Pain Management and End-of-Life Care CME Program

Module 4

Registration: The registration page and test questions are at the end of this article (pages 82-83). The ten questions must be answered and submitted to the CSA in order to receive the CME credit. The full text of each module of this CME program, along with references, also will be accessible through the CSA Web Site, **www.csahq.org**.

Fees: This is a free service for CSA members. Non-members will be charged $25 per CME credit hour. Your CME certificate will be mailed from the CSA office.

Availability: This module is available from December 31, 2004, until December 31, 2007.

Target Audience: California law now requires that every licensed physician complete 12 credit hours in pain management and end-of-life care by the end of 2006. This module fulfills one credit hour of CME toward that requirement. This program is intended for all licensed physicians, including anesthesiologists, residents, and physicians with an interest in pain management.

Faculty and Disclosures for Module 4:

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The California Society of Anesthesiologists Educational Programs Division designates this educational activity for a maximum of 1 credit hour toward the AMA Physician's Recognition Award.

Evaluation: An evaluation of Module 4 of this series is offered after the test questions. Please fill in your responses and return them to the CSA office.

Objectives:

1. Understand the difference between nociceptive and neuropathic pain
2. Understand the difference between hyperalgesia and allodynia and underlying mechanisms
3. Understand the mechanisms underlying neuropathic pain

Resources: These materials are offered online at the CSA Web Site at **www.csahq.org** also. The questions are also available online. Please fill out the registration form, answer the questions, fill out the evaluation form and fax or mail these to the CSA office at 951 Mariner's Island Boulevard #270, San Mateo, CA 94404. Our fax number is (650) 345-3691.

Pain Physiology

By Mark S. Wallace, M.D., Associate Professor, Clinical Anesthesiology, University of California San Diego

Dr. Wallace received his M.D. degree at Creighton University in 1987 after which he completed his anesthesiology residency in 1991 and a pain research/clinical fellowship at the University of California San Diego in 1994. He became the Program Director of the UCSD Center for Pain and Palliative Medicine in 1996. Dr. Wallace heads a busy clinical trials program that is funded through federal and state agencies as well as industry. His research interests include human experimental pain models and analgesic efficacy of smoked cannabis.

-Joshua Prager, M.D., Coordinator, CSA Bulletin Pain Management Series

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. The

definition recognizes pain as a subjective experience with both psychological and sensory components. It also recognizes that tissue damage does not need to be present in order to experience pain. Pain is a symptom of an underlying illness that cannot be cured. This is consistent with over 90 percent of medicine in which medical doctors simply treat the symptom of illnesses without affecting the course of the underlying illness (e.g., hypertension, diabetes). It should be recognized that pain is a symptom with underlying mechanisms and neuranatomic pathways. By better understanding the anatomy and physiology of pain, the practitioner can better target treatments at the underlying mechanisms.
Nociceptive pain results from activity in neural pathways caused by actual tissue damage or potentially tissue-damaging stimuli. Examples include postoperative pain, arthritis, mechanical low back pain, and sports injuries. Neuropathic pain is caused by a primary lesion or dysfunction of the nervous system. Examples include peripheral neuropathy, postherpetic neuralgia, central post stroke pain, spinal cord injury pain, and trigeminal neuralgia. Often, patients experience a "mixed type" with both nociceptive and neuropathic components.

Physiology of Pain

Mechanistically, pain can be divided into three categories: acute, facilitated and neuropathic. There is no clear boundary between these categories, and clinically there is some overlap that is often observed. **Acute pain** results from activation of peripheral nociceptors with thermal or mechanical stimuli that do not result in tissue injury. When the stimulus is removed, the pain ceases. **Facilitated pain** results when tissue injury occurs resulting in the release of chemicals that sensitize the peripheral nociceptors. There is also the central release of neuropeptides that sensitize the dorsal horn cells resulting in both a peripheral and central sensitization. A very low level of peripheral input is required to maintain the central sensitization. **Neuropathic pain** is pain caused by a primary lesion or dysfunction in the peripheral and/or central nervous systems.

Acute Pain

Transducer receptor/ion channel complexes on peripheral nociceptor terminals respond to noxious stimuli from mechanical, chemical, or heat sources by generating depolarizing currents. If the current is sufficient, action potentials are initiated and then conducted to the CNS, where they invade central nociceptor terminals and cause the release of neurotransmitters, thus eliciting pain perception.[1]

The functional specialization of primary sensory neurons enables, under normal circumstances, the response to low- and high-intensity peripheral stimuli to be

differentiated. Low-intensity peripheral stimuli activate low-threshold receptors generating innocuous sensations, and high-intensity stimuli activate high-threshold nociceptors, which can lead to the sensation of pain. This pain is a physiologic sensation acting as a warning of potentially harmful stimuli.

Facilitated Pain

After tissue injury, there is the local release of chemicals that activate and sensitize free nerve endings. The activation results in dromic conduction into the central nervous system and antidromic conduction which results in the release of substance P from the nerve endings. The substance P degranulates mast cells and platelets to release histamine and serotonin respectively that in turn further activates the free nerve endings from which the substance P was released as well as neighboring free nerve endings. This will result in a flare response due to the vasodilatory effect of the substance P, serotonin and histamine. A-delta fibers are thought to transmit the initial sharp, easily localized, pain experienced by a person who has just been injured (first pain). C fibers are thought to transmit the dull, poorly localized, and prolonged pain experienced after injury (second pain). A-delta fibers also act to suppress activity in C fibers. If the C fibers go unopposed by the A-delta fibers, the second pain is exaggerated.

Hyperalgesia is an exaggerated response to stimuli that activate nociceptors, both A-delta and C fibers. A-delta and C nociceptors are high threshold afferents in that they require a high intensity stimulus for activation. However, if they become sensitized, their threshold of activation is decreased to where a low intensity stimulus (thermal or mechanical) results in activation and the report of pain.

Primary hyperalgesia corresponds with the injured area and the area of flare response. It is the result of lowered pain thresholds to both thermal and mechanical stimuli and involves sensitization of the peripheral nociceptor as well as sensitization of the central nervous system.

The activity in the peripheral nociceptors will also result in the release of central neuropeptides which will sensitize the dorsal horn cells. When activated, these sensitized dorsal horn cells have an exaggerated response that is perceived as much more painful than would occur in the unsensitized state. Therefore, hyperalgesia, can occur through central mechanisms as well as peripheral mechanisms.

Heat hyperalgesia occurs within the area of primary hyperalgesia after injury as described previously. Therefore, the threshold of detecting a rise in temperature

applied to the skin approaches the threshold at which the rise in temperature is painful. Clinically, this occurs in postoperative pain in which the area immediately surrounding the surgical site has heat hyperalgesia. Also, in some early neuropthic pain states such as Complex Regional Pain Syndrome, the extremity is warm and erythematous and demonstrates heat hyperalgesia. This is hypothesized to be the result of "angry backfiring C fibers" resulting in the release of substance P and degranulation of mast cells and platelets as described above. It may also be the result of an exaggerated response to circulating inflammatory mediators.

C-fibers enter the dorsal horn of the respective dermatome to make connections on second order neurons located in Lamina II. However, C-fibers also branch cephalad and caudad to make connections on Lamina II neurons above and below the dermatome of origination. This results in an activation of dorsal horn cells in dermatomes outside the original injury resulting in secondary hyperalgesia.

Secondary hyperalgesia is located in the dermatomal area outside the area of injury. The area of secondary hyperalgesia has lowered pain thresholds to mechanical but not thermal stimuli (as compared to the area of primary hyperalgesia which has lowered pain thresholds to both mechanical and thermal stimuli). Whereas the area of primary hyperalgesia involves both peripheral and central mechanisms, the area of secondary hyperalgesia involves central mechanisms only. However, a continued low level of peripheral nociceptive input is required to maintain the area of secondary hyperalgesia.

Zones of secondary hyperalgesia are measured with a punctate stimulus and involve activation of A-delta fibers that in turn activate sensitized dorsal horn cells that produce an exaggerated pain response. **Mechanical allodynia** is measured with a brushing stimulus which activates low threshold A-beta mechanoreceptors. Under normal circumstances, dorsal horn nociceptive neurons will not respond to this stimulus; however, when they become sensitized, a non painful stimulus such as a touch, brush or pressure will activate these neurons leading to pain (allodynia).[2]

Neuropathic Pain

Neuropathic pain (NeP) is chronic pain initiated by nervous system lesions or dysfunction and maintained by a number of mechanisms. Excess stimulation of nociceptive pathways or damage to non-nociceptive pathways alters the balance between painful and nonpainful inputs so that pain results without nociceptor stimulation.

Neuropathic pain is described by a variety of terms such as burning, shooting, or lancinating and may be present without demonstrable physical findings. NeP sensations are diverse, but three symptoms-numbness, tingling, and increased pain due to touch-appear to predominate.[3] These symptoms illustrate the negative (sensory deficit) as well as positive (paresthesia and allodynia/hyperalgesia) phenomena that distinguish neuropathic from nociceptive pain.

Despite its clinical heterogeneity, NeP may result from a limited number of peripheral and central mechanisms that may be related to specific symptoms. For example, Gregg proposed correlations between specific neural mechanisms and four symptoms that often follow trigeminal nerve injuries, on the basis of surgical observations and animal pain models. In this paradigm, anesthesia dolorosa is associated with traumatic neuromas and central deafferentation; sympathetically mediated pain with C-fiber crosstalk in peripheral injured zones; hyperalgesia with abnormal connections between mechanosensitive A-beta fibers and irritable central nervous system neurons; and hyperpathia with ephaptic transmission between adjacent fibers in neuromas. Although this proposal may be a simplification, it provides a useful framework for relating experimental and clinical results.[4]

The following cellular and molecular mechanisms operating over different periods of time are thought to be involved in the abnormal peripheral and central nervous system activity associated with NeP.

1. Ion Channels and Demyelination

Nerve injury is reported to evoke spontaneous discharges from the cell bodies of myelinated fibers at the levels of the dorsal root ganglia, but not from the cell bodies of unmyelinated axons. The mechanism of the spontaneous activity is thought to be secondary to an increase in concentration of sodium channels in neuromas, dorsal root ganglion cells and areas of demyelination.[5]

Pain is a frequent symptom of demyelinating disease such as multiple sclerosis. Normal intact nerves transmit impulses through well-insulated channels. Following nerve injury, this insulation can be disrupted, and the impulses carried in one nerve fiber may be transmitted to a neighboring fiber. Ephaptic communication or “cross-talk” has been demonstrated following stimulation of adjacent fibers in the same trunk.[6]

2. Cytokines, Enzymes and Neuropeptides

There are also certain receptors that may accumulate that respond to cytokines and enzymes associated with inflammation. Receptors for inflammatory cytokines such as tumor necrosis factor ∀ (TNF-∀) can accumulate in injured sensory neurons and alter their function. Interleukins 1 and 6 and TNF-∀ are elevated in vasculitic neuropathy, chronic inflammatory demyelinating neuropathy, and noninflammatory chronic neuropathy. Cytokine levels also rise after nerve transection, and this elevation is correlated with allodynic behavior that may be linked to glutamate release and NMDA receptor activation.[7]

Membrane-type 5 matrix metalloproteinase (MT5-MMP) has been implicated in injury-associated spinal cord remodeling and development of NeP. Sciatic nerve damage results in sprouting of A-beta afferents from laminae III-VI and into lamina I of the dorsal horn and in the development of mechanical allodynia (see discussion below). Neither sprouting nor allodynia occurs after nerve damage in mice lacking the gene for MT5-MMP.[8]

Nerve injuries associated with the development of NeP alter the expression of neuropeptides and their receptors. Vanilloid receptor 1 (VR1) is expressed on peripheral terminals of A-delta and C fibers. However, in rats with streptozotocin-induced diabetes, peripheral terminals of A-beta fibers also express VR1. Substance P (SP) is normally released from the central terminals of A-delta and C fibers to bind with neurokinin-1 (NK-1) receptors on nociceptive neurons in the dorsal horn. NK-1 mRNA expression in the mouse lumbar dorsal horn is increased after partial sciatic nerve ligation, and this rise is correlated with thermal hyperalgesia. These results have prompted the suggestion that nerve injury results in synthesis and tonic release of SP by A-beta fibers, which initiates ongoing excitation of NK-1-expressing spinal nociceptive neurons.[9]

3. A-Beta Sprouting

Peripheral nerve injury triggers central sprouting of myelinated afferents. The myelinated afferents located in deeper layers of the dorsal horn cells (laminae III and IV) sprouting superficially to reach superficial layers of the dorsal horn (laminae I and II). Therefore, tactile nonpainful stimuli that activate large myelinated afferents will in turn activate superficial layers of the dorsal horn in turn activating spinothalamic tract neurons which will result in a painful state (allodynia).[10]

4. Sympathetic-Somatosensory Crosstalk

Discharge of afferent fibers has been observed following stimulation of sympathetic nerve fibers in the same nerve trunk. Sympathetic communication with afferent neurons is hypothesized to be the result of an increase in alpha adrenergic receptors in damaged primary afferent axons. Crosstalk between sympathetic and somatosensory afferents can develop in neuromas and dorsal root ganglions (DRG). Sympathetic axons are present in neuromas, and ∀-adrenoceptor-mediated excitatory coupling has been demonstrated in both neuromas and DRGs.[11]

In addition to alterations in adrenergic receptor expression, a recent report indicated that nerve injury causes sprouting of sympathetic fibers that invade the DRG to form functional synapses. These sprouting fibers contain catecholamines, and it has been demonstrated that ectopic discharges may originate at the DRG by direct innervation from these sympathetic fibers that form basket like structures around large diameter cell bodies of the DRG.[12]

5. GABA Down-Regulation

Spinal inhibitory interneurons modulate the peripheral-to-central transmission of pain signals, thus "gating" ascending sensory information. (-Aminobutyric acid (GABA) and glycine and their receptors are abundant in the superficial dorsal horn, but their levels are regulated by primary afferent input and change significantly after nerve injury. Sciatic nerve transection decreases the number of GABA-immunoreactive cells in dorsal horn laminae I-III, and this may "open the gate" to allow more excitatory signals from pain (or nonpain) pathways to reach the brain. Nerve damage also reduces expression of $GABA_A$ receptor ∀2 subunit mRNA in DRG cells, and this may disrupt the normal presynaptic inhibition that modulates neurotransmitter release by these cells.[13]

6. Glutamatergic Neurotransmission

Increased glutamatergic neurotransmission may also contribute to hyperexcitability and NeP. Repeated noxious stimulation leads to temporal summation of dorsal horn excitatory postsynaptic depolarizations, and this amplification is reduced by the n-methyl-d-aspartate (NMDA) receptor antagonist d-2-amino-5- phosphonovaleric acid (d-APV), suggesting mediation by an increase in glutamate release from primary afferents and subsequent binding to NMDA receptors. Intrathecal NMDA causes an increase in spontaneous activity of dorsal horn neurons that can be reversed by d-APV.

Persistent inflammation that gives rise to hyperalgesia is also associated with up-regulation of metabotropic glutamate receptors in the dorsal horn.

Dorsal horn neurons express amino-3-hydroxy-5-methylisoxazol propionic acid (AMPA)/kainate-type glutamate receptors; these non-NMDA receptors are thought to be primarily involved in detecting and responding to innocuous stimuli, but AMPA/kainate-NMDA receptor interactions are involved in C-fiber wind-up and long-term potentiation in dorsal horn neurons.

Glutamatergic transmission is potentiated by neuropeptides. For example, thyrotropin-releasing hormone has a slow priming effect that enhances NMDA receptor-mediated nociceptive transmission in the dorsal horn. Peripheral interactions between NK1 and NMDA receptors may also potentiate pain. NK1 receptor activation is thought to potentiate glutamatergic transmission in the spinal cord via NMDA-independent mechanisms.

Protein kinase C (PKC) potentiates NMDA currents by reducing the magnesium block and increasing the probability of channel openings. An additional consequence of protein phosphorylation is tolerance to opioids, which may result from desensitization of the opioid receptor by G-protein kinase 3.

Glutamatergic neurotransmission, most notably that involving NMDA receptors, also results in significant damage-associated changes in the anatomy of the spinal cord. For example, sciatic nerve transection results in degeneration of spinal dorsal horn neurons, and this apoptosis can be prevented when the NMDA antagonist MK-801 is injected before transection and then continuously infused.

Nociceptive processing also involves the expression of immediate early genes, a process partially regulated by glutamate receptors. Activity-dependent stimulation of kinases (such as extracellular signal-regulated protein kinase), the Ras cascade, and other transcriptional factors appears to be involved in inflammatory pain and NeP.[14]

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Registration

To register for the CSA CME Course in Pain Management and End-of-Life Care, Module 4, fill out this form. Then make copies of the test and evaluation. Once you have answered the questions, **mail or fax** the form, the test answers and the evaluation to the CSA office at:

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Questions

1. Nociceptive pain results from activity in neural pathways caused by actual tissue damage or potentially tissue-damaging stimuli.

   a. True
   b. False

2. Neuropathic pain is caused by a primary lesion or dysfunction of the nervous system.

   a. True
   b. False

3. Hyperalgesia is an exaggerated response to non-painful stimuli that activate A beta fibers.

   a. True
   b. False

4. Primary Hyperalgesia

   a. Corresponds with the injured area and the area of flare response.
   b. Is the result of lowered pain thresholds to both thermal and mechanical stimuli.
   c. Involves sensitization of the peripheral nociceptor as well as sensitization of the central nervous system.
   d. All of the above

5. Secondary Hyperalgesia

   a. Is located in the area of injury and flare response
   b. Has lowered pain thresholds to mechanical and thermal stimuli
   c. Involves both peripheral and central mechanisms
   d. Requires a low level of peripheral nociceptive input

6. Which of the following are mechanisms of neuropathic pain

   a. Increase concentration of sodium channels in areas of injury or demyelination
   b. Abnormal communication between the sympathetic and somatic nervous system
   c. Down regulation of spinal inhibitory (GABA containing) interneurons
   d. All of the above

7. Receptors for inflammatory cytokines such as tumor necrosis factor ∀ (TNF-∀) can accumulate in injured sensory neurons and alter their function.

d. True
b. False

8. Nerve injuries associated with the development of NeP alter the expression of neuropeptides and their receptors

a. True
b. False

9. Peripheral nerve injury triggers central sprouting of myelinated afferents from the deeper layers of the dorsal horn into the superficial layers resulting in nonpainful stimuli activating the spinothalamic tract

a. True
b. False

10. Prolonged glutamatergic neurotransmission, most notably that involving NMDA receptors, can result in significant damage-associated changes in the anatomy of the spinal cord.

a. True
b. False

Evaluation of Module 4

As part of the CSA Educational Programs Division's ongoing efforts to offer continuing medical education, the following evaluation of this program is requested. This is a useful tool for the EPD in preparing future CME programs.

1. How well were the learning objectives of this program met?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

2. How relevant was the information in this program to your clinical practice?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		

3. How would you rate this program overall?

Very Well	5	Above Average	4
Average	3	Below Average	2
Not Well at All	1		