ABSTRACT

Pain is a broad term that encompasses a wide range of conditions that exist on a continuum. This article reviews various types of pain—namely, acute, chronic, and neuropathic pain—with a focus on pathophysiology and drug therapy. This is followed by a discussion of the issues underlying inadequate pain management, and how these concerns may be rectified in order to achieve desired therapeutic effects. (Adv Stud Pharm. 2009;6(4):94-99)

THE ACUTE TO CHRONIC PAIN CONTINUUM

Throbbing, burning, aching, stabbing—patients may describe pain in a variety of different ways because it is a subjective sensation that differs based on its cause, as well as on the individual who is experiencing it. Commonly defined as “an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage,” pain is typically classified as either acute or chronic. Acute pain generally results from an identifiable cause (ie, disease, surgery, or tissue injury). It is immediate and intense, and may be accompanied by anxiety or emotional distress, but is usually short-lived. In fact, in most cases, acute pain does not last longer than 6 months because it ceases to exist once the underlying cause has been resolved (though there are times when it may last longer than expected). Acute pain frequently requires aggressive intervention because it may progress to chronic pain if left untreated. Although it is usually relatively manageable, literature indicates that acute pain, similar to other types of pain, is often poorly managed in this country.

Unlike acute pain, chronic pain may occur in the absence of injury, or may persist long after the initial trauma has subsided. It typically lasts for longer than 3 months, and frequently interferes with a patient’s quality of life, sleep, and productivity, often resulting in depression and undesirable socioeconomic consequences. Common chronic pain complaints include headache, low back pain, cancer pain, and arthritis pain. Unfortunately, treatment is often complicated by a lack of access to care because patients suffering from chronic pain require a significant amount of follow-up care.

Dr Lipman: Chronic pain is pain that either continues longer than the time it takes for the acute precipitating event to resolve, or pain that is due to an ongoing process or underlying pathophysiology.

Although acute and chronic pain may be separate entities, the distinction is often blurred, as the conditions may overlap and intertwine. Specifically, many patients with chronic pain experience acute exacerbations, making it difficult to differentiate chronic from acute pain. Furthermore, neither condition can be optimally managed without understanding the other. Therefore, it is best to view pain as a steady continuum, with each of its components requiring individualized treatment.
SOMATIC, VISCERAL, NOCICEPTIVE, AND NEUROPATHIC PAIN

Pain may be further characterized by location (somatic vs visceral) and by pathophysiology (nociceptive vs neuropathic). Somatic and visceral pain are considered nociceptive, because they arise from the stimulation of specific pain receptors that respond to heat, cold, vibration, stretch, and chemical stimuli released from damaged cells. Neuropathic pain, on the other hand, is a type of non-nociceptive pain that arises from within the peripheral nervous system or central nervous system (CNS). Receptor activation is not required for this type of pain to occur; instead, it is generated by nerve cell dysfunction and, by definition, a type of chronic pain.

Dr Lipman: Physicians frequently use the term “neurogenic” in place of “neuropathic,” but this is a misnomer because all pain is neurogenic. Neuropathic pain is a second pain that occurs after the initial nerve insult has resolved, is characterized by allodynia, and always follows a nerve distribution.

Dr Koo: A single or isolated nerve distribution component is not mandatory because there are situations in which multiple nerves may be involved (ie, diabetic neuropathy).

Somatic pain originates in the cutaneous or musculoskeletal tissues (ie, muscles, joints, or bones) and is generally well defined and localized. Common causes include dental pain and postsurgical pain following an incision. Deep somatic pain is usually described as dull or aching in nature, whereas superficial somatic pain is sharper and may have a burning or pricking quality. This type of pain generally responds well to acetaminophen, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs). Visceral pain, on the other hand, originates in the internal organs of the main body cavities. It is poorly localized and often described as a generalized aching or squeezing. Unlike somatic pain, visceral pain is difficult to pinpoint because it is very diffuse and is often referred to other locations. This type of pain is usually most responsive to opioid analgesics.

Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the nervous system, and modifications in the CNS are believed to sustain pain even after an injury heals. Most people who experience this type of pain describe it as a tingling, burning, or stabbing sensation, and some even say it feels as if electricity is running through the area. Neuropathic pain is only partially responsive to conventional pain medications, and often requires treatment with antidepressants or anticonvulsants. Neuropathic syndromes may be classified as mononeuropathies (conditions involving 1 isolated nerve), polyneuropathies (conditions involving multiple nerves), deafferentation pain (pain due to loss of sensory input into the CNS), or sympathetically mediated pain. Table 1 provides examples of each of these syndromes, as well as specific definitions.

MECHANISMS OF NOCICEPTIVE AND NEUROPATHIC PAIN

Nociceptive pain occurs when various substances (ie, bradykinin, serotonin, substance P, potassium, and prostaglandins) are released in response to tissue injury. These substances activate nociceptors, thereby generating an action potential, which carries the pain signal along the length of the peripheral nerve. Pain impulses are then transmitted to the CNS via primary afferent fibers that enter the spinal cord by way of the dorsal horn. Finally, second and third order neurons relay pain messages to the brain’s higher structures (ie, limbic system and somatosensory cortex), which enables an individual to perceive pain.

Patients with neuropathic pain may continue to experience discomfort long after the initial trauma has resolved because their nerve fibers develop abnormal ectopic excitability at or near the site of nerve injury. This phenomenon may be due to an unusual sodium channel distribution, as well as abnormal responses to endogenous pain-producing substances and cytokines, such as tumor necrosis factor-α. The resulting ectopic excitability leads to spontaneous impulse discharge, and potentially, to persistent abnormal excitability of sensory nerve endings. Continued abnormal input following nerve injury eventually activates several intracellular second messenger systems and brings about a widespread change in protein synthesis, thereby sensitizing the nervous system and increasing pain and hyperalgesia.

Furthermore, non-neuronal glial cells in the periphery and CNS modify nociception in response to inflammation or injury. The increased release of excitatory amino acids (most commonly glutamate) from damaged afferent nerve fibers subsequently activates N-methyl-D-aspartate (NMDA) receptors in the dorsal horn of the spinal cord, where the primary process-
ing of nociceptive information occurs. This process plays a key role in the induction of neuronal sensitization and, therefore, the use of an NMDA antagonist may help to produce analgesia. Unfortunately, however, the drugs that inhibit NMDA are generally not well tolerated. Finally, hypersensitivity to norepinephrine (NE) has also been reported in various neuropathic pain conditions that exhibit sympathetically mediated pain.

**Dr Lipman:** Ketamine, an NMDA antagonist, does not effectively relieve pain in all patients because NMDA receptor activation is only one of the many possible mechanisms responsible for neuropathic pain.

**Dr Koo:** A low-dose ketamine drip is often used as a postoperative analgesic in patients with chronic pain.

**Dr Lipman:** One of the isomers of methadone is also a weak NMDA antagonist, but there is currently no evidence to support its clinical effectiveness.

**Dr Koo:** Methadone has a long half-life, which often results in toxicity when used by inexperienced clinicians.

**Dr Lipman:** Methadone has also been associated with central sleep apnea, which is another reason why its use as a first-line drug is discouraged. The Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain, published by the Utah Department of Health in 2009, recommend that “methadone should only be prescribed by clinicians familiar with its risks and use, and who are prepared to conduct the necessary careful monitoring.”

**Dr Strassels:** Does tolerance to respiratory depression develop rapidly with methadone?

**Dr Lipman:** The central sleep apnea associated with methadone is different from generalized respiratory depression, and patients do not appear to become tolerant to this effect.

**ATTACKING THE PAIN PATHWAY**

The pain pathway consists of 4 distinct components (ie, transduction, transmission, modulation, and perception), each of which can be altered by various medications that are used to relieve pain (Figure). Local anesthetics (eg, lidocaine), NSAIDs, anticonvulsants, and capsaicin may be used to inhibit transduction. Local anesthetics blunt electrical activity at the nerve endings, whereas NSAIDs reduce the synthesis of prostaglandins, leukotrienes, and bradykinin. Anticonvulsants, which are primarily used to treat

**Table 1. Neuropathic Syndromes**

<table>
<thead>
<tr>
<th>Neuropathic Syndrome</th>
<th>Definition</th>
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<tr>
<td>Radiculopathy</td>
<td>Pathological condition of the nerve roots</td>
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<td>Acute herpetic neuralgia/shingles</td>
<td>A viral disease that involves the dorsal root ganglion and its peripheral nerve; due to reactivation of the herpes zoster virus</td>
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<td>Trigeminal neuralgia</td>
<td>An intense paroxysmal neuralgia involving ≥1 branch of the trigeminal nerve (5th cranial nerve)</td>
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<tr>
<td>Post-mastectomy/stump pain</td>
<td>Pain arising in the stump in a person with an amputated limb; originates from damaged nerves near the site of the amputation</td>
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<tr>
<td>Diabetic neuropathy</td>
<td>Nerve damage as a result of hyperglycemia</td>
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<tr>
<td>AIDS-related neuropathy</td>
<td>Nerve damage as a result of an HIV-related condition or certain medications, such as nucleoside analogs</td>
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<tr>
<td>Alcoholic neuropathy</td>
<td>A disorder involving decreased nerve functioning caused by damage that results from excessive alcohol consumption</td>
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**Deafferentation Pain**

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<th>Phenomenon</th>
<th>Definition</th>
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<tr>
<td>Phantom pain</td>
<td>An often painful sensation of the presence of a limb that has been amputated; originates and ends in the brain</td>
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<td>Postherpetic neuralgia</td>
<td>A complication of herpes zoster infection that persists after the acute phase of the illness</td>
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<tr>
<td>Brachial plexus avulsion</td>
<td>Severing of a nerve that conducts signals from the spine to the shoulder, arm, and hand</td>
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**Sympathetically Mediated Pain**

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<th>Phenomenon</th>
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<td>CRPS I</td>
<td>A painful disorder that usually follows a localized injury, that is marked by burning pain, swelling, and motor and sensory disturbances especially of an extremity, and that is associated with sympathetic nervous system dysfunction</td>
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<td>CRPS II</td>
<td>A constant, usually burning pain resulting from injury to a peripheral nerve</td>
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CRPS = complex regional pain syndrome.

Data from Merriam Webster Medical Dictionary; Plehn; Medical dictionary; Diabetic neuropathy; Williams et al; Alcoholic neuropathy; Postherpetic neuralgia; and National Institute of Neurological Disorders and Stroke brachial plexus injuries information page.
neuropathic pain, block sodium channels (eg, carbamazepine, lamotrigine, and zonisamide), modulate calcium channels (eg, gabapentin, zonisamide, and pregabalin), increase γ-aminobutyric acid release (eg, zonisamide), and inhibit glutamate release (eg, lamotrigine), whereas capsaicin depletes substance P. Spinal and local nerve anesthetics interrupt neuronal transmission at the peripheral or central level, and tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors, and opioids alter modulation in the spinal cord. TCAs reduce pain by blocking the reuptake of NE and serotonin, substances that may act to inhibit pain impulses. Phenothiazines may decrease pain by relieving anxiety and blocking post-synaptic α-adrenergic receptors, but, with the possible exception of methotrimeprazine, which is no longer available in the United States, evidence does not support their having a place in pain management. Opioid analgesics bind opioid receptors in the CNS, thereby suppressing neuronal activity. Finally, opioids and, to a lesser extent, antidepressants, alter an individual’s perception of the signal received by the cerebral cortex. Interestingly, patients being treated with opioids often report that they still feel the pain, but that it no longer bothers them.

**Dr Lipman:** Central stimulants can also alter pain perception.

**Dr Koo:** This explains why central stimulants often reduce opioid requirements in patients with cancer.

**The Dynamics of Pain and Pain Management**

**ABCDES of Pain Management**

Appropriate pain management requires a variety of factors, including systematic assessment, belief in the patient’s pain report, commitment to a therapeutic agreement, appropriate medication delivery, patient education/empowerment, and evaluation of the regimen’s effectiveness (ie, the ABCDES of pain management). Unfortunately, the lack of access to healthcare presents a huge barrier to commitment, education, and reevaluation, because these goals cannot be achieved if patients are unable to see their healthcare practitioners on a regular basis. As a result, many patients fail to receive adequate therapy, resulting in unnecessary pain and suffering, as well as other related issues such as anxiety, depression, insomnia, and an overall reduction in quality of life. These factors, in turn, may further exacerbate an individual’s perception of pain.

**The Undertreatment of Pain**

In addition to inadequate healthcare access, the undertreatment of pain may also be attributed to a variety of other factors, as outlined in Table 2. A physician survey designed to uncover barriers to the use of opioids in the treatment of chronic pain found addiction potential, abuse/misuse potential, and adverse effects to be the most commonly identified obstacles, whereas another survey of healthcare professionals treating patients with cancer reported that inadequate pain assessment, patient reluctance to report pain, and inadequate staff knowledge regarding pain management were the most significant barriers to optimal pain management. Thus, effective pain man-

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**Figure. The Pain Pathway**

- **Transduction:** The conversion of a painful stimulus into electrical activity at the nerve endings
- **Transmission:** The propagation of electrical signals from the nerve endings to terminals in the spinal cord, which relay afferent signals to the brain stem, thalamus, and cerebral cortex
- **Modulation:** Alteration of the pain signal in the CNS by selectively inhibiting pain transmission; norepinephrine and serotonin may act to inhibit pain impulses
- **Perception:** Subjective awareness of pain, involving the thalamus and cerebral cortex

**CNS = central nervous system; NSAID = nonsteroidal anti-inflammatory drug.**

Data from *The pathophysiology of pain*; Davies and Taylor; Backonja; Capsaicin; Yalcin et al; Hendler; and Richeimer and Spinasanta.
management relies on the combined efforts of the patient and his healthcare providers. Pain must be promptly reported and properly assessed, to develop an appropriate management regimen that all parties agree to. Therapy must then be closely monitored and reevaluated to ensure that the patient's treatment is effective. Furthermore, honest communication will help to eliminate and/or address fears regarding adverse effects and addiction-/abuse-related issues.

Dr Koo: Many primary care physicians are not well equipped to treat pain because they have not gone through extensive pain management training.

Dr Barkin: Primary care clinicians today must see approximately 10 patients per hour, which does not allow enough time to properly evaluate an individual with pain, in a comprehensive manner. Thus, many patients request treatment at pain centers, where the comprehensive workup begins, and later transition out to primary care.

Dr Lipman: The vast majority of pain resolves spontaneously, but pain that does not do so typically requires more than a simple primary care visit.

Dr Koo: Only 20% of pain patients have persistent pain that requires an in-depth evaluation, but these patients consume 80% of a primary care physician's resources. Thus, it would be advantageous, both from a practical and from an economic standpoint, for these individuals to be managed by pain centers.

Dr Barkin: When patients experience difficulty accessing adequate pain relief, they often turn to illegitimately obtained medications or self-treatment, thereby compounding the problem.

Dr Brown: How commonly is acute pain treated inadequately, allowing it to progress to chronic pain?

Dr Koo: Not all acute pain progresses to chronic pain. Acute pain typically improves with time, but this may take anywhere from 2 to 6 months, depending on the cause.

Dr Strassels: There is enormous interpatient variability in recovery time following trauma or surgery.

Dr Lipman: Many physicians are concerned about opioid-related adverse events. Using an agent with a dual mechanism of action, such as tapentadol, might reduce the required µ agonist requirement, thereby lessening the potential for adverse events. However, using multimodal therapy is very expensive.

Dr Koo: The high acquisition cost of a medication may be justified if it translates into overall patient well-being. One must consider the overall cost of patient care, and not only drug cost.

Dr Strassels: Fear of regulatory scrutiny presents a major barrier to adequate pain management, because such scrutiny could potentially destroy a physician's career, even if it is unwarranted.

Dr Hahn: It is also important to keep in mind that pain management is a high-risk practice with tremendous liability risks.

Dr Koo: Detailed documentation would help healthcare practitioners avoid these types of issues.

CONCLUSIONS

Although acute, chronic, and neuropathic pain may differ in presentation and management, they often overlap, necessitating individualized treatment of each component. Such treatment may be achieved by inhibiting specific processes involved in the pain pathway, and selecting medications based on the type of pain that an individual experiences. Regardless of pain type, however, all patients require clinical assessment, evaluation, and follow-up, to ensure appropriate pain management and optimal therapeutic outcomes.

Table 2. Barriers to Appropriate Pain Management

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<th>Healthcare Professional Barriers</th>
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<tr>
<td>Lack of provider knowledge regarding pain assessment and management</td>
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<td>Fear of addiction</td>
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<td>Fear of regulatory scrutiny</td>
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<tr>
<td>Inability to establish rapport with patients</td>
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<td>Prejudice and bias in dealing with patients</td>
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<th>Patient/Societal Barriers</th>
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<tbody>
<tr>
<td>Fear of addiction</td>
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<tr>
<td>Fear of intolerable adverse effects</td>
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<tr>
<td>Economic barriers</td>
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<tr>
<td>Lack of access to care</td>
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<tr>
<td>Reluctance to report pain due to fear of not being believed</td>
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Data from Fink and Gates; Morley-Forster et al; and Anderson et al.
REFERENCES


