal characteristics (frequency, onset, duration)
- Pain severity
- Pain location
- Relationship to fixed analgesic dose
- Precipitating event (none/spontaneous, incident, nonvolitional)
- Pathophysiology (somatic, visceral, neuropathic, mixed)
- Etiology (related to neoplasm, related to treatment, or not related to either)
- Palliative factors (actions that alleviated or reduced frequency or intensity of breakthrough cancer pain)

The investigators found that the results of this survey allowed them to make certain generalizations regarding the characteristics of breakthrough pain. It is common (64%), extremely varied in characteristics, often rapid in onset, usually of brief duration, and almost always (96%) occurred in the same location as their continuous pain.

This study provided a reason to identify breakthrough cancer pain as a separate phenomenon when addressing pain in patients with cancer.

Breakthrough Pain Characteristics Portenoy 1990 n=41	
Time to peak severity, mean	<3 minutes in 43%
Intensity	Severe or excruciating
Duration, median	30 minutes (range: 1 to 240 minutes)
Number of episodes per day, median	4 (range, 1 to 3600)
Precipitated by event	55%

Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain.* 1999;81(1-2):129-134.

A second important study by Dr Portenoy and his colleagues demonstrated that not only could breakthrough pain be characterized as distinct from baseline pain, but it was associated with an independent and profound negative impact on the quality of life, function, and mood of patients with cancer. In this study, 178 eligible patients with controlled background pain were surveyed using a number of validated psychometric instruments.

The prevalence of breakthrough pain in this study was 51%. As we will discuss later, the investigators found that patients who reported having episodes of breakthrough cancer pain had statistically significant greater pain-related functional impairment, worse mood, and more anxiety than those who did not report breakthrough cancer pain. Additional analysis confirmed that breakthrough pain independently contributed to impaired functioning and psychological distress. The significant impact of breakthrough cancer pain on function and psychological well-being underscores the need for aggressive pain management strategies in this population. Next, 48% of the incidents were never predictable in duration.

Breakthrough Pain Characteristics Portenoy 1999 n=84	
Time to peak severity, mean	3 min (range: 1s to 30 min)
Intensity	Severe or excruciating
Duration, median	Not reported
Number of episodes per day, median	6 (range, 1 to 60)
Precipitated by event	62%

Zeppetella G, O'Doherty CA, Collins S. Prevalence and characteristics of breakthrough pain in cancer patients admitted to a hospice (published correction appears in *J Pain Symptom Manage.* **2001;21(3):265).** *J Pain Symptom Manage.* 2000;20(2):87-92.

The third sentinel study was conducted to determine the prevalence and characteristics of breakthrough pain in cancer patients admitted for hospice care. Two hundred forty-five patients reported 404 pains (range: 1–14 per patient daily). 89% of these patients were reported to have breakthrough pain (range: 1–5 per patient). Thirty-eight percent of the breakthrough pains were reported as severe or excruciating, approximately half occurred suddenly and many (59%) were unpredictable. Seventy-three percent of the pains lasted less than 30 minutes. Although 92% of the patients with chronic pain were prescribed some type of analgesic, 43% did not have a prescription for any type of "rescue" medication. Twenty-five percent of the patients with breakthrough pain were satisfied with their pain control regimens. The authors concluded that breakthrough pain was common among patients admitted to hospice, and that it was frequent, short lasting, and often unpredictable, making satisfactory treatment difficult to achieve. They recommended that assessment of breakthrough pain should be specifically addressed in the overall pain assessment and management plan, and that clinicians need to be better educated about the importance of accessibility to rescue medications for breakthrough pain in cancer patients.

(continued next page)

Breakthrough Pain Characteristics Zeppetella 2000 n=218	
Time to peak severity, mean	Not reported
Intensity	Severe or excruciating (38%)
Duration, median	<30 minutes
Number of episodes per day, median	4
Precipitated by event	42%

The table below provides a summary of the characteristics of breakthrough pain from the data in the above three studies. This slide has been used in promotional materials in the past.

Breakthrough Pain Characteristics	
Time to peak severity, mean	3 minutes
Intensity	Moderate to severe
Duration, median	30 minutes
Number of episodes per day, median	4–6
Precipitated by event	55%–62%

Portner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *J Pain.* 2002;3(1):38-44.

Several studies have quantified the toll of uncontrolled pain on hospital utilization. In one year at the City of Hope National Medical Center, uncontrolled pain accounted for 26% of unscheduled admissions at an average length of stay of 12 days and an estimated cost of $5 million. Another study, performed at the MD Anderson Cancer Center, found that 14% of admissions were for uncontrolled pain, resulting in an average stay of 10.5 days and a cost of approximately $4.7 million.

Breakthrough cancer pain has also been demonstrated to have a significant economic impact on the healthcare system. Portner and colleagues surveyed 1000 nonrandom cancer patients by telephone to determine their utilization of physician office and emergency department (ED) visits, as well as unplanned hospitalizations for uncontrolled pain. This analysis revealed that patients who reported experiencing breakthrough cancer pain had significantly more hospitalizations and visits to their physicians' offices, as well as greater utilization of the ED. The investigators then calculated the estimated costs of direct medical services for patients with and without breakthrough cancer pain using average cost figures for each type of service. This resulted in an estimated annual cost of $12,000 per year for each patient with breakthrough cancer pain and $2,400 annually for each patient without breakthrough cancer pain. Although other factors such as severity of underlying disease and strength of patients' social support systems could account for some of the variation, the disparity points to the need for further study and the development of cost-effectiveness models related to the treatment of breakthrough cancer pain.

Chronic Cancer Pain

Advances in the treatment of cancer have resulted in improved remission and cure rates and longer survival times for people with cancer. However, cancer survival does not come without a price to some patients. Surgery, radiation therapy, and chemotherapy can result in chronic pain syndromes due to scar tissue, **osteonecrosis**, and neural damage. For example, one study involving patients with head and neck cancer found that 65% of patients had continued pain despite the absence of tumor recurrence. Chronic pain is typically multidimensional and always leads to changes in the nervous system that may not have been present during the acute phase.

osteonecrosis
the death of a segment of bone, usually caused by insufficient blood supply to a region of the skeleton

Summary

- Cancer is a term used to describe any of a large number of diseases in which abnormal cells divide without control and are able to invade and destroy other tissues. Cancer cells can spread to other parts of the body through the blood and lymph systems.
- The main categories of cancer are carcinoma, including adenocarcinomas; sarcoma; leukemia; lymphoma and myeloma; and cancers of the CNS.
- Staging is a method of describing the progress of a particular cancer. The simplest staging system uses a rating scale from 0 to IV (zero to four), where 0 means the cancer is contained to its site of origin and IV signifies that it has spread to other nonadjacent organs.
- Cancer is the second leading cause of death in the United States and is responsible for significant morbidity.
- Pain that occurs in cancer patients is generally the result of one or more of three causes: (1) direct tumor involvement, (2) cancer-directed therapy, and (3) causes unrelated to the cancer or its treatment. Often, complex patterns of pain due to combinations of these categories are present.
- The site of cancer origin is a key factor in the location, but not the duration, intensity, or etiology of pain. Cancer pain can be persistent or intermittent.
- Breakthrough cancer pain is "a transitory flare of moderate to severe pain that occurs in patients with otherwise stable, controlled persistent pain. 'Stable persistent pain' means that the patient's persistent pain is controlled to a level moderate or less with around-the-clock opioid therapy (persistent pain level ≤ a 6 on a scale of 1 to 10). Patients who have severe or excruciating persistent pain have uncontrolled persistent pain and need to have further adjustments of their around-the-clock opioid therapy."
- The cause and site of breakthrough cancer pain are often the same as that of the baseline persistent pain and are usually associated with tumor.
- Chronic pain syndromes associated with cancer can persist in cancer survivors and may be due to changes in the nervous system secondary to surgery, chemotherapy, and/or radiation treatment.

Self-Check Questions

1. Match each category of cancer to its site of origin.

____ Skin or in tissues that line or cover internal organs

____ Bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue

____ Blood-forming tissue such as bone marrow

____ Immune system

____ Brain and spinal cord

A. Leukemia
B. CNS
C. Lymphoma and myeloma
D. Sarcoma
E. Carcinoma

2. Severe pain is most commonly reported by patients with which type of cancer?

A. Brain
B. Breast
C. Head and neck
D. Prostate

3. Complete the following sentence by filling in the blanks.

In a study of 2266 cancer patients referred to a pain center, _____% of the patients presented with three or more distinct pain syndromes; _____% of patients reported pain caused by the cancer. The majority of this pain was _____ (nociceptive or neuropathic).

4. Which of the following statements about breakthrough cancer pain is not correct?

A. Results in persistent pain in opioid-tolerant patients

B. Typically has a rapid onset, short duration, and extreme intensity

C. Can be characterized as incident pain, idiopathic/spontaneous pain, or end-of-dose failure

D. The cause and site of breakthrough cancer pain are often the same as that of the baseline persistent pain

5. Chronic cancer pain in the absence of tumor recurrence may be due to:

A. Scarring secondary to surgery

B. Chemotherapy

C. Radiation therapy

D. All of the above

LESSON 4. The Evaluation and Management of Pain

Dr Patel, the oncologist to whom Ralph was referred, performed a thorough history and physical exam, including a comprehensive pain assessment, and ordered an MRI and blood work. Ralph explained to Dr Patel that he really didn't have that much pain but couldn't walk his entire mail route without experiencing severe pain during the evening and at night. Dr Patel explained that it was important to get a baseline evaluation of the location, intensity, and type of pain, and to monitor any changes in pain on a regular basis. This would allow her to develop an appropriate pain management plan should Ralph's level of pain worsen.

The MRI revealed a synovial sarcoma of the left knee, which appeared to be localized. Dr Patel recommended a type of surgery called margin-negative resection, followed by radiation therapy. Immediately following the surgery, Ralph's pain would be managed in the hospital by patient-controlled anesthesia (PCA)—morphine given intravenously via a pump that he would control to administer analgesia within set dosage parameters.

One week post-op, Ralph required 27–35 mg morphine daily via PCA around the clock to manage his pain, a dosage that meets the recommendations for opioid tolerance for a rapid-onset opioid. Because he was to soon begin radiation treatments, Dr. Patel decided to switch him to a fentanyl transdermal patch so it would not be necessary to transport the IV equipment to the radiology suite, and ordered one DURAGESIC® 25 patch to be applied transdermally every 3 days along with pain monitoring per hospital protocol every 4 hours.

Learning Objective

After completing this lesson, you will be able to:

- Describe expert recommendations for the evaluation and management of pain, including appropriate goals for pain management

Evaluation of Pain

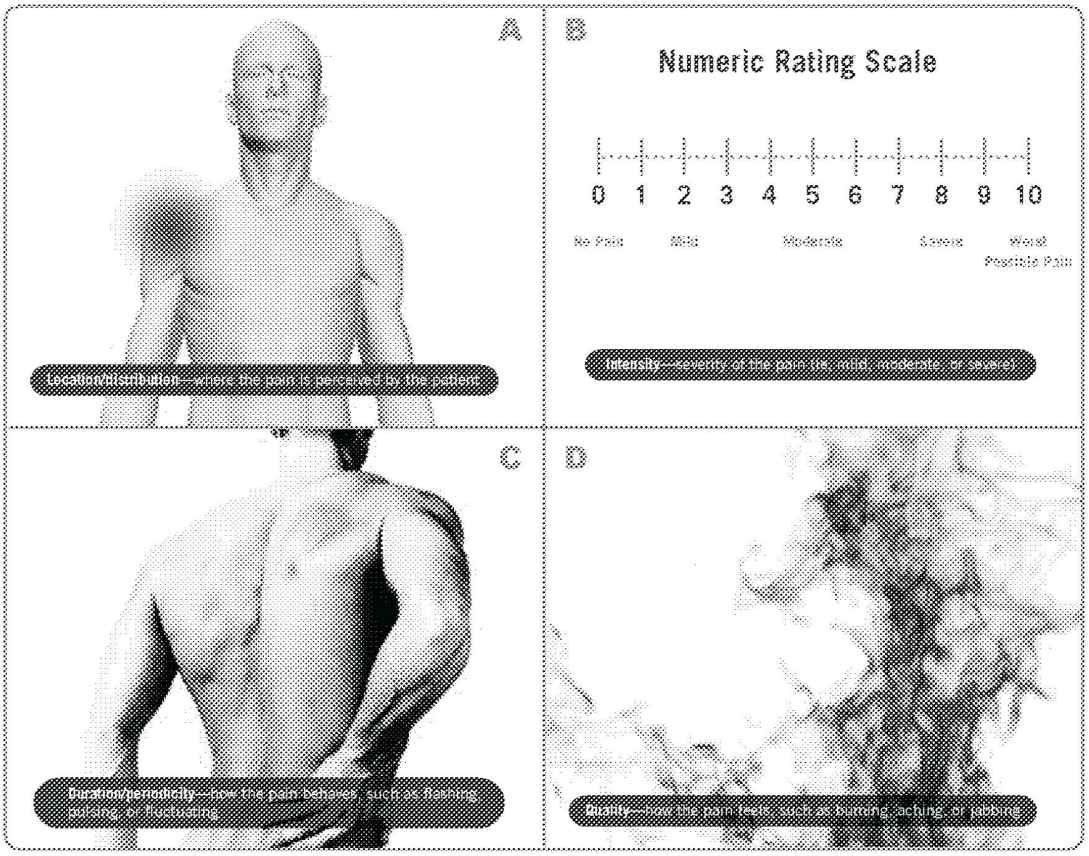
Any self-report of pain on the part of the patient deserves a comprehensive assessment. Many clinical practice guidelines for the assessment and management of pain are available, and some institutions have mandatory, structured pain assessment procedures in place. The pain assessment should include a description of the perceived elements of the pain experience, previous experiences with pain and response to treatment, a psychosocial evaluation as relates to the perception and management of pain, an assessment of potential risk factors for undertreatment, a complete nonpain medical history, a physical examination, and appropriate laboratory and imaging studies to establish a "pain diagnosis" (the etiology and pathophysiology of the pain).

Pain History and Physical Examination

A comprehensive pain assessment should include information such as:

- The location and pattern, including radiation or referral (spreading or branching out) of the pain (Figure 11A)
- The intensity of pain: current, during last 24 hours, at rest, and with movement, using a validated pain rating instrument (Figure 11B; discussed further below)
- A description of how pain interferes with the patient's activities of daily living
- Timing of pain: onset, duration, course (ie, is it persistent or intermittent?) (Figure 11C)
- The quality of the pain (Figure 11D)
- Factors that aggravate or alleviate the pain
- Current approach to pain management, both pharmacologic and nonpharmacologic, and response to this therapy
- Other factors that may have an impact on the pain management plan, such as religious and cultural beliefs, use of alternative therapies, patient and family/caregiver knowledge, and beliefs about pain and pain medications
- Patient goals and expectations for pain management

Figure 11. Multidimensional Nature and Character of Pain



Some physicians use the mnemonic "PQRST" to remember these key components of the pain history:

- **P** (precipitating factors): What causes the pain or makes the pain better or worse?
- **Q** (quality of pain): What does the pain feel like?
- **R** (region or radiation of pain): Is the pain in one place only, or does it radiate anywhere else?
- **S** (subjective description of pain): How severe is the pain on a scale of one to 10?
- **T** (temporal nature of pain): When did the pain start and how long did it last?

Pain Rating Instruments

Use of pain rating scales and other validated assessment tools provides the clinician with an objective way to evaluate a patient's perception of pain and response to treatment over time. There are a number of validated instruments, including unidimensional scales and multidimensional tools (Figure 12). Unidimensional rating scales may oversimplify assessment but are useful for assessing acute pain where the cause is clear (eg, following surgery). To assess complex or persistent pain, most experts recommend using multidimensional tools. In this section, we will examine the types, features, and benefits of commonly used assessment tools.

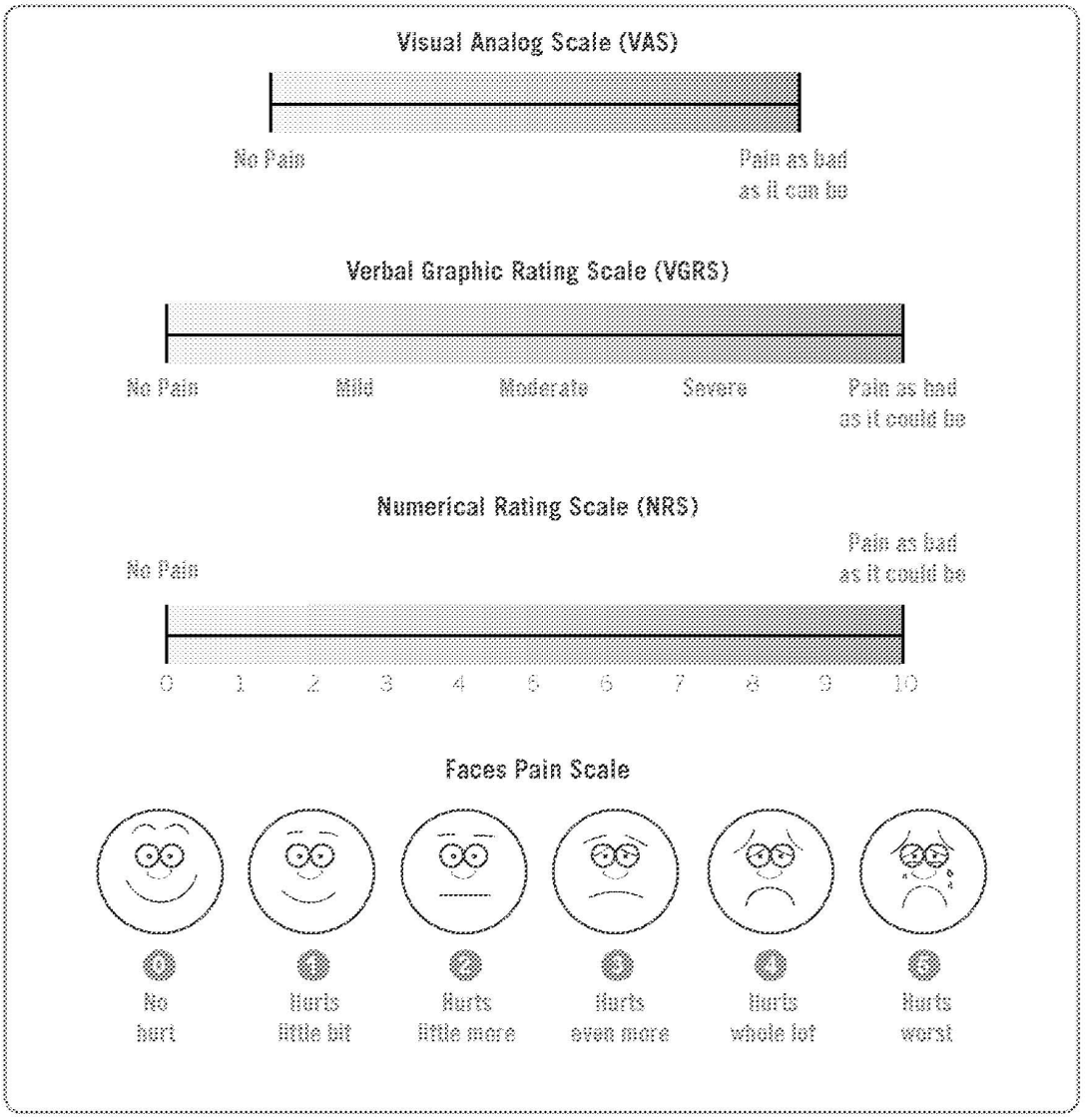
Unidimensional Scales

Numeric Rating Scale (NRS)—Patients rate their pain on a 0-to-10 or a 0-to 5-scale, with 0 representing "no pain at all" and the highest number representing "the worst imaginable pain." This type of scale can be used to measure pain at the initial encounter, following treatment, and at specified periods.

Visual Analog Scale (VAS)—The VAS consists of a line anchored at each end, one end labeled "no pain" and the other end labeled "pain as bad as it can be." The patient marks the place on the line to indicate the degree of pain intensity, which is then measured and recorded by a clinician.

Categorical Scales—These types of scales use verbal or visual descriptors of the pain (mild, discomforting, distressing, horrible, excruciating, etc). Several versions, such as the Faces Pain Scale (FPS) and the Wong-Baker Faces Rating Scale, use a series of faces with visual expressions (smiling, frowning, grimacing, etc) from which the patient chooses to indicate his or her current level of pain. These are particularly helpful for use with children or with adults who do not have localized language skills or who are cognitively impaired.

Figure 12. Pain Intensity Scales



Multidimensional Scales

***Initial Pain Assessment Tool*—**Developed for use during the initial evaluation; elicits information about the characteristics of the pain, how the patient expresses pain, and how the pain is impacting the patient's life. It includes a diagram to record location of pain complaints, a scale for rating intensity, and space to record additional information.

***Brief Pain Inventory (BPI)*—**Consists of a series of questions addressing aspects of the patient's pain experienced in the preceding 24 hours that quantify both pain intensity and associated disability. This tool is quick (5–15 minutes), easy to use, and can be self-administered.

McGill Pain Questionnaire (MPQ)—Assesses pain in three dimensions: sensory, affective, and evaluative. Patients select a word to describe their pain. Available in both long- and short-form versions, the MPQ can be combined with other tools to improve diagnostic accuracy, and is one of the most extensively tested multidimensional scales.

Goals of Pain Management

In the preface to their book *Cancer Pain: Assessment, Diagnosis, and Management*, Drs Fitzgibbon and Loeser assert "the goal in pain management must always be to improve and not impair quality of life." Since pain is a subjective phenomenon and is experienced as well as tolerated differently in individuals, pain management must always be patient-directed. Patients and clinicians need to agree on individualized goals of pain management and a system of pain assessment, defining the maximum level of pain acceptable to the patient, as well as willingness to tolerate side effects that might interfere with the patient's activities.

Overview of Pain Management

In addition to a systematic and comprehensive assessment of any complaint of pain, the American Pain Society (APS) 2005 guidelines recommend the following basic principles of pain management:

- Recognize and treat pain promptly
- Involve patients and families in the pain management plan
- Improve treatment practices, such as **multimodal** therapy
- Reassess and adjust pain management plan as needed; respond not only to pain intensity but to side effects and functional status
- Monitor processes and outcomes of pain management

multimodal
using or relying on multiple methods; multidisciplinary

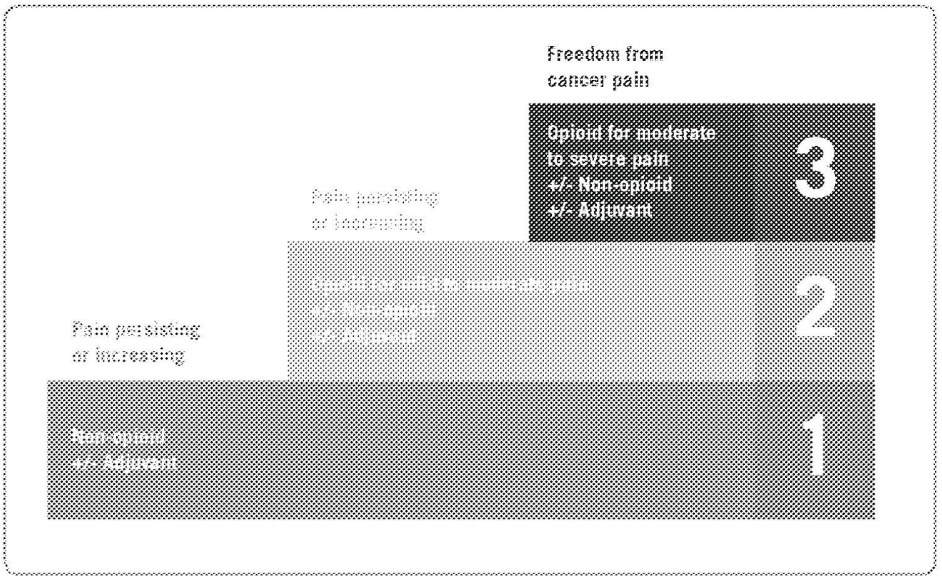
KEY CONCEPT

A multimodal approach to pain management is one that uses combinations of regional or local techniques, with nonopioid, opioid, adjuvant analgesics, and nonpharmacologic methods.

Guidelines

Several organizations have published guidelines for the pharmacologic management of pain, including acute, chronic, and cancer pain. The World Health Organization (WHO) has promoted a three-step analgesic ladder as a basic framework for the management of all types of pain. It uses an easily understood additive approach to pain management in which nonopioids (ie, acetaminophen, and aspirin and other NSAIDs) are recommended as first-line therapy (Figure 13). WHO also recommends these following simple basic principles for pain management: Whenever feasible, analgesic should be given "by mouth, by the clock, by the ladder, for the individual, and with attention to detail." Guidelines developed by the Agency for Healthcare Research Quality (AHRQ) and the APS were developed in the mid-1990s but have since been retired. Although the National Comprehensive Cancer Network (NCCN) published evidence-based guidelines in 2011 specifically for adult cancer pain, they are very complex and more academic than practical. The information in this course will be based in part on the WHO Pain Relief Ladder.

Figure 13. WHO Pain Relief Ladder



Treatment Options

Management of pain in cancer patients often requires both pharmacologic and nonpharmacologic approaches. We will focus on pharmacologic therapy, although integration of more than one approach is central to providing multimodal therapy and achieving optimal outcomes. In Module 3, Pharmacologic Treatment in the Current Marketplace, you will be reintroduced to each of these therapeutic classes in greater detail.

Pharmacologic Approaches

Nonopioid Analgesics—Acetaminophen, aspirin, other NSAIDs, and certain antidepressant (AD) and antiepileptic drugs (AED) are generally used to treat mild to moderate pain. Aspirin and other NSAIDs have anti-inflammatory properties that are particularly effective in treating nociceptive pain, especially pain involving the bone and joints, whereas ADs and AEDs have shown efficacy in the treatment of pain of neuropathic or mixed origin. ADs and AEDs have traditionally been called adjuvant analgesics because they are frequently used in combination with traditional analgesics; however, the term adjuvant probably is not ideal, given that most neuropathic pain guidelines recommend these agents alone or in combination with each other as first-line agents for neuropathic pain.

Opioid Analgesics—As illustrated by the WHO Pain Relief Ladder, moderate to severe pain that does not respond to nonopioid agents will require treatment with an opioid. Opioid analgesics are derived from the opium plant and provide powerful analgesia with no ceiling effect (ie, there is no dose beyond which additional analgesia cannot be obtained). However, opioids have adverse effects including mood changes, sedation, motor and cognitive impairment, respiratory depression, nausea and vomiting, and constipation. These adverse effects limit their tolerability for many patients. In addition, opioids carry the risk of dependence and tolerance. Because of the risk for these effects, especially respiratory depression, opioids must be started at a low dose and titrated gradually so the patient develops some level of tolerance to them.

Opioids are available in long- and short-acting (including rapid-onset) formulations and in a variety of delivery vehicles (eg, oral, intravenous, rectal, transmucosal, by injection). Rapid-onset opioids are a type of short-acting opioid. Preparations with varying durations of activity can be combined to provide intermittent or continuous analgesia as required. Weak opioids include codeine, hydrocodone, tramadol, and propoxyphene. Morphine, hydromorphone, oxycodone, and fentanyl are considered to be strong opioids and are used to treat moderate to severe pain.

"In general, studies on the use of opioids to treat pain in cancer patients indicate that public and professional expectations about relief from cancer pain should be much higher than they are at present."

— *Cancer Pain Relief: With a Guide to Opioid Availability*. (2nd edition.) World Health Organization. 1996.

Combination Analgesics—At each stage of the Pain Relief Ladder, WHO recommends the addition of other agents (eg, adjuvants to nonopioids; adjuvants and/or nonopioids to opioids) before proceeding to the next step. Combination therapy confers the benefit of analgesia via different mechanisms of action and allows the clinician to use lower doses of each agent to achieve optimal pain relief while minimizing side effects. Most opioids are available in combination with acetaminophen, aspirin, or ibuprofen. However, because the nonopioid portions of these formulations have an analgesic duration of only 4–6 hours, these combinations are only available as short-acting opioid (SAO) agents. Many of the most commonly used prescription analgesics are combination SAOs—eg, VICODIN®, PERCOCET®, PERCODAN®, and TYLENOL® with codeine.

Additional Approaches

Treatment of pain in the cancer patient should involve a multimodal approach that addresses the optimal management of pain to improve the overall quality of life for the individual with cancer pain. In the landmark publication *Cancer Pain Relief With a Guide to Opioid Availability*, WHO stresses the following approaches to pain management in addition to drug therapy:

- Modification of pathological processes: surgery; hormone, radiation, and chemotherapy
- Psychological approaches: cognitive behavioral therapies, empathy, and companionship
- Modification of daily activities: use of ambulatory devices such as a walker or wheelchair
- Immobilization: rest, braces, corsets, splints, and slings
- Interruption of pain pathways: use of local anesthetics, **neurolytics**, **ablation**, or neurosurgery

neurolytics
procedures that result in neurolysis, the loosening of adhesions surrounding a nerve or disintegration or destruction of nerve tissue

ablation
the removal of a part, pathway, or function by surgery, chemical destruction, or cauterization, or radiofrequency

Factors Affecting Patient and Clinician Choice of Therapies

There is a paucity of research regarding the factors that influence the choice of pain therapy on the part of patients as well as clinicians. Issues such as the patient's previous experience with pain medications; the desire to maintain mental clarity, especially towards the end of life; the stage of disease; and life expectancy have been cited as factors that affect patient choice. There are certainly cultural norms and attitudes towards the tolerance of pain and use of analgesics, particularly opioids, due to fear of addiction or social stigma. More important, patients' communication skills with their healthcare team have been linked to effectiveness of pain management, as has patient education about their disease and treatment options.

Clinicians' choices of therapies may be influenced by published treatment guidelines, their training and experience, and their degree of expertise in pain management. In some settings, institutional pain policies and quality improvement programs may encourage clinicians to become more attentive to pain control.

Management of Breakthrough Cancer Pain

As in the management of any pain, a thorough assessment is the first step in developing a plan to address breakthrough pain. A pain diary that documents the temporal, incident, and symptomatic characteristics of breakthrough cancer pain episodes will guide the clinician in choosing an appropriate approach. Recall from the previous lesson that incident and end-of-dose pain can be anticipated so that a preemptive strategy for limiting breakthrough cancer pain may be appropriate, such as increasing the baseline opioid dose or frequency of administration, adding an NSAID to improve basal analgesia, or augmenting therapy with an adjuvant agent for emergent neuropathic pain. Common characteristics of breakthrough cancer pain are its rapidity of onset, unpredictability, short duration, and occurrence approximately several times per day. By understanding the characteristics of an individual patient's breakthrough pain episodes, the optimal treatment strategy can be developed. In addition to analgesia, radiotherapy, radionuclides, and bisphosphonates have been shown to reduce bone pain, particularly movement-related pain.

For breakthrough cancer pain, supplemental doses of oral opioids are recommended. Until recently, short-acting, normal ("immediate") release formulations of morphine, hydromorphone, and oxycodone were used to treat breakthrough cancer pain, at a formulaic percentage of the patient's baseline dose; the same compound was used for supplementary doses as was being employed for the basal analgesia. However, when administered orally, these drugs have a relatively slow onset of analgesia (~30 minutes), so relief may not be obtained until the breakthrough cancer pain episode has ended. Oral SAOs also have a relatively long duration of action (4–6 hours), providing unnecessary analgesia.

Fentanyl has the most rapid onset of analgesia of the strong opioids and, as a lipophilic opioid, is rapidly absorbed across **mucosal membranes**. This results in a rapid onset and shorter duration of effect. For this reason, this class of agents has been designated rapid-onset opioids, or ROOs. A number of different formulations of fentanyl have been developed that take advantage of the rapidity of transmucosal delivery for the treatment of breakthrough cancer pain, including **sublingual**, **buccal**, and **intranasal** forms. Clinical trials utilizing ROOs have demonstrated reduction in pain intensity as early as 15 minutes in some patients once the minimum effective dose of the ROO has been determined during a titration phase.

There are currently five ROOs approved by the FDA for use in the United States: ACTIQ® (fentanyl citrate) oral transmucosal lozenge, [C-II], *FENTORA*® (fentanyl citrate) buccal tablet, [C-II], ABSTRAL® (fentanyl citrate) sublingual tablets [C-II], ONSOLIS® (fentanyl buccal soluble film), [C-II], and Lazanda® (fentanyl) nasal spray [C-II]. Although all are fentanyl-based and each is indicated only for the treatment of breakthrough pain in opioid-tolerant patients with cancer, they are not interchangeable. All except Lazanda are administered via the oral cavity; Lazanda is formulated as a nasal spray.

mucosal membrane
the membrane lining body passages and cavities that communicates with the air and contains mucus-secreting cells or glands that provide defense against the entry of pathogens

sublingual
beneath or concerning the area under the tongue

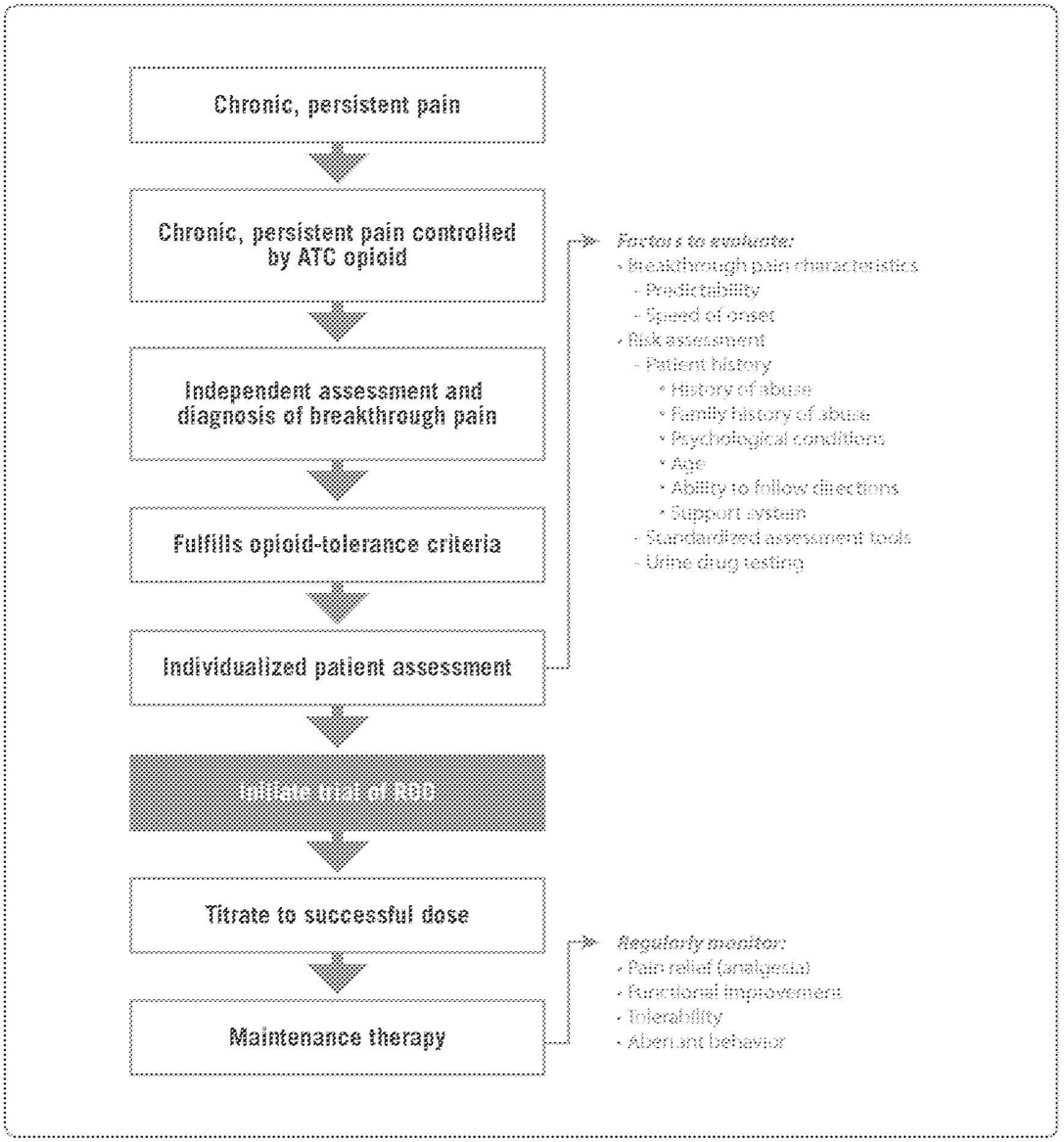
buccal
pertaining to the cheek or mouth; the inner side of the cheek in the mouth

intranasal
within the nasal cavity

Any signals of potential risk should be appropriately addressed before a ROO is prescribed. Patient characteristics that appear to be most strongly associated with risk of abuse, misuse, or other aberrant drug-related behaviors are personal or family history of alcohol or drug abuse, younger age, and presence of severe psychiatric conditions. In most cases, a ROO would not be appropriate for patients with a history of chemical coping (reliance on a drug for psychological stability), abuse, or addiction.

The decision to initiate a ROO should be based on an overall analysis of risks and benefits for each patient (Figure 14). As with any opioid, counseling about therapy with a ROO is important. The discussion with each patient should include a review of the goals, expectations, potential risks, and alternatives to a ROO. In addition, the existing opioid agreement plan may be updated to include the physician's and the patient's responsibilities and expectations with regard to a ROO. For example, patients should acknowledge that they will continue to take their ATC opioid medication(s) while taking a ROO and that they understand and will follow the dosing directions.

Figure 14. Factors to Be Evaluated When Considering and Implementing Therapy for Breakthrough Cancer Pain



It is important to remember that concerns about misuse, abuse, addiction, and diversion should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of misuse, abuse, and addiction, since the use of opioids carries the risk of addiction even when medically required and under appropriate medical care. Often, physicians are faced with the challenge of managing patients with some characteristic suggestive of increased risk (eg, family history of substance abuse), but who would likely benefit from a ROO therapy. In these cases, physicians must conduct a frank assessment of their own experience and their practice's capacity to appropriately manage this type of patient (who often require more frequent visits, urine drug testing [UDT], pill counts, etc) to determine whether they can safely prescribe a ROO. For these patients, a multidisciplinary approach to treatment implemented by a clinician with experience managing patients at increased risk for misuse, abuse, or addiction can be an option to ensure adequate pain management while minimizing risk. Alternately, these patients can be referred to a practice adequately equipped to provide care.

An understanding of the contextual meaning of opioid tolerance in the prescribing of ROOs is essential. In this context, tolerance means that patients have had the requisite exposure to ATC opioids for persistent pain such that they are at reduced risk for serious, opioid-related adverse events (eg, respiratory depression). This pragmatic determination of tolerance should not be confused with the more common understanding of tolerance, which refers to the need for increasing doses of opioids to maintain analgesia in the absence of disease progression or other external factors. More precisely, tolerance is the state of adaptation in which exposure to a drug induces changes that result in a reduction of one or more of the drug's effects over time—a definition that encompasses both analgesic tolerance as well as tolerance to side effects. Because of the potential for confusion about tolerance, healthcare providers must understand the use of the term in the context of safe prescribing of ROOs and communicate this clearly to all those involved in the care of patients for whom these breakthrough pain medications are prescribed. You will have the opportunity to explore ROOs in more detail in the Pain Products Learning System Pharmacological Treatment in the Current Marketplace module.

Factors Affecting Pain Reporting and Treatment

According to the APS, inadequate pain management, including that for cancer pain, is prevalent. They cite inadequate knowledge among healthcare professionals, patients, and the public, as well as a lack of institutional commitment, regulatory obstacles, and limitations on access and reimbursement, as issues underlying the shortcomings in effectively addressing pain.

As discussed earlier, pain is a subjective phenomenon and patients vary in their level of pain tolerance, attitudes, and beliefs towards pain and analgesia. Patients may be reluctant to report or discuss pain for a variety of reasons, such as stoicism, fear of what the pain might mean, or misconceptions and prejudices surrounding the use of analgesics. Concerns about addiction or other side effects of medications, including impairment of ability to work, may prevent a patient from seeking relief. For example, a school bus driver or airline pilot might fear losing his or her commercial license if taking certain classes of medications. Other factors can impair the patient's ability to effectively communicate the presence or degree of the pain. These include age, language,

cognitive abilities, and illness or disability (including psychiatric illnesses). There are also cultural norms and mores that influence whether or not a patient will seek relief, especially pharmacologic relief, from pain.

You will recall that clinical practice guidelines recommend that any patient self-report of pain should be addressed. Because there are many reasons that patients may be reluctant to broach the subject of pain with their healthcare providers, quality improvement guidelines recommend routine screening of all patients for pain. Use of a method of recording pain intensity in a manner that is highly visible and easily understood, such as a validated pain rating scale, is also encouraged. Even when pain is recognized, either via self-report or through clinician probing, there are a number of barriers to satisfactory pain management. A clinician may harbor attitudes, beliefs, and behaviors that result in the undertreatment of pain, may lack sufficient or current education in pain management strategies, or may have concerns about regulatory scrutiny or the side effects of strong analgesics, including the potential for drug tolerance and addiction. Finally, the most carefully developed plan for pain management can be thwarted by inadequate financial resources, complicated access to medications (such as insurance preauthorization or high co-pays), or poor patient adherence. Therefore, it is imperative that clinicians involved in pain management have a coordinated and proactive system for monitoring pain, changes in pain, and patient response to treatment.

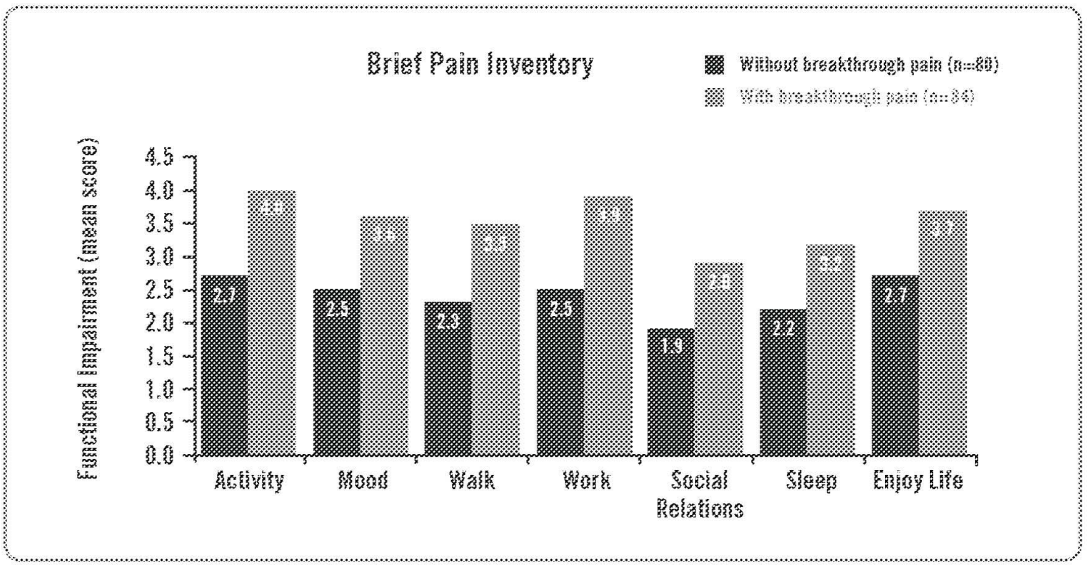
Consequences of Undertreatment

According to meta-analysis of pooled data from 52 articles published between 1966 and 2005, 64% of patients with metastatic or advanced-stage cancer reported pain, as did 59% of patients on anticancer treatment and 33% following curative treatment. One-third of these patients reported pain that was moderate to severe.

Another review performed the same year of 26 published articles revealed that, on average, 43% of patients with cancer pain were undertreated. In this analysis, patients who were rated less ill and at an early stage of disease were more likely to receive inadequate analgesia, as were patients who were less educated or belonged to a minority group. These statistics are sobering when one considers that the WHO Pain Ladder, which was developed to provide simple guidelines using basic analgesics available worldwide, has been disseminated and widely accepted since 1986. Studies conducted to validate the WHO guidelines estimate that 70% to 90% of patients with cancer pain should be able to achieve adequate pain relief if the guidelines are followed and appropriate doses of medications administered. Many of these studies were carried out prior to the wide availability of LAOs and the introduction of ROOs, medications that can now enable clinicians to better close the pain gap in cancer treatment.

Untreated pain has enormous individual and socioeconomic consequences, as you learned in Lesson 2 (Figure 15). Even when baseline chronic cancer pain is controlled, breakthrough cancer pain can negatively impact patients' quality of life and create financial hardships. Breakthrough cancer pain is common in patients with cancer: one-half to two-thirds of patients who have controlled persistent pain report regular and recurrent episodes of breakthrough cancer pain. In a 2009 survey of 545 patients with breakthrough cancer pain, 91% said they believed their quality of life would improve if they could get their breakthrough cancer pain under control, 82% said breakthrough cancer pain negatively affects their emotional health, and 87% reported that breakthrough cancer pain has affected their medical treatment in some way. Furthermore, the majority of the respondents to this survey said they were experiencing financial hardships. However, when talking about breakthrough cancer pain with their healthcare provider, only about half (53%) typically discussed available treatment options. This poor rate of targeted treatment for breakthrough cancer pain underscores the importance of educating physicians about the therapeutic options for this debilitating symptom.

Figure 15. Breakthrough Pain Can Impair Physical Functioning and Quality of Life*



*FENTORA has not been demonstrated to improve the above outcomes associated with breakthrough cancer pain.

> "Treating pain is like looking at the sun: it is blinding, so we look away and thus many times by doing 'nothing wrong' we do something wrong."
>
> —James Maxfield, *Suffering and Moral Responsibility*, Oxford University Press, 1999

Summary

- Since pain is a subjective experience and varies among individuals, any self-report of pain should be evaluated.
- A multimodal approach to pain management includes both nonpharmacologic and pharmacologic interventions and is established in concert with the patient to achieve mutually agreed-upon goals.
- There are several sets of published guidelines for the pharmacologic management of pain, including acute, chronic, and cancer pain. Most are based partly on WHO's Pain Relief Ladder, which advocates a stepwise and additive approach to pharmacologic therapy.
- Experts agree that current pain management guidelines and available therapeutic options are adequate to relieve up to 90% of cancer pain complaints.
- Although statistics regarding the undertreatment of cancer pain vary by type of study, one-third to two-thirds of patients with cancer report experiencing pain at some stage of their disease.
- The APS cites inadequate knowledge among healthcare professionals, patients, and the public, as well as a lack of institutional commitment, regulatory obstacles, and limitations on access and reimbursement as issues underlying the shortcomings in effectively addressing pain.
- A comprehensive assessment of pain includes an assessment of the current pain episode, including the nature and character of the pain; previous pain experience; other current symptoms; and current pharmacologic and nonpharmacologic pain management approaches and response including side effects. The assessment should also include an evaluation of psychosocial issues that may impact pain management, a complete medical history, physical examination, laboratory and imaging studies as appropriate, and goal setting to include the patient.
- The nature and character of pain varies widely and can be described by its location and distribution, duration and periodicity, quality, and intensity.
- Pharmacologic agents available to treat pain include nonopioids, which encompass NSAIDs and adjuvants such as antidepressants and antiepileptic agents; and opioids, which can be administered via a variety of routes and are available in long- and short-acting (including rapid-onset) formulations.
- Breakthrough pain requires careful assessment to determine whether it is incident pain or spontaneous pain.
- Five fentanyl-based rapid-acting opioids (ROOs) have been approved for use in the United States: ACTIQ, *FENTORA*, ABSTRAL, ONSOLIS, and Lazanda. All of these products are indicated only for the treatment of breakthrough pain in opioid-tolerant patients with cancer. All except Lazanda are administered via the oral cavity; Lazanda is formulated as a nasal spray.

Self-Check Questions

1. Which of the following always merits an assessment of pain?

A. Injury or trauma

B. Patient self-report of pain

C. Abnormal laboratory or imaging studies

D. Cessation of pain medications

2. Which of the following is NOT a unidimensional pain scale?

A. NRS

B. VAS

C. BPI

D. FPS

3. Complete the following sentence by filling in the blanks.

In setting goals for pain management, the patient and clinician must agree on the _____ level of pain acceptable, a system of _____, and the patient's willingness to tolerate _____.

4. According to the WHO Pain Ladder, what should be used to treat moderate to severe pain?

A. An LAO + SAO + ROO

B. An opioid ± an NSAID

C. An opioid ± ROO

D. An opioid ± a nonopioid ± an adjuvant

LESSON 5. Misuse, Abuse, Addiction, Overdose, Diversion, and Serious Complications

Ralph returned home following the surgery to remove the tumor in his knee and began a light physical therapy program 3 days a week, as well as walking around the house on crutches. As his activity level progressed, he began to experience excruciating pain during and for about an hour after physical therapy, even though he was still using the fentanyl transdermal patch every 3 days. He was giving the physical therapist a hard time, but it was important that he rehabilitate his knee. Ralph consulted with Dr. Patel, who suggested a short-acting opioid to be taken on the days he had physical therapy. He prescribed OxyIR®, 5 mg to be taken by mouth 1 hour before physical therapy. The OxyIR helped with the pain but made Ralph nauseous, and by the third week he started skipping it. His leg was getting stronger and the exercises were getting easier. When his 25-year-old son Dennis complained of ankle pain following a fall off a ladder, Ralph offered his prescription painkillers to him since he was no longer taking them. Actually, Dennis' ankle didn't hurt that badly, but he liked the way the oxycodone "took the edge off" of his stress and began taking them regularly, knowing that Ralph's doctor would refill his prescription if needed.

Learning Objectives

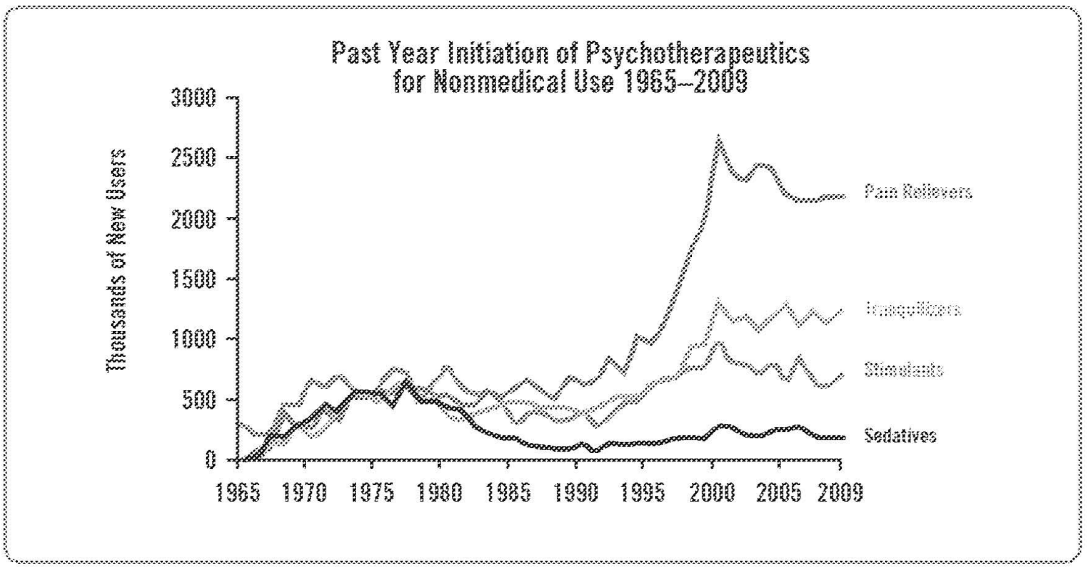
After completing this lesson, you will be able to:

- Quantify prescription drug abuse in the United States
- Differentiate between opioid tolerance, physical dependence, and addiction
- Identify factors that contribute to opiophobia
- Discuss the consequences of prescription drug diversion and misuse

Misuse and Abuse

Surveillance data indicate that prescription drug abuse increased by 42.5% between 2001 and 2005, from an average of eight million people to 11.4 million people. According to the 2009 National Survey on Drug Use and Health, there was an increase from 2002 to 2009 in the rate of nonmedical use of prescription-type drugs (from 5.5% to 6.3%), and this was primarily in the category of pain reliever misuse (Figure 16). Fifty-five percent of the survey respondents reported that they got the drug for free from a friend or relative. The National Institute on Drug Abuse (NIDA) reports that because these drugs are prescribed by physicians, they are often perceived to be safer than illicit drugs, when in fact prescription drugs can have the same addictive properties as illicit drugs.

Figure 16. Nonmedical Use of Opioids



Data from 1965–2001 include all ages; data from 2002–2009 include ages 12 and older.

dopamine
A catecholamine synthesized by the adrenal gland that affects nerves and blood vessels, among other tissues. In the brain, it works as a neurotransmitter, affecting cells that influence body movement, emotional states, and pleasure/reward.

Opioids alleviate pain by binding to mu-opioid receptors in spinal and supraspinal sites, but also activate endogenous receptors in the brain to release neurotransmitters such as **dopamine** that produce pleasurable feelings. This reward circuit, which evolved to reinforce behaviors such as eating and sexual activity to enable survival, can become overloaded when stimulated by exogenous opioids. In response to the overload, the brain adapts by producing less dopamine and reducing the number of dopamine receptors. It therefore takes more of the exogenous stimulator (in this case, opioids) to produce a pleasurable response, a phenomenon we call "tolerance." Tolerance can lead a person to take higher doses of a prescribed drug, which in turn just produces higher tolerance. Unfortunately, The National Center for Health Statistics reports that the number of fatal poisonings involving opioid analgesics more than tripled from 4000 to 13,800 from 1999 through 2006, indicating a need to carefully monitor the access and use of opioid analgesics.

Tolerance, Physical Dependence, and Addiction

Both patients and clinicians express concern about tolerance, physical dependence, and addiction to stronger analgesics, particularly opioids. In a survey of 805 chronic pain sufferers, 60% said they were very concerned about side effects when first prescribed a narcotic analgesic, 49% were concerned the medication would be addictive, 42% expressed concern that they would have to take the medication for the rest of their lives, and 38% thought they would develop tolerance. These concerns overrode their fear that taking a narcotic might somehow stigmatize them. Interestingly, these percentages increased in patients who were past users of opioids, except for the concern that they would have to take the medication indefinitely.

Opiophobia, or fear of prescribing opioids, extends to physicians as well as patients. A number of physician surveys have indicated that clinicians are reluctant to prescribe opioid analgesics in noncancer patients due to fear of iatrogenic addiction, lack of understanding of addiction, concerns about differentiating drug-seeking patients from those with legitimate pain, and regulatory scrutiny. Therefore, opiophobia leads to undertreatment of patients who are suffering from pain, but, according to the statistics, does not seem to be reducing misuse, abuse, and diversion. In fact, a recent report indicates that rehab admissions for substance abuse increased in the United States between 1999 and 2009. Twenty-one percent of the nearly 2 million admissions to treatment facilities were related to opiates, and 33% of these were due to prescription drugs.

"Patients with chronic pain need medications; the potential for abuse should not deter physicians from prescribing pharmacologic medications in adequate dosages. To help primary care providers confidently select the most appropriate medication for the situation, NIDA is working to develop screening and diagnostic tools that primary care physicians can use to assess the potential for misuse, abuse, and dependence on prescription drugs in their patients."

Nora D. Volkow, MD
Director, NIDA

You will notice that Dr Volkow has used the term dependence and addiction interchangeably. You should know that many addiction specialists and psychiatrists use the term dependence to mean addiction. Most pain specialists use the term dependence to mean physical dependence. When your customer uses the word dependence, you should try to understand if he or she means addiction or physical dependence. Physical dependence is defined below. It is helpful to understand the difference between tolerance, physical dependence, and addiction to a drug. The American Society of Addiction Medicine (ASAM) and the American Academy of Pain Medicine (AAPM) have developed definitions that they recommend be used in the context of pain management versus addiction or other psychiatric disorders.

"**Tolerance** is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time."

"**Physical dependence** is a state of adaptation that often includes a tolerance and is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist."

"**Addiction** is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving."

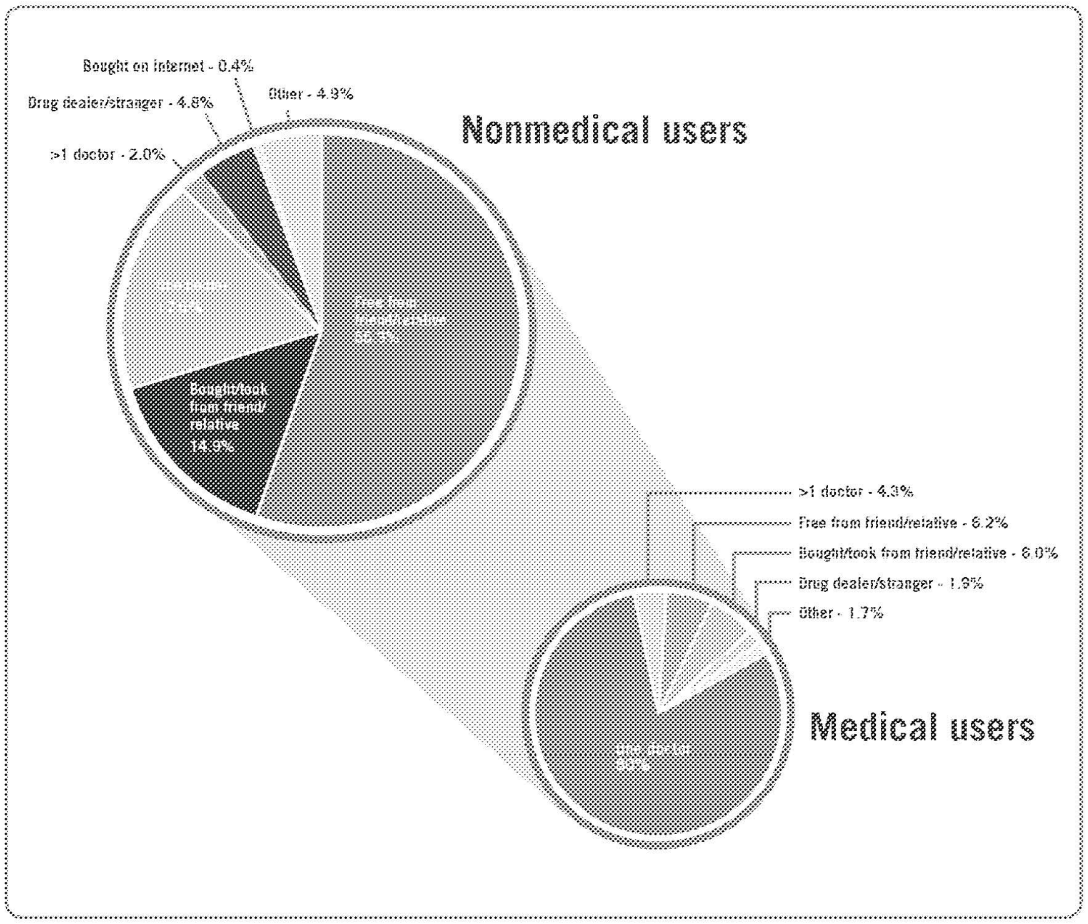
Exposure to a potentially addictive drug, such as an opioid, does not necessarily result in addiction. Although the actual risk of addiction is unknown, in general, patients in pain do not become addicted to opioids. One study cited by the NIDA found that only 4 out of about 12,000 patients prescribed opioids for acute pain became addicted; in one small study of patients with chronic pain who received opioids for 4 to 7 years, about 5% (2 of 38) became addicted, and these patients had a prior history of drug abuse. Genetic, social, and psychological factors appear to be stronger determinants of addiction than does drug exposure alone. However, surveys suggest that clinicians often overestimate the risk of addiction.

In patients with cancer, drug-seeking behavior is usually a manifestation of undertreatment—the patient is engaged in "relief seeking" behavior that generally ceases when an effective level of analgesia is achieved. However, in patients with a previous history of drug abuse, the risk of relapse is high because of the stress of dealing with the cancer and the availability of centrally acting drugs. Therefore, clinicians who treat patients for cancer or any chronic pain syndrome must be trained to identify and manage patients at risk for addictive disorders. They must also be prepared to negotiate and set limits designed to prevent harm while providing relief and should have access to a multidisciplinary team that includes professionals with expertise in addiction medicine.

Overdose, Diversion, and Serious Complications

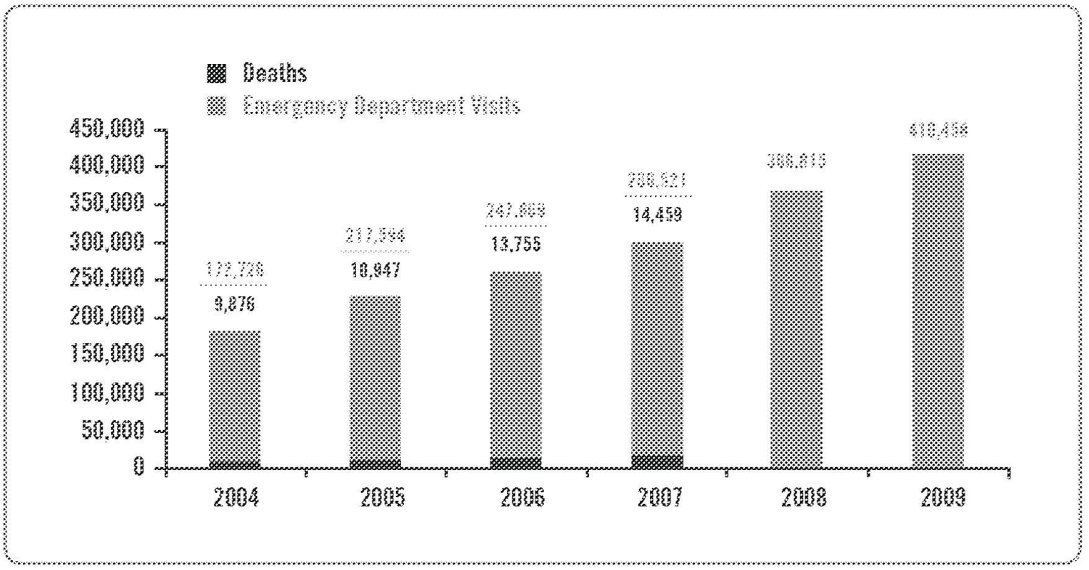
Diversion is the transfer of a pharmaceutical controlled substance to an unauthorized user. This practice may be as isolated as sharing one or two doses of a prescribed substance with a family member, or as complex as an organized crime scheme to supply illicit drug dealers or an internet scheme laundering important illegally manufactured drugs. While most nonmedical users of opioids obtained their drugs from friends or family members, who in turn obtained them from a single physician presumably for medical reasons (Figure 17), there are reports of individuals who visit multiple physicians with complaints of pain in order to obtain prescription medications with the intent to distribute. For example, a person in Michigan obtained 41 Schedule II prescriptions from 24 physicians and had them filled by 27 pharmacies in 14 different cities. Supply chain theft is also common; during the period from 2000 to 2003, 7 million missing dosage units (74% opioids) were reported each year to the Drug Enforcement Agency. In 2003 alone, 46,101 dosage units of fentanyl were diverted from distributors and retail pharmacies.

Figure 17. Sources of Diverted Opioids



Misuse of opioids can have serious health consequences. The CDC reported that opioid analgesics were involved in almost 40% of all poisoning deaths in 2006, although it could not be determined whether the drug involved in the deaths was prescribed for the decedent or for another person. Increased nonmedical use of opioids is reflected by a rise in ED visits; from 2004 to 2009, ED visits for nonmedical use of opioids have increased by 141%. Likewise, deaths from opioid poisoning due to overdose or misuse have more than tripled from 1999 through 2007 (Figure 18). Data on deaths from 2008 and 2009 are not yet available.

Figure 18. Deaths and Emergency Department Visits Involving Opioids



Opioid painkillers are especially dangerous when taken in high doses, in combination with certain other prescription medications, and with alcohol. Rapid-acting opioids are intended for use only in opioid-tolerant patients; adverse effects may be amplified in patients with no established tolerance to opioids.

Summary

- Surveillance data indicate that prescription drug abuse increased by 42.5% between 2001 and 2005, from an average of eight million people to 11.4 million people.
- Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
- Addiction is a neurobiological disease characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
- Exposure to a potentially addictive drug, such as an opioid, does not necessarily result in addiction.
- Clinicians often overestimate the risk of addiction to opioids in patients with pain, although those at risk for addictive disorders will require additional monitoring.
- Drug-seeking behavior in patients with cancer is often a manifestation of undertreatment and is more accurately described as "relief seeking" behavior.
- Diversion is the transfer of a pharmaceutical controlled substance to an unauthorized user and can result in serious, even fatal, consequences.

Self-Check Questions

1. **Between 2001 and 2005 prescription drug abuse increased by approximately ____%.**

   A. 14

   B. 24

   C. 42

   D. 44

2. **Complete the following sentence by filling in the blank.**

   A state of adaptation in which exposure to a drug induces changes that result in diminution of one or more of the drug's effects over time is known as _____.

3. **The transfer of a pharmaceutical controlled substance to an unauthorized user is known as:**

   A. Misuse

   B. Diversion

   C. Opiophobia

   D. Intent to distribute

4. **Which of the following is most likely to occur due to misuse of rapid-acting opioids?**

   A. Addiction

   B. Tolerance

   C. Breakthrough pain

   D. Respiratory depression

5. **In a survey of 805 patients with chronic pain, what was the most common concern expressed when first prescribed a narcotic analgesic?**

   A. Addiction

   B. Side effects

   C. Social stigma

   D. Development of tolerance

Answers to Self-Check Questions

Lesson 1

1. Cell body, dendrites, axon
2. D
3. B
4.

	Excitatory	Inhibitory
Norepinephrine	X	X
Serotonin		X
ATP	X	X
GABA		X
Enkephalin		X
Substance P	X	

5. D

Lesson 2

1. Actual or potential tissue damage
2. D
3. C
4. B
5. (P) Ability to perform chores at home
   (N) Anxiety
   (O) Deep vein thrombosis
   (N) Depressed mood
   (N) Impaired cognitive function
   (P) Inability to complete full day's work
   (O) Increased blood pressure
   (E) Pharmacy and medical costs
   (N) Poor concentration
   (N) Sleep disturbances
   (P, N) Socialization
   (O) Weight loss

Lesson 3

1. (E) Skin or in tissues that line or cover internal organs
   (D) Bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue
   (A) Blood-forming tissue such as bone marrow
   (C) Immune system
   (B) Brain and spinal cord
2. D
3. 31, 85, nociceptive
4. A
5. D

Lesson 4

1. A, B
2. C
3. Maximum, assessment, side effects
4. D

Lesson 5

1. C
2. Tolerance
3. B
4. D
5. B

GLOSSARY

ablation:
the removal of a part, pathway, or function by surgery, chemical destruction, or cauterization, or radiofrequency

adjuvant:
a word meaning to aid; may be used to describe a drug that is added to a prescription to hasten or increase the effect of a main ingredient

afferent:
in neurology, to transport impulses toward the CNS

allodynia:
pain in response to a non-nociceptive stimulus

axillary:
pertaining to the armpit

axon:
a segment of a neuron that conducts nerve impulses away from the cell body

basal cell:
a type of cell found in the deepest layers of the epidermis

basal nuclei:
also known as basal ganglia—a group of nuclei that lie deep in the cerebral hemispheres that contribute to some of the subconscious aspects of voluntary movement but do not initiate it. They are affected by the neurotransmitters acetylcholine, dopamine, GABA, and serotonin.

benign:
not recurrent or progressive; not malignant

bradykinin:
a peptide that, when coupled to appropriate receptors, causes a broad spectrum of activity, including relaxation of venular smooth muscle and hypotension, stimulation of sensory neurons, release of cytokines

buccal:
pertaining to the cheek or mouth; the inner side of the cheek in the mouth

central sensitization:
a state in which the response to normal neuronal inputs is greatly enhanced due to increases in excitability and a reduction in inhibitory transmission, occurring with repeated peripheral noxious stimulation

cytokines:
numerous distinct proteins produced primarily by white blood cells that provide signals regulating cell growth and function during inflammatory states, each secreted by a specific cell in response to a specific stimulus. Examples include the interleukins, interferons, and tumor necrosis factors.

dopamine:
A catecholamine synthesized by the adrenal gland that affects nerves and blood vessels, among other tissues. In the brain, it works as a neurotransmitter, affecting cells that influence body movement, emotional states, and pleasure/reward.

dorsal horn:
the posterior (back) portion of the gray matter of the spinal cord

dysesthesia:
an unpleasant abnormal sensation, whether spontaneous or evoked

efferent:
in neurology, the type of nerve that conducts impulses from the CNS to the periphery

endogenous opioids:
a group of more than 15 substances found in the brain, certain endocrine glands, and the GI tract that have morphine-like activity. Examples are endorphins and enkephalins.

endorphin:
a polypeptide produced in the brain that binds to opioid receptors and produces analgesia, increasing an individual's threshold for pain

etiology:
the cause of disease and the study of the cause of disease

exocrine:
referring to the external secretion of a gland, or to glands whose secretion reaches epithelial tissue either directly or through a duct

gamma-aminobutyric acid (GABA):
the principal inhibitory neurotransmitter in the brain

ganglia:
plural for a mass of nervous tissue (ganglion) made up principally of neuron cell bodies that lies outside of the brain or spinal cord

hematologic:
pertaining to the blood and blood-forming tissues

histamine:
a substance released from mast cells during allergic reactions that causes vasodilation, increased secretion of stomach acid, constriction of smooth muscle, tissue swelling, and itching

hyperalgesia:
increased pain sensitivity

in situ:
in the normal place; localized, not disturbing or invading surrounding tissue

intercostal:
between the ribs

intranasal:
within the nasal cavity

ion channel:
proteins that span the lipid bilayer of the cell membrane, regulating the movement of charged particles (ions) into and out of cells

limbic system:
a group of brain structures that is activated by motivated behavior and arousal, influencing the endocrine glands and autonomic nervous system

lymph, lymphatic:
an alkaline, clear, colorless tissue fluid that contains albumin, globulins, salts, urea, neutral fats and glucose. It is collected by lymph capillaries, traveling through progressively larger vessels and through lymph nodes, until it empties into the subclavian veins. The lymph nodes contain macrophages that phagocytize ("eat") bacteria and other pathogens. The term "lymphatic" refers to any portion of this system.

lymphatic system:
includes all of the lymph vessels that collect and return tissue fluid to the blood, including the lymph nodes and nodules, the spleen, and the thymus

malignant:
growing worse; resisting treatment, said of cancerous growths; harmful

metastasis:
change in location of a disease or its manifestations from one part of the body to another due to the movement of body cells, especially cancer cells, from one body part to another

mucosal membrane:
the membrane lining body passages and cavities that communicates with the air and contains mucus-secreting cells or glands that provide defense against the entry of pathogens

multimodal:
using or relying on multiple methods; multidisciplinary

myelin:
the phospholipid-protein of the cell membranes of the CNS and PNS that forms a sheath, acting as an electrical insulator and increasing the velocity of impulse transmission in the neurons

myeloma:
a tumor that originates in the portion of the bone marrow responsible for forming red blood cells

neuron:
the structural and functional unit of the nervous system, consisting of a cell body and its processes, an axon, and one or more dendrites

neuropathic (pain):
originating in the peripheral nerves or CNS rather than arising from damaged organs or tissues

neurolytics:
procedures that result in neurolysis, the loosening of adhesions surrounding a nerve or disintegration or destruction of nerve tissue

neuropeptides:
an endogenous peptide that influences neural activity or functioning (eg, endorphin)

neurotransmitter:
a chemical that is released when the axon of a presynaptic neuron is excited; neurotransmitters act to inhibit or excite a target cell

nociceptor:
a free nerve ending that acts as a receptor for painful stimuli

nonsteroidal anti-inflammatory drug (NSAID):
a drug with analgesic, anti-inflammatory, and antipyretic activity that is used to treat acute and chronic pain and to prevent the complications of sepsis

norepinephrine:
a neurotransmitter released by most sympathetic postganglionic neurons and by some neurons of the brain

noxious:
harmful; not wholesome

opiate:
a drug containing or derived from opium

osteonecrosis:
the death of a segment of bone, usually caused by insufficient blood supply to a region of the skeleton

paresthesia:
an abnormal or unpleasant sensation that results from injury to one or more nerves, often described by patients as numbness or as a prickly, stinging, or burning feeling

postsynaptic terminal:
the end of the neuron, either a dendrite or part of the cell body that receives impulses via neurotransmitters from an adjacent neuron

presynaptic terminal:
the terminal at the axonic end of the neuron that relays impulses via neurotransmitters to an adjacent neuron

proprioception:
the awareness of posture, movement, and changes in equilibrium and the knowledge of position, weight, and resistance of objects in relation to the body

prostaglandins:
a group of biologically active unsaturated fatty acids produced via the cyclooxygenase (COX) pathway and mediate inflammation; formation is blocked by NSAIDs

reticular (activating) system:
the alerting system of the brain extending from the central core of the brain to all parts of the cerebral cortex

serotonin:
a chemical found in platelets, the GI mucosa, mast cells, carcinoid tumors, and the CNS that acts as a neurotransmitter to produce vasoconstriction

somatosensory:
pertaining to sensory activity that arises from sites other than the special sense organs (eyes, ears, nose) and conveys information about the body and its immediate surroundings

somatosensory cortex:
either of two regions in the brain that receive and process somatosensory stimuli

sublingual:
beneath or concerning the area under the tongue

substance P:
a peptide involved in the body's response to noxious stimuli, depression, and anxiety, as well as eliciting local tissue reactions that resemble inflammation

synapse:
the space between two neurons where the axon of one neuron comes into close proximity to the cell body or dendrites of another neuron and where neurotransmitters are released; synapses are susceptible to the effects of therapeutic drugs and toxic substances

synaptic cleft:
the synapse of a neuromuscular junction

thalamus:
the largest subdivision of the diencephalon of the brain that receives all sensory stimuli except olfactory. In the thalamus, sensory stimuli are associated, integrated, and then relayed to specific areas of the cortex. Primitive uncritical sensations of pain, crude touch, and temperature are recognized in the thalamus.

thoracotomy:
a surgical incision of the chest wall

tricyclic antidepressant (TCA):
a class of antidepressant whose chemical structure has three fused rings; blocks the reuptake of norepinephrine and serotonin at nerve endings

viscera:
internal organs that are enclosed within a cavity, especially the abdominal organs

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