Recent Advances in Understanding Pain Mechanisms Provide Future Directions for Pain Management

Christine Miaskowski, RN, PhD, FAAN

Purpose/Objectives: To review current knowledge of neurobiologic mechanisms that generate and maintain chronic pain and to explain how they might be applied in targeting treatment of chronic, inflammatory, and neuropathic pain syndromes.

Data Sources: Published research, literature review articles, and abstracts as well as national statistics.

Data Synthesis: Treatment for chronic pain associated with cancer and other syndromes remains suboptimal and falls significantly short of clinical needs. Data highlight the role that multiple neurobiologic mechanisms play in modulating and maintaining pain at various levels of the central and peripheral nervous systems. Novel agents have been developed that use a more targeted approach to treating chronic pain.

Conclusions: A growing body of evidence highlights the critical role that neurobiologic mechanisms play in the initiation and maintenance of chronic pain. A thorough understanding of these mechanisms ultimately may result in targeted treatment approaches that focus on the central and peripheral mechanisms involved in mediation of chronic, inflammatory, and neuropathic pain syndromes.

Implications for Nursing: A majority of patients undergoing active treatment for cancer experiences unrelieved pain. By gaining a better understanding of the mechanisms that generate and maintain chronic pain, oncology nurses can promote targeted pain management strategies that incorporate novel therapeutic agents.

Key Points . . .

- Pain is an evolutionary warning system activated in response to potential or actual tissue damage, but it often becomes a chronic medical condition that offers no biologic advantage.
- A growing body of evidence suggests that pain is not a passive consequence of defined peripheral input but rather an active process that results from activation of complex mechanisms that interact at many different levels of the neuraxis.
- Neuronal plasticity, the processes by which the central nervous system responds to shifts in nociceptive pain thresholds and responsiveness, essentially characterizes the development of various chronic pain syndromes.
- Ultimately, effective pain treatments will depend on thoroughly elucidating the neurobiologic mechanisms that generate and maintain chronic pain and the development of therapeutic agents that target specific receptors, neurotransmitters, and sites involved in its mediation.

Pain represents a fundamental protective mechanism or warning system that is activated in response to potential or actual tissue damage. Although pain (and the capacity to experience it) commonly is considered an essential protective component in the evolutionary survival drive, it also can become a chronic medical condition that offers no biologic advantage.

Chronic pain represents one of the most disabling and costly afflictions in North America, Europe, and Australia (Harstall & Ospina, 2003). Recent data demonstrate that the prevalence of chronic pain in the general populations of developed countries ranges from 10%–55% (Harstall & Ospina). In the United States, approximately 9% of the adult population (American Pain Society, 2003) (approximately 20 million adults [U.S. Census Bureau, 2003]) suffers from noncancer-related chronic pain. Importantly, this 9% increases to an estimated 70%–90% when patients with advanced cancer are surveyed (Caraceni & Portenoy, 1999; Murray, Grant, Grant, & Kendall, 2003; Potter, Hami, Bryan, & Quigley, 2003). Overall, the economic burden of chronic pain in the United States is estimated to be as high as $100 billion (Nitu, Wallihan, Skljarevski, & Ramadan, 2003), of which almost two-thirds (i.e., $61 billion) can be attributed to lost time in work productivity (Stewart, Ricci, Chee, Morganstein, & Lipton, 2003).

Although various etiologic factors (e.g., cancer, joint syndromes, herpes zoster) play a critical role in the initiation of chronic pain, the complex interaction of multiple mechanisms at many different levels of the neuraxis produces actual pain symptoms (Woolf & Decosterd, 1999; Woolf & Max, 2001). A growing body of evidence suggests that pain is not a static or passive consequence of defined peripheral input but rather an active process that is generated partially in the peripheral

Christine Miaskowski, RN, PhD, FAAN, is a professor and chair of the Department of Physiological Nursing at the University of California, San Francisco. She also is an advisor to Cephalon, Janssen Pharmaceuticals, Ligand Pharmaceuticals, Merck & Co., Inc., and Purdue Pharma, LP. *(Submitted December 2003. Accepted for publication April 2, 2004.)* *(Mention of specific products and opinions related to those products do not indicate or imply endorsement by the* Oncology Nursing Forum *or the Oncology Nursing Society.)*

Digital Object Identifier: 10.1188/04.ONF.S4.25-35

nervous system (PNS) and partially in the central nervous system (CNS) and then subsequently transferred to a pain center within the brain (Woolf & Salter, 2000). Shifts in the threshold for pain and responsiveness to stimuli (termed "neuronal plasticity") may result in exaggerated pain sensitivity or hypersensitivity and, consequently, chronic inflammatory or neuropathic pain (Scholz & Woolf, 2002; Woolf & Mannion, 1999).

Clearly, a greater understanding of the neurobiologic mechanisms that generate and maintain chronic pain will facilitate the development of novel therapeutic targets and promote effective and innovative pain management strategies. For patients with cancer who develop inflammatory pain (e.g., pain from bone metastases) or neuropathic pain (e.g., postmastectomy pain, chemotherapy-induced neuropathy, postherpetic neuralgia [PHN]), this may entail the use of rational polypharmacy targeted at the underlying biologic mechanisms. The key to rational polypharmacy is understanding the specific mechanisms that contribute to the chronic pain problem and having agents available that target each mechanism. At this point, multiple types of pain medications should be used carefully, particularly in older adults. Routine assessments should be done to evaluate the potential additive or synergistic effects of using analgesic medications that act on different pain mechanisms. Equally important is that patients should be monitored for unwanted side effects that may occur with the use of multiple analgesic medications.

Differences Between Acute and Chronic Pain

Pain results from diverse mechanisms that occur either solely in one condition or are expressed in multiple syndromes at different times (Scholz & Woolf, 2002). Pain is characterized as either acute or chronic. Although pain is associated with emotional, cognitive, and learned behaviors, two anatomic sites are essential for pain processing: the primary sensory neurons and the dorsal horn of the spinal cord, where sensory neurons make synaptic connections (Basbaum & Woolf, 1999).

Nociceptive pain (acute pain) is initiated when intense or damaging noxious stimuli activate high-threshold peripheral terminals (i.e., nociceptors) of primary sensory neurons. High-threshold receptors respond to mechanical stimuli within the noxious range, such as noxious heat, intense pressure, or irritant chemicals (Regan & Peng, 2000). Once activated, nociceptors convert environmental stimuli into electrochemical signals (i.e., action potentials) that are conducted to the dorsal horn and transmitted along the rest of the spinal cord to the CNS, where the sensation of pain is experienced (see Figure 1).

Nociceptors are a heterogeneous group of neurons that differ on a variety of factors ranging from the neurotransmitters and receptors they contain to their response to noxious stimuli and conduction of action potentials following activation (Stucky, Gold, & Zhang, 2001). They generally are classified by type: A fiber nociceptors (Aδ, Aδ) conduct action potentials rapidly and mediate fast, prickly pain, whereas C fiber nociceptors conduct action potentials slowly and mediate slow, burning pain (Stucky et al.). Roughly 70% of all nociceptors are C fibers (Stucky et al.). Because of the presence of high-threshold, specialized mechanisms on their peripheral terminals, C fiber and Aδ fiber nociceptors are involved predominantly in transducing (i.e., converting) external noxious stimuli into electrical activity (Mannion & Woolf, 2000). On the other hand, Aβ fibers are activated by low-intensity stimulation, such as touch or vibration, and do not evoke pain sensations under normal circumstances (Mannion & Woolf).

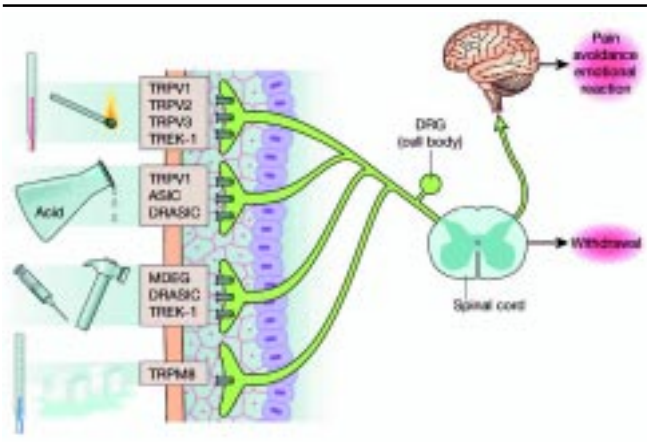


Figure 1. Nociceptive Pain

Note. From "Can We Conquer Pain?" by J. Scholz and C.J. Woolf, 2002, *Nature Neuroscience, 5*(Suppl.), p. 1062. Copyright 2002 by Nature Publishing Group. Reprinted with permission.

Under acute pain situations, in which intense or noxious stimuli are localized, brief, and nondamaging, nociceptor response is stable and the pain sensation is reflective of the intensity, localization, and duration of the stimulus (Mannion & Wolf, 2000; Woolf & Decosterd, 1999). However, with chronic pain, responses are modified substantially and the functional activity of neurons in the pain pathways increases. Repeated stimulation or modification in the chemical milieu surrounding the nociceptors, particularly during inflammation, leads to hypersensitivity at the site of damage and in the surrounding areas (Woolf & Decosterd). Inflammatory pain (which is initiated when damaged tissue and inflammatory and tumor cells release a variety of chemical mediators that activate or modify the stimulus response properties of nociceptors) (Scholz & Woolf, 2002) and neuropathic pain (which results from lesions that arise in the nervous system or dysfunctions that occur as a result of neurologic deficits, such as carpal tunnel syndrome or stroke) are characterized by this hypersensitivity. Pain may appear (a) to arise spontaneously and without any apparent peripheral stimulus (i.e., stimulus-independent hypersensitivity), (b) in an exaggerated and prolonged fashion to noxious stimuli (i.e., hyperalgesia), or (c) in response to innocuous or nonnoxious stimuli that would not normally begin to produce pain (i.e., allodynia).

Making Sense of Neuronal Plasticity: Hypersensitivity and Chronic Pain

Neuronal plasticity, the neurobiologic processes by which nervous system changes modulate responses to any stimulus, essentially characterizes the development of chronic pain syndromes (Scholz & Woolf, 2002). Two general forms of neuronal plasticity are responsible for pain hypersensitivity: modulation and modification (Woolf & Salter, 2000). **Modulation** represents reversible changes in the excitability (i.e., the response) of primary sensory and dorsal horn neurons (Woolf & Salter). Modulation is mediated by alterations in the functional

properties and expression of receptors and ion channels that are responsible for generating currents in response to noxious stimuli. Conversely, **modification** represents long-lasting changes in the expression of neurotransmitters, receptors, and ion channels and in the structure, connectivity, and survival of neurons (Woolf & Salter). These alterations grossly modify and distort normal stimulus responses and result in abnormal responses, such as hyperalgesia and allodynia.

Modulation-Driven Peripheral Sensitization

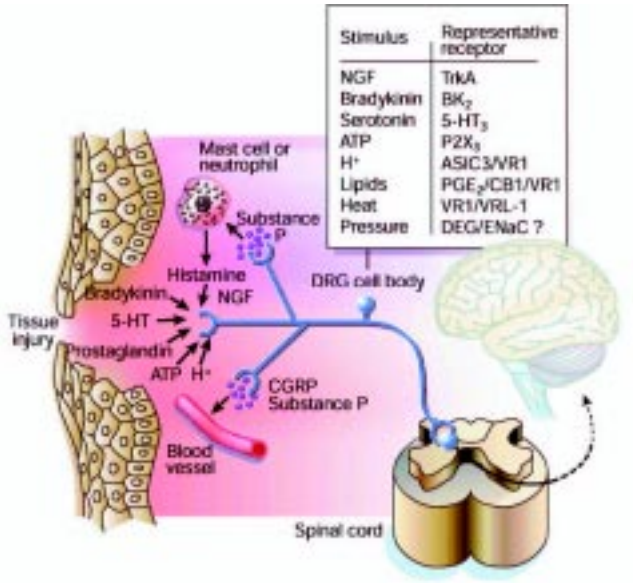
Modulation can occur in the peripheral and central terminals of nociceptors. In the peripheral pain pathways, modulation is triggered by exposure to agents that reduce the degree of stimulus required to initiate or trigger an action potential discharge (i.e., depolarization) (Woolf & Salter, 2000). This effect is referred to as sensitization, or a lowering of the excitability threshold of the nociceptor. The onset of peripheral sensitization is rapid, and the changes are substantial (Bolay & Moskowitz, 2002). Among the most important agents directing peripheral sensitization are mediators of tissue damage and inflammation (collectively known as the inflammatory soup) that are released from primary sensory neurons during tissue injury or by inflammatory and nonneuronal cells and vascular tissue (e.g., leukocytes, platelets, vascular endothelium, mast cells) (see Figures 2 and 3).

Peripheral sensitization is thought to reflect changes in the kinetics of transduction ion channels (which are responsible for detecting stimuli) and specific ion channels in nociceptor terminals that determine excitability and initiate the conduction of action potentials (Woolf & Decosterd, 1999). Although some inflammatory mediators directly activate nociceptor terminals, others sensitize them by reducing their transduction thresholds (Basbaum & Woolf, 1999). One of the many molecules expressed by nociceptors that has been implicated recently in this action is the tetrodotoxin- (TTX-) resistant sodium channel. TTX is a potent puffer fish toxin; sodium channels insensitive to tetrodotoxin are found only on nociceptor sensory neurons (Woolf & Mannion, 1999). Following phosphorylation, TTX affects the rate of activation or inactivation and increases the magnitude of the sodium current. This facilitates a higher rate of action potential conduction out of the terminal and into the CNS (Basbaum & Woolf; Woolf & Salter, 2000). The TTX-resistant sodium channel is mediated by activation of intracellular kinases and increases in intracellular calcium.

Vanilloid receptors (e.g., VR1, VRL1) are temperature-sensitive ion channels that participate in the sensation of thermal and inflammatory pain (Bolay & Moskowitz, 2002). They also play an important role in peripheral sensitization. Phosphorylation of VR1, which is dependent on activation of protein kinase C or tyrosine kinases, potentiates the activity of certain ligands, such as proinflammatory bradykinin (Bolay & Moskowitz).

- Bradykinin
- Serotonin
- Histamine
- Prostaglandins
- Leukotrienes
- Cytokines
- Nitric acid
- Protons
- Neurotrophic growth factors

Figure 2. Inflammatory Mediators Contributing to Modulation-Driven Peripheral Sensitization



ATP—adenosine triphosphate; CGRP—calcitonin gene-related peptide; DRG—dorsal root ganglion; NGF—nerve growth factor

Figure 3. Modulation-Driven Peripheral Sensitization to Inflammation

Note. From "Pain" by A.I. Basbaum and C.J. Woolf, 1999, *Current Biology, 9*(12), p. R430. Copyright 1999 by Nature Publishing Group. Reprinted with permission.

Modulation-Driven Central Sensitization

In the central pain pathways, modulation is triggered by input from peripheral nociceptors after they have been affected by noxious stimuli. This results in an enhanced responsiveness of pain transmission neurons in the CNS and a loss in the ability of the CNS to modulate and inhibit pain signals, meaning that low-threshold afferent input is maintained well after the initiating stimulus (Woolf & Salter, 2000). Termed central sensitization, this process is driven by activation of intracellular signal transduction cascades, an increase in neuronal membrane synaptic excitability, and a loss of pain inhibition.

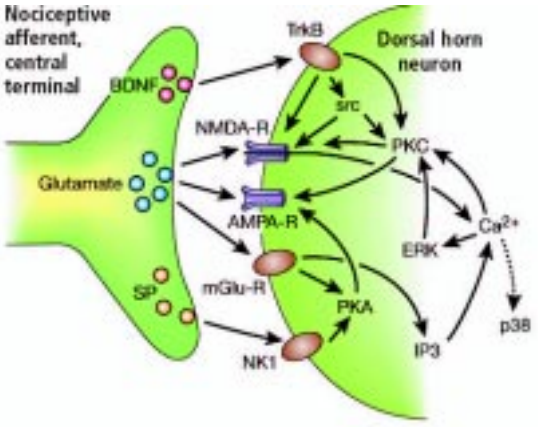
Although many receptors are involved in central sensitization, a key "culprit" is the N-methyl-D-aspartate (NMDA) receptor, which is critical for the development of hyperalgesia and the maintenance of pathologic pain following inflammation or nerve injury (Bolay & Moskowitz, 2002). NMDA receptors are complex molecular entities that mediate responses to glutamate and aspartate. They generally are inactive during normal pain processing, in which glutamate largely acts on alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors instead. However, during pathologic conditions, sustained and intense noxious stimulation results in the release of glutamate from primary afferent synaptic terminals, and this causes a rapid depolarization in dorsal horn neurons that eventually leads to action potential discharge (Woolf & Mannion, 1999). In turn, depolarization causes the NMDA ion channels, which normally are blocked, to open and allow an influx of calcium into the cell. Increases

in intracellular calcium directly activate protein kinases (Woolf, 1993). Neuropeptides, including substance P and brain-derived neurotrophic factor (BDNF), also are released and contribute directly to this action. Ultimately, NMDA receptors undergo phosphorylation, which increases neuronal excitability and changes the way that the neurons will respond to subsequent input (Woolf & Mannion, 1999) (see Figure 4). The implication is great: Not only does central sensitization reduce the threshold at which dorsal horn neurons are activated and increase their response to suprathreshold input, but it also increases the size of the field in which dorsal field neurons respond to stimuli (Mannion & Woolf, 2000), meaning that pain sensitivity extends well beyond the site of injury (Costigan & Woolf, 2002).

Central sensitization also results in a long-lasting reduction of pain inhibition mechanisms. Inhibition is regulated by a variety of transmitters and receptors that are expressed in the dorsal horn (e.g., gamma-aminobutyric acid [GABA], opioid, cannabinoid, glycine). Disinhibition requires activation of NMDA receptors and increases in postsynaptic intracellular calcium levels (Woolf & Salter, 2000) and is caused by decreased activation of neurons, downregulated receptors and their transmission, and cell death (Woolf & Max, 2001) (see Figure 5). A loss of inhibitory control may occur at many different levels along the CNS pathway and contributes to spontaneous firing by dorsal horn neurons or exaggerated response to noxious stimuli (Regan & Peng, 2000).

Modification in Chronic Pain: Inflammation

Systemic processes that contribute to modification include alterations in the expression of genes, changes in the phenotypic expression of nerves, and PNS or CNS denervation (i.e., modification of nerves or nerve supply, possibly as a result of noxious damage). In adults, neurotrophins such as nerve growth factor and its tyrosine kinase receptor trkA and BDNF and its tyrosine kinase receptor trkB maintain neuronal phenotypes. Any increase or decrease (such as that following inflammation or peripheral axon damage, respectively) can initiate alterations in the expression of neurotransmitters, synaptic neuromodulators, ion channels, receptors, and proteins (Woolf & Salter, 2000). Modification in inflammation generally results in an upregulation of VR1 and the sodium ion channel SNS (meaning sensory neuron specific) and may lead to an increase in neural sensitivity to inflammatory mediators and susceptibility to peripheral sensitization (Woolf & Salter). Notably, a phenotypic shift also occurs, and Ab fiber-type neurons adopt a C fiber phenotype and begin to express the neuropeptides substance P and BDNF. This change contributes to an increased capacity of tactile, low-threshold stimuli to generate hyperexcitability typically associated with nociceptive input and to induce central sensitization (Woolf & Salter; Bolay & Moskowitz, 2002).



AMPA—alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF—brain-derived neurotrophic factor; ERK—extracellular signal regulated kinase; NK1—neurokinin receptor 1; NMDA—N-methyl-D-aspartate; PKA—protein kinase A; PKC—protein kinase C; SP—substance P

Figure 4. Modulation-Driven Central Reorganization

Note. From "Can We Conquer Pain?" by J. Scholz and C.J. Woolf, 2002, *Nature Neuroscience, 5*(Suppl.), p. 1065. Copyright 2002 by Nature Publishing Group. Reprinted with permission.

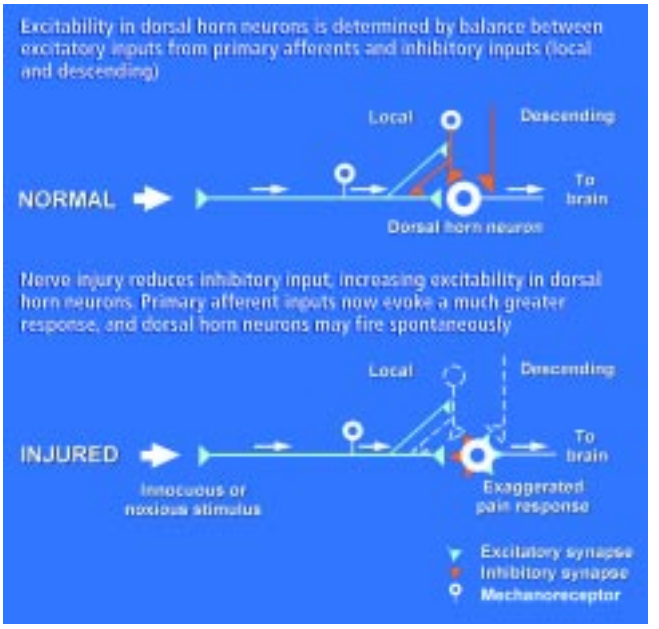


Figure 5. Disinhibition in Which Nerve Injury Reduces Inhibition in Dorsal Horn Through Various Mechanisms

Note. From "Neuropathic Pain: Etiology, Symptoms, Mechanisms, and Management," by C.J. Woolf and R.J. Mannion, 1999, *Lancet, 353,* p. 1964. Copyright 1999 by Elsevier. Reprinted with permission.

Modification in Chronic Pain: Peripheral Nerve Injury

Importantly, peripheral nerve injury leads to complex changes in sensory neurons. In contrast to the changes observed after inflammation (e.g., increased expression of VR1 and SNS), declines in VR1 and SNS have been observed following nerve damage (Woolf & Salter, 2000). Nerve injury also causes synaptic reorganization, whereby the low threshold Ab fiber-type neurons, whose axons normally terminate in the deep dorsal horn (i.e., laminae III–VI) (Mannion & Woolf, 2000), begin to grow into lamina II, which normally receives only nociceptive information from C fibers that terminate there (see Figure 6). The functional relevance of this sprouting is that new synaptic connections allow lamina II, which typically receives input from nociceptors, to now receive input from non-noxious, low-threshold stimuli (Woolf & Mannion, 1999; Woolf, 1993). This change results in mechanical

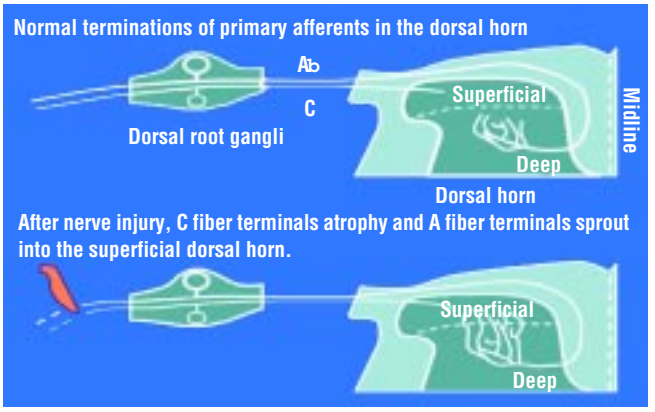


Figure 6. Nerve Injury and Central Reorganization

Note. From "Neuropathic Pain: Etiology, Symptoms, Mechanisms, and Management," by C.J. Woolf and R.J. Mannion, 1999, *Lancet, 353,* p. 1962. Copyright 1999 by Elsevier. Reprinted with permission.

allodynia (i.e., what once was interpreted as touch now is misinterpreted as pain). The changed synaptic connectivity also may play an important role in the intractable nature of many neuropathic pain syndromes (Woolf & Salter).

Modification, Pain Transmission Neurons, and Inhibitory Controls

At its most fundamental level, the prevailing pain model is based on the premise that pain arises from the relay of signals from primary sensory neurons to the brain that are subject to certain modulatory mechanisms, including the body's endogenous inhibitory controls, that act essentially as "bouncers" to keep out undesirable inputs and shut down pain as necessary for survival (Costigan & Woolf, 2002). Inhibitory controls also may descend from the brain (see Figure 6). Regardless, certain excitatory mechanisms may sensitize central neurons and allow "uninvited gate crashers" into the "pain party" (Costigan & Woolf).

Data suggest that a series of intracellular molecular switches may facilitate or suppress pain transmission by acting on these inhibitory controls (Costigan & Woolf, 2002) (see Figure 7). The expression of the transmitter dynorphin is important particularly in this regard. At high concentrations, dynorphin appears to activate the NMDA receptor and facilitate pain by inducing central sensitization. It also may reduce inhibitory neuron activity to facilitate an overall increase in nociceptor excitatory activity, possibly through its actions on kappa receptors. Conversely, dynorphin expression that results in a reduced input to neurons is responsible for decreased pain transmission that promotes analgesia (Costigan & Woolf).

Dynorphin expression is mediated, at least partially, by activation of the mitogen-activated protein kinase (MAPK) cascade (Woolf & Salter, 2000). MAPK appears to be a master switch for transcriptional changes that occur in dorsal horn neurons following inflammation and nerve injury (Woolf & Salter) and central sensitization (Ji & Woolf, 2001). Other mechanisms that contribute to disinhibition include reduction of GABA and its receptors, downregulation of opioid receptors, and the death of interneurons in lamina II, many of which are inhibitory (Woolf & Mannion, 1999).

Novel Approaches and Agents to Treat Chronic Pain

Despite research advances that continue to elucidate the molecular and cellular mechanisms underlying chronic pain, therapy has remained suboptimal for many patients. Not only is treatment often partially effective, but it also may be associated with significant side effects or potential abuse issues (Scholz & Woolf, 2002). For patients with cancer in particular, improved tumor control achieved by increased use of advanced therapeutics has led to increased survival. As cancer becomes a chronic disease, patients will live longer with chronic pain.

A novel approach to treating chronic pain is based on targeting the mechanisms of central and peripheral sensitization through selected receptors, enzymes, or sites involved in its mediation (Nitu et al., 2003) (see Table 1). Although reviewing all compounds in advanced and medium phases of clinical development is beyond the scope of this article, a select few are highlighted based on their proposed mechanisms of action.

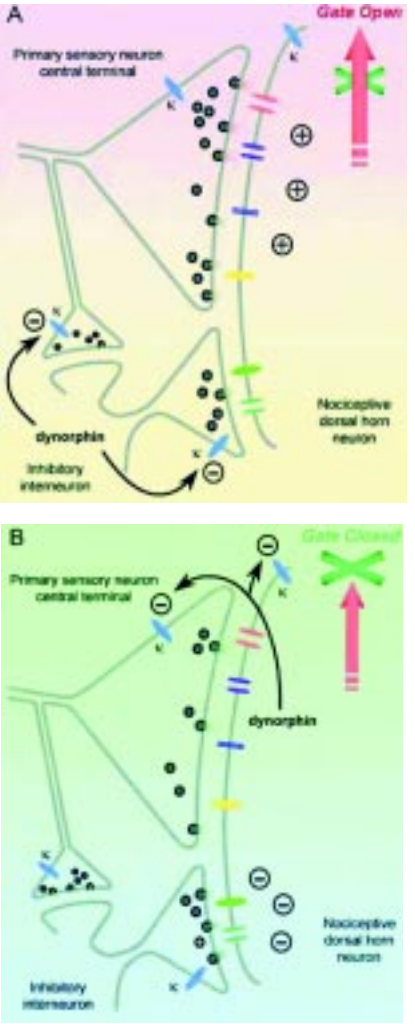


Figure 7. Molecular Switches Facilitate or Suppress Pain Transmission

Note. From "No DREAM, No Pain: Closing the Spinal Gate," by M. Costigan and C.J. Woolf, 2002, *Cell, 108,* p. 299. Copyright 2002 by Elsevier. Reprinted with permission.

Table 1. Pharmacologic Classes and Targets That May Be Implicated in Persistent Pain

Parameter	Classification	Type
Receptor		
Glutamate	Metabotropic glutamate receptors ($mGluR_1$–$mGluR_8$)	G protein coupled
	Ionotropic glutamate receptors (glutamate site, N-methyl-D-aspartate-glycine site, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, kainite, other)	Ionotropic
Serotonin (5-HT)	5-HT_1 receptor	G protein coupled
	5-HT_2 receptor	G protein coupled
	5-HT_3 receptor	Ionotropic
	5-HT_4 receptor	G protein coupled
	5-HT_5 receptor	Unknown
	5-HT_6 receptor	G protein coupled
	5-HT_7 receptor	G protein coupled
Vanilloid	Vanilloid receptor 1	Ionotropic
Cannabinoid (CB)	CB_1 receptor	G protein coupled
	CB_2 receptor	G protein coupled
Adenosine (A)	A_1 receptor	G protein coupled
	A_{2A} receptor	G protein coupled
	A_{2B} receptor	G protein coupled
	A_3 receptor	G protein coupled
Acetylcholine (Ach)	Muscarinic Ach receptors (M_1–M_5)	G protein coupled
	Nicotinic Ach receptors	Ionotropic
Opioid	m-opioid receptor	G protein coupled
	d-opioid receptor	G protein coupled
	k-opioid receptor	G protein coupled
Gamma-aminobutyric acid (GABA)	$GABA_A$ receptor	Ionotropic
	$GABA_B$ receptor	G protein coupled
	$GABA_C$ receptor	Ionotropic
Adrenergic	a_1-adrenoceptors (1A, 1B, 1D)	G protein coupled
	a_2-adrenoceptors (2A–2D)	G protein coupled
	b-adrenoceptors	G protein coupled
Kinins	Neurokinin receptors (NK_1–NK_3)	G protein coupled
	Bradykinin receptors (BK_1,BK_2)	G protein coupled
	Cholecystokinin receptors (CCK_A, CCK_B)	G protein coupled
Histamine (H)	H_1 receptor	G protein coupled
	H_2 receptor	G protein coupled
	H_3 receptor	G protein coupled
	H_4 receptor	G protein coupled
Melanocortin (MC)	MC1 receptor	G protein coupled
	MC2 receptor	G protein coupled
	MC3 receptor	G protein coupled
	MC4 receptor	G protein coupled
	MC5 receptor	G protein coupled
	MC6 receptor	G protein coupled
Enzyme		
Cyclooxygenase (COX)	COX-1	Not available (NA)
	COX-2	NA
	COX-3	NA
Kinase	Protein kinases	NA
	Tyrosine kinases	NA
NAALADase	NA	NA
Nitric oxide synthase (NOS)	Endothelial NOS	NA
	Inducible NOS	NA
	Neuronal NOS	NA

Note. From "Emerging Trends in the Pharmacotherapy of Chronic Pain," by A.N. Nitu, R. Wallihan, V. Skljarevski, and N.M. Ramadan, 2003, *Expert Opinion on Investigational Drugs, 12,* p. 546. Copyright 2003 by Ashley Publications. Reprinted with permission.

Central Mechanisms of Inflammatory Pain and Molecular Targets: Focus on Cyclooxygenase and Lipoxygenase

Pain that occurs during inflammation is related to an increase in noxious inputs peripherally and to central sensitization (Bolay & Moskowitz, 2002). Not only do inflammatory cells trigger sensitization of primary afferent neurons in the periphery, but they also produce chemical signals that penetrate the CNS and generate cyclooxygenase (COX) (Bolay & Moskowitz). COX is involved intricately in the metabolism of the lipid messenger arachidonic acid that synthesizes proinflammatory prostanoid products, most notably prostaglandin E_2 (PGE_2). Prostaglandins probably are the best characterized sensitizing agents and mediators of inflammatory pain. PGE_2, in particular, contributes to peripheral sensitization by binding to certain receptors (known as G protein-coupled receptors) that increase levels of cyclic adenosine monophosphate (AMP) within nociceptors (Julius & Basbaum, 2001). Activation of the cyclic AMP pathway can result in increased signaling and synaptic transmission. Data also suggest that COX products are present in the spinal cord and interact with receptors on central terminals of nociceptors. This implies that COX antagonists may exert pain control by modulating nociception in peripheral and central sites (Julius & Basbaum). However, COX inhibition can be a double-edged sword.

Two COX enzymes, COX-1 and COX-2, comprise the COX pathway and contribute to inflammation and the synthesis of prostaglandins (see Figure 8). The COX-1 enzyme is constitutive (always "on" in most normal tissue), synthesizing prostaglandins necessary for a variety of physiologic functions, including the maintenance of normal renal function and protection of the gastrointestinal mucosa. Nonsteroidal anti-inflammatory drugs have been linked to significant renal and gastrointestinal adverse effects primarily because of nonselective COX inhibition, which includes inhibition of COX-1. The COX-2 enzyme is undetectable in most normal tissue, but its expression is induced at inflammatory sites by growth factors, cytokines, tumor promoters, and other agents (Subongkot, Frame, Leslie, & Drajer, 2003). COX-2 participates mostly in the synthesis of proinflammatory prostanoids involved in the mediation of inflammation and, therefore, occurs only with tissue injury (Nitu et al., 2003). The COX-1-sparing characteristics of selective COX-2 antagonists facilitate inhibition of inflammation while preserving the COX-1 role in maintaining

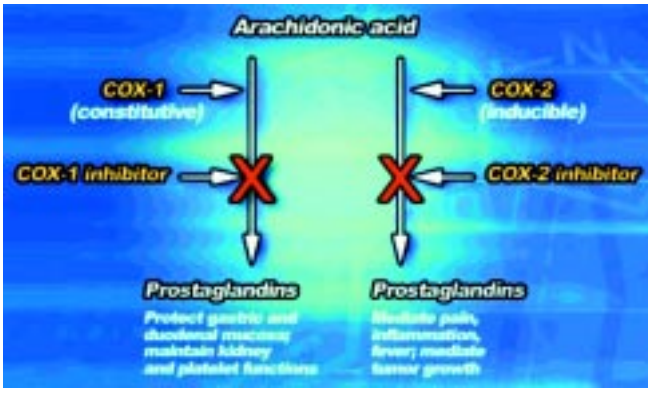


Figure 8. Cyclooxygenase (COX) Function

vascular, renal, and gastric homeostasis, thereby minimizing adverse effects (Nitu et al.).

The second major pathway involved in peripheral nociceptor sensitization is the lipoxygenase (LOX) pathway (Miaskowski, 2001). The LOX pathway plays a critical role in inducing the synthesis of proinflammatory mediators such as interleukin-8 and platelet activating factor (Skelly & Hawkey, 2003). LOX forms hydroperoxyeicosatetranoic acid compounds that are metabolized into leukotrienes. One in particular, 5-LOX, converts arachidonic acid to leukotrieneA4. In certain cell populations, leukotrieneA4 is further metabolized to leukotrieneB4, whose generation at the site of tissue injury plays an important role in recruiting proinflammatory mediators. These proinflammatory mediators contribute to the inflammatory soup and increase pain.

Selective Cyclooxygenase/Cyclooxygenase-Lipoxygenase Antagonists in the Development of Cyclooxygenase-189

COX-189 (lumiracoxib) is a second-generation selective COX-2 inhibitor currently approved in the United Kingdom for symptomatic treatment of osteoarthritis (100–200 mg per day) and relief of moderate to acute pain associated with primary dysmenorrhea, dental surgery, and orthopedic surgery. Theoretically, second-generation COX-2 antagonists should address any lingering doubts about the positive effects of the COX-2 antagonists on the gastrointestinal system as well as potential cardiovascular toxicities (the latter have not yet been completely characterized in terms of COX-2 antagonists as a class).

The safety profile of COX-189 appears to be favorable, with results of an initial phase II trial that compared 200 mg or 400 mg per day of COX-189 to celecoxib 200 mg per day or ibuprofen 800 mg three times daily in 1,042 patients with osteoarthritis over a three-month period; COX-189 demonstrated superior safety and gastrointestinal tolerability compared to ibuprofen and a similar profile as celecoxib (Hawkey et al., 2003). Significant differences were observed between COX-189 and ibuprofen in terms of the rate of gastroduodenal ulcers (4.3% and 4.0% versus 15.7% for COX-189 200 mg and 400 mg and ibuprofen 800 mg, respectively, $p < 0.01$) and in treatment-related discontinuations (6.8% and 5.0% versus 12.7%, respectively, $p < 0.01$). Early data comparing the efficacy of COX-189 (50 mg twice daily to 400 mg twice daily) to diclofenac (75 mg twice daily) or placebo in 583 patients with osteoarthritis treated over four weeks also were highly favorable, with results demonstrating a treatment response of 20% reduction in pain intensity (as measured by visual analog scale) comparable to that observed with diclofenac (Moore, Alberighi, Gitton, Sloan, & Gimona, 2003).

More recent data from a 39-week extension trial of patients with primary knee osteoarthritis comparing COX-189 200 mg per day and 400 mg per day to celecoxib 200 mg per day (following a 13-week placebo controlled trial in which 1,702 patients were randomized) concurred and demonstrated long-term pain relief and improved functional status. At a six-month follow-up, patients who were randomized to COX-189 200 mg per day demonstrated superior pain reduction compared to celecoxib 200 mg per day, and both doses were superior to celecoxib for patients' global assessment of disease (10.25 mm and 10.49 mm differences for 200 mg and 400 mg, respectively, $p < 0.05$) (Schell et al., 2003). At nine months, efficacy among the agents was similar. Safety and tolerability profiles were similar among the groups. Importantly, COX-189 reportedly does not affect platelet aggregation, which may translate into a reduced risk of bleeding complications (Nitu et al., 2003). Final data from an ongoing study assessing efficacy and tolerability of COX-189 versus ibuprofen and naproxen in 18,000 patients should elucidate its long-term gastrointestinal and cardiovascular toxicity potential.

ML-3000 (licofelone) represents an emerging category of agents known for their dual COX/LOX inhibition. The underlying rationale for the dual mechanism of action is to equally inhibit the synthesis of the proinflammatory mediators prostaglandin and 5-LOX while avoiding gastrointestinal side effects. COX/LOX inhibition also might offer an advantage not observed with current osteoarthritis treatments in terms of regulation of renal function and blood pressure.

In a 12-week trial comparing the efficacy of ML-3000 200 mg twice daily to celecoxib 200 mg per day in 608 patients with knee osteoarthritis, ML-3000 treatment resulted in significant mean changes in Western Ontario and McMaster Universities Arthritis Index pain scores from baseline that were equivalent to celecoxib treatment (34.7 mm mean change for 77.2% of responders versus 36.6 mm mean change for 77.8% of responders using ML-3000 or celecoxib, respectively) (Pavelka, Bias, Buchner, Lammerich, & Schulz, 2003). ML-3000 treatment also was associated with superior tolerability (i.e., side effects rates of 31.9% versus 36.4% for ML-3000 and celecoxib, respectively) and less frequent peripheral edema (2% versus 5.9%, respectively).

This favorable tolerability profile was borne out in two additional studies in which the gastrointestinal tolerability of twice the fully active dose ML-3000 (i.e., 400 mg twice daily) was studied in patients with osteoarthritis of the knee and compared to that of naproxen 500 mg twice daily for either 6 weeks (study A) or 26 weeks (study B). In study A, all patients also received concomitant enteric-coated aspirin 81 mg per day (Buchner, Bias, & Lammerich, 2003). In both studies, ML-3000, even at twice the normal therapeutic dose, had a significantly superior tolerability profile compared to naproxen, with the cumulative incidence of gastroduodenal ulcers and mucosal integrity of the gastrointestinal mucosa demonstrably worse in naproxen-treated patients (study A: 5.6% versus 25.6%, respectively, $p = 0.26$, gastroduodenal modified Lanza scores of 1.37 versus 3.21, respectively; study B: 2.4% versus 23.0%, $p < 0.01$, 1.37 versus 3.78, respectively) (Buchner et al.). Coadministration of low-dose aspirin did not result in any demonstrably higher ulcer rate, thereby demonstrating good gastrointestinal tolerability. In a second in vitro trial investigating the effect of ML-3000 on primary hemostasis compared to results observed with aspirin, ML-3000 was shown to diminish platelet aggregation and significantly reduce platelet adhesion, thereby supporting a lower thrombotic potential (Hernandez et al., 2003). Further research will answer questions regarding how these findings correspond to clinical practice.

Central Mechanisms of Neuropathic Pain and Molecular Targets

Neuropathic pain is a significant problem for a broad array of patients with cancer. Neuropathic pain results from damage to or inflammation of the nervous system that occurs either peripherally or centrally; it may result in paresthesias (abnormal

perception of a nonpainful nature), dysesthesias (abnormal pain perception), continuous burning pain, and paroxysmal shooting or lacinating pain.

After nerve injury, sodium channels accumulate to form the foci of hyperexcitability that result in ectopic action potential discharge in axonal terminals (Regan & Peng, 2000). Spontaneous activity in Ab fibers, normally responsive only to innocuous stimuli, is responsible for sensory changes such as paresthesias and dysesthesias and for continuous burning pain in C fibers. Many sodium channel subtypes are expressed throughout the nervous system. Those that are TTX resistant are responsible for initiating action potentials, whereas those that are TTX sensitive have slower activation and inactivation kinetics and are implicated in pathologic pain (Woolf & Mannion, 1999).

Brief afferent inputs have the capacity to produce long-lasting changes in excitability (Woolf, 1993). In aggregate, C fiber-mediated synaptic potentials operate via glutamate, which, in turn, acts on NMDA receptors. NMDA activation results in a surge in intracellular calcium, activation of other dorsal horn receptors, and sustained depolarization. The release of protein kinases, substance P, and other neuropeptides leads to NMDA-receptor phosphorylation, removal of the magnesium block, and increased excitability. The end result (i.e., central sensitization) manifests itself as tactile, cold, and pinprick hyperalgesia and mechanical and cold allodynia (Woolf & Mannion, 1999).

Importantly, spontaneous activity in primary sensory neurons explains only part of the neuropathic pain paradigm. As mentioned, primary afferent activity is determined not only by excitatory input but also by inhibitory input that essentially acts as a "spinal gate." Peripheral nerve injury appears to reduce the amount of inhibitory control through reduction of GABA (an inhibitory transmitter in the dorsal horn) and downregulation of GABA and opioid receptors, which exist presynaptically on primary sensory neurons and postsynaptically on dorsal horn neurons around the C fiber terminal zone in lamina II. Inhibitory interneurons in lamina II also die after peripheral nerve injury. The resulting disinhibition increases the likelihood that dorsal horn neurons will fire spontaneously or in an exaggerated fashion (Woolf & Mannion, 1999).

Sodium channel antagonists: Cutaneous terminals of damaged, sensitized nociceptors are important sites for pain generation. Dysfunctional sodium channels, in particular, play an important role in depolarizing the excitable membrane. This may provide an explanation as to why local anesthetics that block voltage-gated channels and reduce aberrant ectopic firing are effective as analgesics (Gammaitoni, Alvarez, & Galer, 2003).

Lidoderm® (lidocaine patch 5%, Endo Pharmaceuticals Inc., Chadds Ford, PA), the first drug with a U.S. Food and Drug Administration-approved indication for the treatment of PHN, is comprised of a 10" x 14" nonwoven adhesive patch containing 700 mg of aqueous lidocaine. It can be cut to fit the dimensions of the painful skin area. Currently, approved dosing of the lidocaine patch is up to three patches applied to the painful area for up to 12 hours within a 24-hour period. Recent pharmacokinetic and pilot studies have demonstrated safety and tolerability of up to four patches applied for 18–24 hours (Endo Pharmaceuticals Inc., 2000; Gammaitoni et al., 2002, 2003). As the patch is applied, a low dose of lidocaine is diffused into the epidermis and dermis and reduces abnormal spontaneous and evoked activity of damaged afferent nerves via sodium channel blockade (Endo Pharmaceuticals Inc.). It acts locally on damaged peripheral nerves and soft tissue underlying the patch and produces analgesia without a loss of normal sensation. The patch also provides a barrier against mechanical stimulation and related allodynia.

Systemic absorption (3% ± 2%) from the lidocaine patch is minimal and directly proportional to the duration of application and the surface over which it is applied (Gammaitoni et al., 2003) (see Figure 9). Pharmacokinetic studies conducted in healthy volunteers, in which four patches were applied to the upper back for 24 hours per day for three consecutive days (study 1) or four patches were applied for either 24 hours per day or for every 12 hours per day for three consecutive days (study 2), demonstrated mean peak plasma concentrations at levels approximately 1/10–1/12 that needed for a therapeutic antidysrhythmic effect, despite repeated maximum daily dose applications (Gammaitoni & Davis, 2002; Gammaitoni et al., 2002, 2003).

The efficacy of the lidocaine patch 5% in the treatment of PHN has been examined in several randomized, controlled clinical trials and an open-label, nonrandomized study that assessed treatment impact in a "real-world" clinical practice setting (Galer, Jensen, Ma, Davies, & Rowbotham, 2002; Galer, Rowbotham, Perander, & Friedman, 1999; Katz, Gammaitoni, Davis, Dworkin, & the Lidoderm Patch Study Group, 2002; Meier et al., 2003; Rowbotham, Davies, Verkempinck, & Galer, 1996). The most recent randomized, double-blind, vehicle-controlled, crossover trial of 40 patients with various focal peripheral neuropathic pain syndromes (22 of whom had PHN) reported that 31% of patients had at least 50% reduction in ongoing pain intensity with seven days of lidocaine patch 5% treatment compared with 8.1% of patients during vehicle patch treatment. Based on these response rates, a number-needed-to-treat (i.e., number of patients that would need to be treated to see one positive response) was calculated at 4.4 (95% confidence interval, 2.5–17.5). The authors noted that this value is similar to those reported with other treatments for PHN: 4.0 (2.6–8.9) for tricyclic antidepressants, 2.7 (1.9–4.2) for opioids, 3.2 (2.4–5.0) or 5.0 (3.2–11.4) for

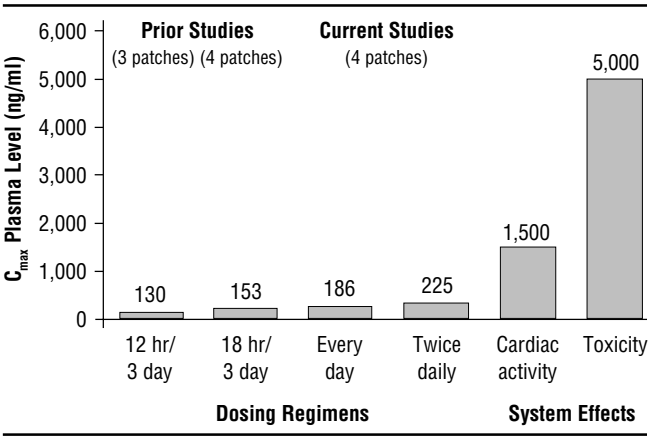


Figure 9. Pharmacokinetic Study Results at a Glance

Note. From "Safety and Tolerability of the Lidocaine Patch 5%, a Targeted Peripheral Analgesic: A Review of the Literature," by A.R. Gammaitoni, N.A. Alvarez, and B.S. Galer, 2003, *Journal of Clinical Pharmacology, 43,* p. 115. Copyright 2003 by Sage Publications, Inc. Adapted with permission.

gabapentin, and 5.3 (2.3–infinity) for topical capsaicin. This rigorously designed trial further underscores that the lidocaine patch 5% produces a degree of efficacy in peripheral neuropathic pain that is similar to other commonly used systemic agents while offering a distinct safety advantage (i.e., no systemic side effects) (Meier et al.).

In another study to assess the effectiveness of the lidocaine patch 5% in the treatment of refractory neuropathic conditions other than PHN, moderate pain relief was reported in 13 of 16 patients (81%) over a mean treatment duration of 6.2 weeks (Devers & Galer, 2000). Only one patient reported a side effect, a mild skin irritation. The efficacy of the lidocaine patch 5% alone or in combination with existing pain regimens is being explored in chronic pain types such as cervical spine pain, osteoarthritis, myofascial pain, postmastectomy pain, and chronic low back pain.

NMDA receptor antagonists: CNS 5161 is a selective, noncompetitive, NMDA antagonist currently in phase II clinical trials. It interacts with the NMDA receptor and ion channel sites to block glutamate (Walters, Bradford, Fischer, & Lees, 2002). Data from two phase I trials in male volunteers who received IV CNS 5161 demonstrated statistically significant reductions in perceived pain intensity compared to morphine or placebo (CeNeS Pharmaceuticals, 2003). In a dose escalation study, 32 healthy volunteers who received IV CNS 5161 infused over 15 minutes or placebo were observed for 24 hours and then received dose escalations ranging from 0.30–2 mg (Walters et al.). A dose-dependent increase in systolic and diastolic blood pressure and mean arterial pressure was observed, although all patients returned to baseline values within 24 hours after the drug was discontinued. Initial phase II data in 10 patients with chronic, intractable neuropathic pain also demonstrated significant pain relief and favorable tolerability. Thus far, common side effects associated with treatment include transient paresthesias or dysesthesias, light-headedness, and dizziness (Nitu et al., 2003).

AMPA/kainate receptor antagonists: LY-293558 is a selective AMPA/kainate receptor antagonist. In a small phase I trial, in which LY-293558 1.2 mg/kg was compared to IV lidocaine 2 mg/kg or ketamine 0.15 mg in two groups of six patients with lumbar monoradiculopathy, LY-293558 demonstrated significant analgesic activity for up to four hours, with 50% of patients reporting moderate to significant pain relief (Nitu et al., 2003).

Results of a phase II, randomized, controlled trial in 70 postoperative oral surgery patients receiving LY-293558 1.2 mg/kg or placebo demonstrated significant reductions (34%) in movement-evoked postoperative pain compared to placebo (Gilron, 2001). Preliminary data from another trial suggested that LY-293558 also might be effective in treating pain associated with migraine headaches (Gilron).

Tolerability data from phase I and II trials suggested that the most "striking" adverse event associated with LY-293558 treatment is hazy vision (Gilron, 2001). Typically described as "white clouds in the periphery that spare central vision," it appears to be associated with doses greater than 1 mg/kg and resolves within an hour of administration with no lasting effects. Other common adverse events include sedation and dizziness (Gilron).

The roles of different AMPA versus kainate receptors in producing chronic pain are not understood entirely. Moreover, an important clinical limitation of LY-293558 may be its apparent short duration of action. The results of ongoing research are expected to address both of these issues.

Mu opioid receptor agonists: Despite certain limitations (e.g., side effects, variable efficacy, abuse potential), opioids remain the gold standard for treatment of chronic cancer pain. Importantly, available data to facilitate effective selection and utilization of opioids have been lacking because few controlled studies have been performed and many pain subtypes remain unstudied (Rowbotham et al., 2003). Inconsistencies in trial methodology also have been noted.

Because "one size does not fit all" (i.e., efficacy is variable and related to patient, pain, and agent characteristics such as the proximity to the CNS lesion and stimulation of opiate system), new dosing strategies and formulations are needed. For example, a growing body of literature suggests that a key means of reducing the development of drug tolerance is to rotate opioids (Indelicato & Portenoy, 2002; Morley, 1998). Other data suggest that dosage may be an important factor in reducing pain intensity. In a double-blind trial in which 81 patients with refractory peripheral or central neuropathic pain were randomized to 0.75 or 0.15 mg of levorphanol over eight weeks, high-strength treatment reduced pain by 36% as measured by a visual analog scale, compared to a 21% reduction with low-strength treatment (Rowbotham et al., 2003). Moreover, on average, patients assigned to the high-strength group required almost half as many capsules per day to achieve pain relief (i.e., 11.9 capsules per day versus 18.3 capsules per day, high versus low strength, respectively) (Rowbotham et al., 2003).

The duration of delivery also appears to facilitate better pain control. Currently, strategies to control chronic and persistent pain entail the use of controlled-release formulations coupled with the use of short-acting analgesics as needed to manage breakthrough pain.

Oxymorphone extended-release (ER) is a pure semisynthetic mu receptor agonist derived from the chemical thebaine. Oxymorphone ER is a novel formulation of oxymorphone employing the TIMERx® (Penwest Pharmaceuticals Co., Danbury, CT) delivery system that has pharmacokinetic characteristics consistent with 12-hour dosing. Data demonstrate that it has a significant specificity for mu opioid receptor sites in the CNS (which are most important for analgesia) and relatively little activity directed at kappa or delta receptor sites. Oxymorphone also possesses a higher potency ratio than parenteral morphine or oxycodone. Because of its lipid solubility, oxymorphone has rapid access into the brain and spinal cord, where it remains in an aqueous phase. This property is especially important for efficacy because in its aqueous, unionized form, an agent will move more readily across biologic lipid membranes like the blood-brain barrier into the CNS.

Several clinical trails have demonstrated the efficacy and tolerability of oxymorphone ER in treating chronic lower back pain, osteoarthritis pain, and cancer pain. In a double-blind, controlled trial, patients with chronic lower back pain were randomized to a 7- to 10-day run-in phase with oxycodone controlled release (CR) or oxymorphone CR twice daily followed by an 18-day double-blind treatment with placebo or run-in phase opioid on which they stabilized (Hale, Dvergsten, Kurkimilis, & Ahdieh, 2003). Among the 213 patients included in the efficacy analysis (71 oxymorphone ER, 75 oxycodone CR, 67 placebo), oxymorphone ER was significantly superior to placebo in terms of change in pain intensity from baseline ($p = 0.0001$) and for most of the other variables (i.e., pain relief,

Brief Pain Inventory, patient and physician global evaluations, and use of rescue medication). Although oxymorphone ER and oxycodone CR were equivalent in terms of efficacy parameter results and tolerability profiles, patients stabilized on oxymorphone ER at an approximate 40 mg twice daily dose, compared to an approximate 80 mg twice daily oxycodone CR dose. This finding suggests a 2:1 ratio for relative potency between oxymorphone ER and oxycodone CR (Hale et al.)

Interim data from an ongoing, two-year, open-label extension study to determine the long-term effectiveness and dosing requirements of oxymorphone ER in 153 patients with chronic osteoarthritis pain refractory to acetaminophen, nonsteroidal anti-inflammatory drugs, or COX-2 inhibitors also are promising. At one year, 106 patients on active drug treatment in a previous study who had stabilized on oxymorphone ER treatment maintained stable pain scores and dosing, whereas 47 patients previously on placebo and entering the open-label phase stabilized after visit two and were maintained thereafter (McIlwain, Burch, Frailey, Ma, & Ahdieh, 2003). The majority of patients, who rated oxymorphone treatment as "excellent," "very good," or "good" at each visit, stabilized at 40 mg twice daily. The most frequently reported adverse events were nausea, vomiting, constipation, and sedation.

Importantly, these results are quite similar to interim data from a two-year, open-label extension trial exploring the effectiveness and safety of oxymorphone ER in patients with cancer with chronic pain (Slatkin, Frailey, Ma, & Ahdieh, 2003). Data demonstrated that in the 16 of 44 enrolled patients who completed 52 weeks, effectiveness was maintained with the same degree of pain relief as was observed in the previous randomized, controlled trial (i.e., an average visual analog scale pain intensity score of 33.5 mm was reported at baseline, and 31.7 mm was reported at 52 weeks). The average daily dose of oxymorphone ER ranged from 80–140 mg twice daily, with minimal use of rescue medication. Based on patients' global assessment, oxymorphone ER was rated as "excellent," "very good," or "good" at relieving pain by more than 90% of patients. Adverse events were similar to those reported in the previous trial and typically are associated with opioid use (i.e., nausea, vomiting, constipation, and sedation).

Conclusion

Chronic pain affects more than 50% of adult populations in developed countries. Its prevalence is even higher among patients with cancer, whose pain is associated with not only the disease itself but also its treatment. In fact, recent studies suggest that a majority of patients undergoing active treatment for cancer and 70%–90% of patients in the terminal phase of the disease experience unrelieved pain (Caraceni & Portenoy, 1999; Murray et al., 2003; Potter et al., 2003). Clearly, pain treatments are falling short of clinical needs.

A growing body of evidence highlights the role that the complex interaction of multiple mechanisms at various levels of the nervous system plays in modulating and maintaining chronic pain. Inflammatory and neuropathic pain are characterized by hypersensitivities that may be irreversible depending on nociceptor sensitivity and responsiveness, alterations in ion channel conduction, and the degree of disinhibition. Other important factors, including neurotransmitters, nerve factors, molecular processes, receptors, and phenotypic neuron expression, also contribute to the sensation known as "pain" and its reversible or intractable nature.

Although tools to identify specific chronic pain mechanisms present in any given patient have yet to be developed, an understanding of the mechanisms that elicit specific pain sensations may facilitate more targeted and efficacious treatments. Presently, several novel agents in the pipeline focus on such a strategy and appear to offer pain control that is superior to many currently available options. In the interim, evolving data on distinct pain mechanisms have created innumerable possibilities that, when used in combination with more sophisticated history-taking (Woolf & Max, 2001) and advanced diagnostic techniques, ultimately may unravel the clinical paradigms for more accurate assessments and treatments for patients with chronic pain.

Author Contact: Christine Miaskowski, RN, PhD, FAAN, can be reached at chris.miaskowski@nursing.ucsf.edu, with copy to editor at rose_mary@earthlink.net.

References

American Pain Society. (2003). Chronic pain in America: Roadblocks to relief: Conclusions. Retrieved June 1, 2004, from http://www.ampainsoc.org/whatsnew/conclude_road.htm

Basbaum, A.I., & Woolf, C.J. (1999). Pain. *Current Biology, 9*(12), R429–431.

Bolay, H., & Moskowitz, M.A. (2002). Mechanisms of pain modulation in chronic syndromes. *Neurology, 59*(5, Suppl. 2), S2–S7.

Buchner, A., Bias, P., & Lammerich, A. (2003, June). *Twice the therapeutic dose of licofelone—an inhibitor of COX-1, COX-2, and 5-LOX—results in a significantly lower GI ulcer incidence than naproxen in OA patients when administered with or without concomitant low-dose aspirin.* Paper presented at the annual meeting of the European League Against Rheumatism, Lisbon, Portugal.

Caraceni, A., & Portenoy, R.K. (1999). An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain. *Pain, 82,* 263–274.

CeNeS Pharmaceuticals. (2003). Product pipeline: Postoperative pain. Retrieved June 7, 2004, from http://www.cenes.com

Costigan, M., & Woolf, C.J. (2002). No DREAM, no pain: Closing the spinal gate. *Cell, 108,* 297–300.

Devers, A., & Galer, B.S. (2000). Topical lidocaine patch relieves a variety of neuropathic pain conditions: An open-label study. *Clinical Journal of Pain, 16,* 205–208.

Endo Pharmaceuticals Inc. (2000). Lidoderm® (lidocaine patch 5%) [Patient information brochure]. Chadds Ford, PA: Author.

Galer, B.S., Jensen, M.P., Ma, T., Davies, P.S., & Rowbotham, M.C. (2002). The lidocaine patch 5% effectively treats all neuropathic pain qualities: Results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. *Clinical Journal of Pain, 18,* 297–301.

Galer, B.S., Rowbotham, M.C., Perander, J., & Friedman, E. (1999). Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: Results of an enriched enrollment study. *Pain, 80,* 533–538.

Gammaitoni, A.R., Alvarez, N.A., & Galer, B.S. (2002). Pharmacokinetics and safety of continuously applied lidocain patches 5%. *American Journal of Health-System Pharmacy, 59,* 2215–2220.

Gammaitoni, A.R., Alvarez, N.A., & Galer, B.S. (2003). Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: A review of the literature. *Journal of Clinical Pharmacology, 43,* 111–117.

Gammaitoni, A.R., & Davis, M.W. (2002). Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing. *Annals of Pharmacotherapy, 36,* 236–240.

Gilron, I. (2001). LY-293558. Eli Lilly & Co. *Current Opinion in Investigational Drugs, 2,* 1273–1275.

Hale, M., Dvergsten, C., Kurkimilis, E., & Ahdieh. (2003, June). *Oxymorphone extended-release (ER) provides equianalgesia at half the dose compared to oxycodone controlled-release (CR) in chronic low back pain: Results of randomized, parallel group, placebo-controlled study.* Paper presented at World Congress of the International Society for the Study of Pain, Lisbon, Portugal.

Harstall, C., & Ospina, M. (2003, June). How prevalent is chronic pain? [Special newsletter]. *Pain Clinical Updates, 9*(2). Retrieved August 26, 2003, from http://www.iasp-pain.org/pcu03-2.pdf

Hawkey, C.J., Karateev, D., Codreanu, C., Dobronte, Z., Gomez Reino, J., Hopkinson, N., et al. (2003, June). *Improved upper gastrointestinal (UGI) safety and tolerability of a new coxib, COX 189 compared with ibuprofen in osteoarthritis patients.* Paper presented at the annual meeting of the European League Against Rheumatism, Lisbon, Portugal.

Hernandez, M., Tonda, R., Pedreno, W., Arderiu, G., Pino, M., Serradell, M., et al. (2003, June). *Evaluation of the effects of licofelone, an inhibitor of COX-1, COX-2, and 5-LOX, on platelet function in an in vitro model of thrombosis with circulating human blood.* Paper presented at the annual meeting of the European League Against Rheumatism, Lisbon, Portugal.

Indelicato, R.A., & Portenoy, R.K. (2002). Opioid rotation in the management of refractory cancer pain. *Journal of Clinical Oncology, 20,* 348–352.

Ji, R.R., & Woolf, C.J. (2001). Neuronal plasticity and signal transduction in nociceptive neurons: Implications for the initiation and maintenance of pathologic pain. *Neurobiological Disorders, 8*(1), 1–10.

Julius, D., & Basbaum, A.I. (2001). Molecular mechanisms of nociception. *Nature, 413,* 203–210.

Katz, N.P., Gammaitoni, A.R., Davis, M.W., Dworkin, R.H., & the Lidoderm Patch Study Group. (2002). Lidocaine patch 5% reduces pain intensity and interference with quality-of-life in patients with postherpetic neuralgia: An effectiveness trial. *Pain Medicine, 3,* 324–333.

Mannion, R.J., & Woolf, C.J. (2000). Pain mechanisms and management: A central perspective. *Clinical Journal of Pain, 16*(3, Suppl.), S144–S156.

McIlwain, H., Burch, F., Frailey, A., Ma, T., & Ahdieh, H. (2003, June). *Oxymorphone in extended-release offers long-term safety, effectiveness, and dose stabilization in osteoarthritis pain: Results of a one-year interim report.* Paper presented at the World Congress of the International Society for the Study of Pain, Lisbon, Portugal.

Meier, T., Wasner, G., Faust, M., Kuntzer, T., Ochsner, F., Hueppe, M., et.al. (2003). Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: A randomized, double-blind, placebo-controlled study. *Pain, 106,* 151–158.

Miaskowski, C. (2001). Biology of mucosal pain. *Journal of the National Cancer Institute Monographs, 29,* 37–40.

Moore, A., Alberighi, D.C., Gitton, X., Sloan, V., & Gimona, A. (2003, June). *Responder rate of COX189 in osteoarthritis: A multi-national study.* Paper presented at the annual meeting of the European League Against Rheumatism, Lisbon, Portugal.

Morley, J.S. (1998). Opioid rotation: Does it have a role? *Palliative Medicine, 12,* 464–466.

Murray, S.A., Grant, E., Grant, A., & Kendall, M. (2003). Dying from cancer in developed and developing countries: Lessons from two qualitative interview studies of patients and their carers. *BMJ, 326,* 368.

Nitu, A.N., Wallihan, R., Skljarevski, V., & Ramadan, N.M. (2003). Emerging trends in the pharmacotherapy of chronic pain. *Expert Opinion on Investigational Drugs, 12,* 545–559.

Pavelka, K., Bias, P., Buchner, A., Lammerich, A., & Schulz, U. (2003, June). *Licofelone, an inhibitor of COX-1, COX-2, and 5-LOX, is as effective as celecoxib and shows improved tolerability during 12 weeks of treatment in patients with osteoarthritis of the knee.* Paper presented at the annual meeting of the European League Against Rheumatism, Lisbon, Portugal.

Potter, J., Hami, F., Bryan, T., & Quigley, C. (2003). Symptoms in 400 patients referred to palliative care services: Prevalence and patterns. *Palliative Medicine, 17,* 310–314.

Regan, J.M, & Peng, P. (2000). Neurophysiology of cancer pain. *Cancer Control, 7,* 111–119.

Rowbotham, M.C., Davies, P.S., Verkempinck, C., & Galer, B.S. (1996). Lidocaine patch: Double-blind controlled study of a new treatment method for post-herpetic neuralgia. *Pain, 65,* 39–44.

Rowbotham, M.C., Twiling, L., Davies, P.S., Reisner, L., Taylor, K., & Mohr, D. (2003). Oral opioid therapy for chronic peripheral and central neuropathic pain. *New England Journal of Medicine, 348,* 1223–1232.

Schell, E., Boucher, L., Tamasi, L., Ouellet, J., Moore, A., Lee, A., et al. (2003, June). *Long-term efficacy and tolerability of lumiracoxib in osteoarthritis of the knee.* Paper presented at the annual meeting of the European League Against Rheumatism, Lisbon, Portugal.

Scholz, J., & Woolf, C.J. (2002). Can we conquer pain? *Nature Neuroscience, 5*(Suppl.), 1062–1067.

Skelly, M.M., & Hawkey, C.J. (2003). COX-LOX inhibition: Current evidence for an emerging new therapy. *International Journal of Clinical Practice, 57,* 301–304.

Slatkin, N., Frailey, A., Ma, T., & Ahdieh, H. (2003, June). *Oxymorphone extended release offers long-term safety, effectiveness, and dose stabilization in cancer patients: Results of a one-year interim report.* Paper presented at the World Congress of the International Society for the Study of Pain, Lisbon, Portugal.

Stewart, W.F., Ricci, J.A., Chee, E., Morganstein, D., & Lipton, R. (2003). Lost productive time and cost due to common pain conditions in the U.S. workforce. *JAMA, 290,* 2443–2454.

Stucky, C.L., Gold, M.S., & Zhang, X. (2001). Mechanisms of pain. *Proceedings of the National Academy of Sciences of the United States of America, 98,* 11845–11846.

Subongkot, S., Frame, D., Leslie, W., & Drajer, D. (2003). Selective cyclooxygenase-2 inhibition: A target in cancer prevention and treatment. *Pharmacotherapy, 23,* 9–28.

U.S. Census Bureau. (2003). State population estimates—Characteristics. Retrieved October 14, 2003, from http://eire.census.gov/popest/data/states/ST-EST2002-ASRO-01.php

Walters, M.R., Bradford, A.J.P., Fischer, J., & Lees, K.R. (2002). Early clinical experience with the novel NMDA receptor antagonist CNS 5161. *British Journal of Clinical Pharmacology, 53,* 305–311.

Woolf, C.J. (1993). The pathophysiology of peripheral neuropathic pain—Abnormal peripheral input and abnormal central processing. *Acta Neurochirurgica, 58,* 125–130.

Woolf, C.J., & Decosterd, I. (1999). Implications of recent advances in the understanding of pain pathophysiology for the assessment of pain in patients. *Pain, 82*(Suppl. 6), S141–S147.

Woolf, C.J., & Mannion, R.J. (1999). Neuropathic pain: Etiology, symptoms, mechanisms, and management. *Lancet, 353,* 1959–1964.

Woolf, C.J., & Max, M.B. (2001). Mechanism-based pain diagnosis: Issues for analgesic drug development. *Anesthesiology, 95,* 241–249.

Woolf, C.J., & Salter, M.W. (2000). Neuronal plasticity: Increasing the gain in pain. *Science, 288,* 1765–1768.

For more information . . .

- American Pain Foundation
  www.painfoundation.org
- American Academy of Pain Management
  www.aapainmanage.org
- American Chronic Pain Association
  www.theacpa.org

Links can be found at www.ons.org.