Chronic Neuropathic Pain

Mechanisms, Diagnosis, and Treatment

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Background: The management of chronic pain represents a significant public health issue in the United States. It is both costly to our health care system and devastating to the patient's quality of life. The need to improve pain outcomes is reflected by the congressional declaration of the present decade as the "Decade of Pain Control and Research," and the acknowledgment in January 2001 of pain as the "fifth vital sign" by the Joint Commission of Healthcare Organizations.

Review Summary: At present, therapeutic options are largely limited to drugs approved for other conditions, including anticonvulsants, antidepressants, antiarrhythmics, and opioids. However, treatment based on the underlying disease state (eg, postherpetic neuralgia, diabetic neuropathy) may be less than optimal, in that 2 patients with the same neuropathic pain syndrome may have different symptomatology and thus respond differently to the same treatment. Increases in our understanding of the function of the neurologic system over the last few years have led to new insights into the mechanisms underlying pain symptoms, especially chronic and neuropathic pain.

Conclusions: The rapidly evolving symptom- and mechanism-based approach to the treatment of neuropathic pain holds promise for improving the quality of life of our patients with neuropathic pain.

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Chronic pain is not uncommon, although estimates of its prevalence vary widely from 2% to 40% of all adults.[1–13] Chronic pain is composed of both nociceptive and neuropathic (also called "neurogenic") components[14] and is often multifactorial. The estimated 3.75 million cases of chronic neuropathic pain in the United States include conditions as diverse as cancer-associated pain, spinal cord injury, low back pain, and phantom pain.[15] Recurrent and persistent pain ranging from back pain to facial pain was reported by 45% of enrollees in a health maintenance organization in the United States,[11,12] and in the United Kingdom up to 25% of patients who attended pain clinics experienced neuropathic pain syndromes.[2] Neuropathic pain associated with disorders such as diabetes mellitus[16–22] and herpes zoster[23–27] are the most frequently described and studied, but they are certainly not the exclusive causes of neuropathic pain. Radiculopathy, which may be an underlying cause in many cases involving lower back pain, is probably the most frequent cause of a peripheral nerve pain generator.[11,28] A partial list of etiologies for neuropathic pain is presented in Table 1.

Neuropathic pain refers to pain caused by a clinically heterogeneous group of disorders that vary widely in etiology and presentation. It includes signs and symptoms that arise from a primary lesion in the peripheral nerve and/or from dysfunction in the central nervous system in the absence of nociceptor stimulation, such as postherpetic neuralgia (PHN).[29] In contrast, nociceptive pain is a response triggered by an unpleasant damaging or potentially damaging stimulus in the periphery and can be acute in nature, such as acute postoperative pain.[29–33] It may also be chronic, such as the inflammation of arthritis. This basic categorization may have clinical significance; for instance, neuropathic pain may not respond as well to opioid or nonsteroidal antiinflammatory analgesic agents, whereas nociceptive pain is usually easily managed with this class of drugs, at least in the short term.[31,32,34] Neuropathic pain may be treated more effectively by drugs that stabilize or modulate central nervous system function (eg, drugs indicated for seizures or depression) or antiarrhythmic agents such as sodium-channel blockers.[31,35]

Neuropathic pain brings tremendous direct and indirect costs to patients and their families in terms of pain and suffering, health care expenditures, and quality of life, as well as costs to society in lost productivity and vocational disability. Clinically, it is an endlessly challenging problem that lacks a coherent treatment paradigm. At present, the treatment approach to neuropathic pain relies on antiquated classification systems based on the etiology of pain, its anatomic distribution, or whatever historical French neurologist first

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TABLE 1. Causes of Neuropathic Pain

Category	Type
Trauma	Surgery
	Complex regional pain syndrome (CRPS) type II
	Amputation (phantom limb pain/stump pain)
	Spinal cord injury
	Crush injuries
Infection	Herpes zoster
	Infectious mononucleosis
	Human immune deficiency syndrome
	Diphtheria
	Leprosy
	Syphilis
Vasculitis/connective tissue disorders	Churg-Strauss
	Cryoglobulinemia
	Lupus erythematosus
	Rheumatoid arthritis
	Polyarteritis nodosa
	Sjögren syndrome
Toxins	Chemotherapy agents, especially vincristine and cisplatinum
	Other drugs such as nitrofurantoin, isoniazid, phenytoin, hydralazine, thalidomide
	Alcohol
	Arsenic
	Lead
	Gold
	Mercury
	Glue sniffing
Nutritional deficiency	Niacin
	Thiamine
	Pyridoxine
	Folic acid
Immune mediated	Multiple sclerosis
	Boeck sarcoidosis
	Guillain-Barré syndrome
	Some peripheral neuropathies
Compression/entrapment syndromes	Spinal stenosis
	Carpal tunnel syndrome
	Tarsal tunnel
	Plexus disorders
	Chronic radiculopathy
Cancer related	Compressive
	Infiltrative
	Paraneoplastic
	Iatrogenic
Metabolic disturbance	Diabetes mellitus
	Uremia
	Porphyria
	Hypothyroidism
	Amyloidosis
Genetically determined	Fabry disease
	Hereditary sensory neuropathies
Miscellaneous	Syringomyelia
	Painful epileptic crisis
	Chronic progressive or recurrent polyneuropathy

described the syndrome.[36] This is less than ideal for several reasons. First, most neuropathic disease states are associated with more than 1 mechanism of pain—and that mechanism usually changes over time. Second, different disease states may produce mechanistically the same neuropathic pain syndrome. And finally, presenting symptoms, signs, and testing are often diverse within a single type of neuropathic pain syndrome.[37–39]

PHN is a neuropathic pain disorder that can be used to illustrate the pitfalls in treating neuropathic pain according to "etiology." In PHN, at least 3 different mechanisms for pain have been identified, all of which are associated with direct neuronal damage to both the peripheral and central nervous systems (ie, infectious, inflammatory, and ischemic).[40,41] Each of these mechanisms is often associated with different symptomatology. For instance, some patients present with profound sensory loss in an area of pain. Others will have pronounced allodynia and hyperalgesia with minimal or no sensory loss. Still others will present with sensory loss *and* allodynia. This diversity of potential mechanisms and symptoms results in complicated and ill-defined "mechanistic diagnoses," and consequently, the response to treatment is unpredictable. Therefore, 2 different patients with PHN may respond differently to the same treatment.[41]

Adding to the clinical challenge of treating neuropathic pain is that most currently prescribed drugs lack evidence-based support in the form of prospective randomized controlled clinical trials or FDA approval for neuropathic pain. (Exceptions to the latter include carbamazepine, which is approved for trigeminal neuralgia,[42] the lidocaine patch and gabapentin, which are approved for PHN,[42] and pregabalin, which is approved for PHN and diabetic peripheral neuropathy.[42a]) Therefore, agents indicated for the treatment of other syndromes including depression, seizures, and cardiac arrhythmias are used off label for the treatment of neuropathic pain.[16,27,31,35,39,43,44] Without rigorous clinical data to support safety and efficacy in patients with neuropathic pain, formal guidelines for dosage and administration of many of these off-label drugs are lacking. These limitations render the current haphazard treatment approaches cumbersome and often ineffective. With new insights being gained into the biologic mechanisms underlying neuropathic pain, perhaps a more valuable way to view neuropathic pain is not only through a clinical framework that categorizes pain according to the presumed etiology or affected body part, but rather by the presenting signs, symptoms, and electrodiagnostic and quantitative sensory testing, which will all contribute to an analysis of putative mechanisms. This approach has been gaining some acceptance in the pain community.[45]

Close analysis of the published data reveals useful information regarding the clinical utility of commonly used agents for specific neuropathic pain symptoms. Though most of these studies took a historical/empirical approach in treating patients (that is, specific drugs were evaluated in patients with a specific disease), data regarding the efficacy of drugs for specific signs and symptoms may still be extrapolated. Targeting treatment to symptom/signs/testing (SST) and understanding the relationship between mechanisms and SST will result in more effective therapy and improved quality of life, the ultimate goal of treatment.

It is the goal of this article to review the diagnosis and treatment of neuropathic pain in light of what we now know about the underlying SST and mechanisms of the various neuropathic pain syndromes. A discussion of nonpharmacologic treatments is not included here; the reader is referred to the review by Harden[46] as a multidisciplinary approach that includes both pharmacologic and nonpharmacologic treatments for neuropathic pain may be warranted in some patients.

Physiologically, neuropathic pain results from central and/or peripheral nervous system damage, threat of damage or dysfunction.

TYPES OF NEUROPATHIC PAIN

Physiologically, neuropathic pain results from central and/or peripheral nervous system damage, threat of damage or dysfunction, often in the absence of pain-producing stimuli.[2,36,47] Although nervous system damage would logically be expected to cause a sensory loss (negative symptoms)—with the degree of loss approximating the amount of damage—a small proportion of cases present with various kinds of pain and dysesthesia (or positive symptoms).[15]

Complicating the approach to neuropathic pain treatment is confusion over terminology. Most pain experts do not define pain as chronic until it has persisted for 3 to 6 months.[48] Moreover, there are 2 major types of neuropathic pain, stimulus-evoked pain and stimulus-independent pain (ie, spontaneous pain). Stimulus-evoked pain is characterized by signs of hyperalgesia and allodynia that result from mechanical, thermal, or chemical stimulation. Stimulus-independent pain may be persistent or paroxysmal in nature and may be described as shooting, lancinating, or burning. Paresthesias, defined as abnormal sensations, and dysesthesias, defined as unpleasant abnormal sensations, may be spontaneous or evoked.[29]

Hyperalgesia refers to an exaggerated pain response produced by a normally painful stimulus (ie, pinprick), while allodynia is pain produced by a stimulus that is not usually painful (ie, light touch).

SYMPTOMS AND MECHANISMS OF NEUROPATHIC PAIN

Stimulus-Evoked Pain

Hyperalgesia

Within the category of stimulus-evoked pain, hyperalgesia and allodynia are 2 symptoms that may be manifest via mechanical, chemical, or thermal stimulation. Hyperalgesia refers to an exaggerated pain response produced by a normally painful stimulus (ie, pinprick), while allodynia is pain produced by a stimulus that is not usually painful (ie, light touch).[30]

Hyperalgesia can arise from peripheral and/or central mechanisms. Peripherally, sensitization of primary afferent nociceptors (Aδ and C fibers) occurs by inflammatory mediators such as bradykinin, histamine, prostaglandins, and substance P released from injured tissue.[49] Another peripheral mechanism for stimulus-evoked pain involves formation of a neuroma, a tangled mass of regenerating nervous tissue embedded in scar and connective tissue at the site of nerve injury. Neuromas accumulate or "uncover" pathologic and nonpathologic ion channels (eg, sodium channels) and receptors (eg, norepinephrine) that result in foci of hyperexcitability and ectopic activity.[36,50] The "neuroma sign" may be elicited by mechanically stimulating the affected area, triggering exquisite pain because of changes in afferent nerve membrane properties and mechanical threshold (Tinel sign).

Allodynia

Allodynia is evoked by peripheral stimulation. In response to ongoing nociception or overstimulation, changes in spinal cord dorsal horn cells can occur, resulting in central sensitization or central reorganization and finally leading to allodynia.[36,49,51,52] Central sensitization may cause an increase in the size of the sensory receptive field, a reduced threshold for sensory (pain) perception, and hypersensitivity to various innocuous stimuli.[49] At the molecular level, central sensitization occurs when the excitatory amino acids glutamate and aspartate and substance P bind to receptors located on spinal dorsal horn transmission cells (second-order neurons).[53] Specific glutamate receptors include NMDA (N-methyl-D-aspartic acid) and non-NMDA receptors (α-amino 3-hydroxy-5-methyl-4-isoazolepropionic acid [AMPA], kainate), which may enhance and prolong depolarization.[32,33,36] This increases the responsiveness of the nociceptive system and leads to long-lasting changes in the dorsal horn transmission cells.[32,33,36] In addition, NMDA receptors may be involved in potentiating synaptic transmission in the hippocampus, a process that may be responsible for "pain memory," such as that which is evident in phantom limb pain.[54] In fact, it is likely there are pain-associated excitatory amino acid receptors throughout the neuroaxis. Activation of non-NMDA receptors, specifically, the AMPA and kainate receptors and neurokinin-1 (substance P) receptors, may act to further sensitize the NMDA receptor.[49,53]

Central changes also occur through reorganization. As the damaged nerve regenerates or begins firing ectopically or ephaptically, Aβ-fiber sprouting into the pain layers (laminae I and II) may occur.[55] When nerves that do not normally transmit pain sprout into these more superficial regions of the dorsal horn—regions where the first synaptic relay in pain transmission usually occurs—pain may result from nonnoxious stimuli.[49] Regeneration also causes sensory disorganization such that the normal somatotropic organization of inputs becomes disordered ("spreading").[56]

Another central change that contributes to the development of allodynia is the loss of inhibitory controls projecting to the superficial spinal cord dorsal horn. This occurs when segmental inhibitory interneurons (mediated by neurotransmitters like γ-aminobutyric acid (GABA), glycine, and endogenous opioids [enkephalins]), and/or descending inhibitory pathways (mediated by neurotransmitters such as serotonin and norepinephrine) decrease their function.[49,53] Because this inhibition normally acts as a spinal "gate" for sensory information, reduced inhibition increases the likelihood that the dorsal horn neuron will fire spontaneously or more energetically to primary afferent input.[36] Thus, allodynia may result from any of these 3 central mechanisms for stimulus-evoked pain: central sensitization, reorganization, or loss of inhibitory controls.

Stimulus-Independent Pain

Stimulus-independent, or spontaneous, pain by definition occurs without provocation, so symptoms can occur constantly or at any time. Paresthesias and dysesthesias can originate peripherally via ectopic impulses along the Aβ, Aδ, and C fibers, arising as spontaneous activity due to processes such as damaged ("leaky") sodium channels that accumulate along affected nerves, causing a drift toward threshold potential.[36,47] Paroxysmal shooting or electrical pain (once thought to distinguish ectopic activity in myelinated fibers), as well as continuous burning pain (thought to be caused by activity in unmyelinated nerves), actually probably occurs from ectopic or ephaptic discharges arising in any type of

fiber.[36] Stimulus-independent pain may also occur as a result of reduced inhibitory input from the brain or spinal cord.[33]

Mixed Pain Syndromes

In most neuropathic pain syndromes, stimulus-independent pain occurs along with stimulus-evoked pain; for example, spontaneous burning pain and mechanical allodynia in complex regional pain syndrome (CRPS).[57] In some syndromes, the activity at the site of injury seems to maintain the peripheral and/or central sensitivity in some fashion, and blocking the peripheral input may at least temporarily normalize the altered central processing. Thus, symptoms cease until peripheral input returns.[58]

In most neuropathic pain syndromes, stimulus-independent pain occurs along with stimulus-evoked pain.

ASSESSING PAIN

A full complement of symptoms, signs, and testing is necessary to properly and fully define the putative mechanisms involved in a given neuropathic pain syndrome. A detailed medical and surgical history is an essential first step in understanding pain etiology. A comprehensive physical examination allows the physician to integrate the patient's presenting symptoms and to begin to localize which elements of the neuroaxis are involved. It is particularly important to identify the location, quality, intensity, and pattern of pain. The neurologic examination employs simple bedside tests to assess the patient for the presence or absence of specific stimulus-evoked signs (Table 2). Special attention should be paid to the sensory examination, especially searching for hypoesthesia (numbness) or hyperesthesia (hyperpathia and/or allodynia). A distinction between mechanical and thermal allodynia may have clinical relevance. Testing of reflexes, a comprehensive motor examination, and autonomic examination are all essential to understanding neuropathies. Testing can complement and corroborate careful history and physical examinations and has the advantage of being quantitative, although all tests have their known limitations. A comprehensive list of diagnostic tests evaluating the motor, sensory, and autonomic systems is presented in Table 3. In addition, immunohistochemical staining of skin-punch biopsy specimens using antibodies specific for small-diameter myelinated and unmyelinated peripheral nerves can be used to quantify nerve fiber density in patients with peripheral neuropathy.[59] The physician should also be aware of any

TABLE 2. Simple Bedside Tests for the Assessment of Stimulus-Evoked Neuropathic Pain

Stimulus-Evoked Sign	Subtype	Assessment	Pathologic Response
Allodynia	Mechanical static	Manual light pressure of the skin	Dull pain Burning pain
Definition: normally nonpainful stimulus evokes a painful sensation	Mechanical punctate	Light manual pinprick with a sharpened wooden stick or stiff von Frey hair	Sharp superficial pain
Control: identical stimulus in unaffected skin does not evoke pain	Mechanical dynamic	Stroking skin with a brush, gauze, or cotton applicator	Sharp, burning, superficial pain
	Mechanical deep somatic	Manual light pressure at the joints	Deep pain at the joints
	Thermal cold	Contact skin with objects at 20°C*	Painful, often burning, temperature sensation
	Thermal warm	Contact skin with objects at 40°C*	Painful burning temperature sensation
Hyperalgesia	Mechanical pinprick	Manual pinprick of the skin with a safety pin	Sharp superficial pain
Definition: normally painful stimulus evokes a more intense painful sensation	Thermal cold	Contact skin with coolants such as acetone* or cold metal	Painful, often burning, temperature sensation
Control: identical stimulus in unaffected skin evokes a less painful sensation	Thermal heat	Contact skin with objects at 46°C*	Painful burning temperature sensation

*Control: contact with object at skin temperature.

TABLE 3. Neurologic Tests Utilized in the Diagnostic Assessment of Neuropathic Pain

Neurological System	Diagnostic Test	Fibers Studied*	Function Evaluated	Possible Findings in Neuropathic Pain Patients
Motor	Electromyography (EMG) and motor nerve conduction studies (NCS)	Efferent large myelinated motor axons	Motor nerve conduction velocity and compound muscle action potential amplitude	Velocity and amplitude decreased with reduction in number of large myelinated motor axons or with interruption in myelination
Sensory	Sensory NCS	Afferent large myelinated sensory axons (Aβ fibers)	Sensory nerve conduction velocity and action potential amplitude	Velocity and amplitude decreased with reduction in number of large myelinated sensory axons
	Thermotest†	Aδ and C fiber activity arising from nociceptors and mechanoreceptors	Sensory and pain threshold after stimulus with cool and warm temperature	Lower threshold or suprathreshold response to stimuli‡
	Microneurography	Single fiber activity arising from nociceptors (Aδ and C fibers) and mechanoreceptors (Aβ fibers)	Presence of ectopic impulses	Ectopic impulse generation along sensory axons
	von Frey hairs†	Aδ and C fiber activity arising from nociceptors and Aβ fiber activity arising from mechanoreceptors	Mechanical pressure threshold and tolerance	Lower threshold and tolerance or suprathreshold response to stimuli‡
	Algometer†	Aδ and C fiber activity arising from nociceptors and Aβ fiber activity arising from mechanoreceptors	Mechanical pressure threshold and tolerance	Lower threshold and tolerance or suprathreshold response to stimuli‡
	Vibrameter†	Aβ fiber activity arising from mechanoreceptors	Vibration perception thresholds	Increase thresholds‡
Autonomic	Heart rate	Autonomic efferent parasympathetic axons (eg vagus nerve)	Heart rate variation in response to deep breathing	Less variation seen with polyneuropathy affecting vagal function
	Quantitative sudomotor axon reflex test (QSART)	Sympathetic postganglionic sudomotor axons	Sweat gland response to stimulation	Excess or persistent sweat with reduced latency or reduced sweat volume consistent with peripheral neuropathy
	Skin temperature and blood flow measurements with thermistor, thermography and laser Doppler	Sympathetic postganglionic vasoconstrictor axons	Comparison of skin temperature of involved extremity to asymptomatic extremity	Early, warmer skin on involved side from vasodilatation; later, cooler skin from vasoconstriction

*Aδ and C fiber activity arises from nociceptors and may be activated by heat and cold pain as well as painful pressure. Aβ fiber activity arises from mechanoreceptors and may be activated by touch and vibration stimuli.
†Quantitative sensory testing (QST).
‡Lower pain thresholds suggest allodynia. Increased pain or perception thresholds suggest hypoesthesia or hypoalgesia.

comorbid conditions affecting the patient's pain experience and quality of life, such as sleep disturbance, anxiety, or depression, which may help guide treatment decisions.

Measuring Pain

Several subjective and quasi-objective tools have been developed to measure pain. One of the oldest and best validated is the visual analog scale (VAS), which measures pain on a horizontal, 100-mm line.[60,61] The left end is labeled "no pain," while the right end is labeled "worst pain imaginable." Patients mark the point on the line that subjectively corresponds to their pain. The pain level is "quantified" by measuring the distance from the left in millimeters. It is important to remember that putting a mark on a line is a behavior, and

as such is subject to all the usual modifiers of behavior. Although most classic studies evaluating pain use the VAS, other scales are also used both in research and clinically.[14]

The McGill Pain Questionnaire is an extensively validated tool that allows patients to specify subjective pain experience using sensory, affective, and evaluative descriptors. The commonly used "short form" includes a 5-point verbal descriptor scale and a VAS.[61] The Neuropathic Pain Scale (NPS) specifically focuses on adjectives that have been demonstrated to be statistically associated with neuropathic pain. Hence, this questionnaire is also a means to arrive at a quasi-quantitative score.[62] Two items in the NPS assess the global dimensions of pain intensity and pain unpleasantness. The 8 additional qualities of neuropathic pain assessed include sharp, hot, dull, cold, sensitive, itchy, deep, and surface pain.[62] These types of pain scales can also be used to monitor treatment progress and evaluate outcomes in research. However, they are patient controlled and may be driven by multiple nonpain behaviors. Until the promise of functional MRI or similar technology is fulfilled, these types of instruments are the best tools we have for measuring the patient's pain experience.

TREATMENT

Once the patient has been thoroughly assessed and a putative mechanism devised (working diagnosis), a treatment strategy should be developed to hopefully normalize the underlying CNS dysfunction and thus directly alleviate the associated unpleasant signs and symptoms. Drugs thought of traditionally as antidepressants, anticonvulsants, and antiarrhythmics may be used to treat neuropathic pain.[35] It should be noted, however, that randomized, controlled trials evaluating the efficacy of these drugs in alleviating neuropathic pain or reducing specific neuropathic pain symptoms in humans are presently limited. Drugs that have been shown in clinical trials to have a beneficial impact on specific neuropathic pain symptoms are listed in Table 4[63–76] and dosing for selected agents is presented in Table 5.[77]

Because hyperalgesia probably depends on peripheral, as well as central, changes, treatment can logically be initiated with local therapy.

Hyperalgesia

Because hyperalgesia probably depends on peripheral as well as central changes, treatment can logically be initiated with local therapy (Na^+ ion block) including topical anesthetic agents like EMLA® cream (lidocaine), lidocaine-impregnated patches, or local infusions of lidocaine.[63,69,78–80] Topical agents have been used with variable success in patients with neuropathic pain.[41,80,81] However, these results include treatment of a variety of conditions other than just hyperalgesia. In one study, the effects of topical EMLA were tested in patients with hyperalgesia alone, and significant

TABLE 4. Drugs With Clinical Trial Evidence Suggesting Improvement in Specific Neuropathic Pain Symptoms

Symptom	Drug
Hyperalgesia	EMLA cream[63]
	Gabapentin[64,65]
	Lidocaine IV[66]
Allodynia	Gabapentin[65]
	Ketamine IV or IM[67,68]
	Lidocaine IV[69]
	Morphine IV[70]
	Tramadol[71]
Shooting, lancinating pain	Amitriptyline[72]
	Carbamazepine[73]
	Gabapentin[65]
	Imipramine[74]
	Lamotrigine[75]
	Phenytoin IV[76]
	Venlafaxine[74]
Burning pain	Amitriptyline[72]
	Gabapentin[64]
	Phenytoin IV[76]

IM indicates intramuscular; IV, intravenous.

TABLE 5. Dosing for Selected Agents

Agent	Dose Range (mg/d)	Frequency
Anticonvulsants		
Carbamazepine	100–1000 mg/d	bid to qid
Gabapentin	900–3600 mg/d	tid
Lamotrigine	150–500 mg/d	bid
Antidepressants		
Amitriptyline	10–200 mg/d	qd
Imipramine	10–200 mg/d	qd to bid
Venlafaxine	37.5–340 mg/d	tid to bid
Other		
Lidocaine	0.25–2 mg/kg/d	Continuous IV
Ketamine	0.25–0.5 mg/kg/dose	q3h (IV or IM)

Modified with permission from Farrar, 1999.[77]
IM indicates intramuscularly; IV, intravenously.

efficacy was observed.[63] Additionally, a lidocaine patch has been shown to alleviate pain in patients with PHN; however, these studies were not specifically designed to assess hyperalgesia.[79,80] In fact, the 5% lidocaine patch has been approved by the FDA for the treatment of neuropathic pain in patients with PHN.

Capsaicin is believed to relieve pain by selectively stimulating unmyelinated C-fiber afferent neurons, causing the release of substance P.[82–84] Prolonged application depletes substance P stores (and perhaps other neurotransmitters as well) from sensory nerve endings to ultimately prevent or reduce the transmission of pain. Capsaicin is not always well tolerated by patients due to associated burning, messiness, and the need for repeated applications (3 to 4 times daily for 4 to 8 weeks) before clinical effectiveness can be assessed.[14]

Ectopic Activity at a Neuroma

Theoretically, the "neuroma sign" can be at least partially ameliorated by drugs that block ectopic firing secondary to accumulation of dysfunctional ("leaky") pathologic sodium channels. To date, supporting data are limited to animal studies. These show that intravenous lidocaine, tocainide, and mexiletine given in subanesthetic concentrations stop the firing of spontaneously active fibers in the neuroma without blocking conduction.[85] Carbamazepine and phenytoin may also be effective.[86,87] Some studies suggest that, theoretically, other sodium-channel blockers such as lamotrigine or topiramate could be useful, but the data are inconclusive at present.[88–92] All of these drugs have additional and potentially salient effects.

Allodynia

Many pharmacologic agents have been recommended for the management of allodynia. Local anesthetic blocks are effective in temporarily eliminating thermal and sometimes mechanical allodynia. Their success may result from their ability to inhibit the continued nociceptive input needed to initiate and maintain central sensitization, one of the possible causes of allodynia.[58] Topical lidocaine has been used successfully to treat patients with PHN experiencing allodynia. The use of lidocaine gel or a 5% patch was significantly more effective than placebo in relieving pain with only minimal increases in lidocaine serum concentrations.[78–80,93] As mentioned earlier, the lidocaine patch has FDA approval for the "pain" of PHN, but it is unclear from existing data how efficacious it is in treating allodynia per se.

Clinical trials in patients with painful diabetic peripheral neuropathy and PHN have demonstrated that tricyclic antidepressants are effective in relieving neuropathic pain, but these studies do not differentiate between allodynia or stimulus-independent symptoms such as burning and lancinating pain.[43,94] In addition to being excellent Na^+ channel blockers, the tricyclics are known to inhibit the reuptake of serotonin and norepinephrine. The analgesic properties of these drugs may be related at least partially to restoration of inhibitory controls.[27,31,95]

The anticonvulsant gabapentin, a structural analogue of GABA, increases the concentration and possibly the rate of synthesis of native GABA in the brain.[96,97] Although its mechanism of analgesic effect has not been determined, experimental data suggest that gabapentin acts at multiple central sites.[96,97] Gabapentin binds with high affinity to a unique site in the brain, which is associated with an auxiliary subunit of Ca^{+2} channels. Gabapentin most likely modifies/modulates first- and second-messenger calcium currents and ultimately may cause a decrease in firing of the transmission cell or a decrease in the release of certain monoamine neurotransmitters.[97] These mechanisms might underlie the effect of gabapentin on allodynia.[98]

In a pilot study of patients with various peripheral and central neuropathic pain syndromes, Attal et al[65] demonstrated that gabapentin (up to 2400 mg/d) was effective in reducing tactile and cold allodynia. Gabapentin had no effect on normal mechanical and thermal pain thresholds, suggesting a lack of direct antinociceptive effect.

Other GABA-enhancing drugs, including baclofen (a $GABA_B$ agonist), have been shown to be effective in reducing tactile allodynia in rat models.[99]

Traditionally, clinicians have been reluctant to treat pain with opioid analgesics because of multiple concerns, including that of "addiction" to therapy. This approach has been changing, and the clinical use of opioids is becoming more acceptable.[100–103] Although opioids may not be as effective in neuropathic pain as in nociceptive conditions,[34] there is some evidence to support the short-term use of opioids in patients with allodynia. In a randomized, double-blind, placebo-controlled trial, high-dose morphine (mean 19.2 mg infused over 1 hour) was effective in relieving allodynia in 11 of 19 patients with PHN.[70] Although adverse effects were common, respiratory depression or excessive sedation was not observed. When therapeutic response is suboptimal, it is recommended that other routes of administration be tried or combination therapy with other analgesics such as tricyclic antidepressants be considered.[104] There are no trials of sufficient length to comment on the full set of consequences of long-term opioid therapy.[105]

Allodynia may also be treated with drugs that antagonize the NMDA receptors responsible for central sensitization. Some studies suggest that the NMDA antagonist ketamine is effective in treating allodynia in patients with PHN, chronic posttraumatic pain, and chronic neuropathic pain.[67,68,106,107] NMDA antagonists have also been used in patients with phantom limb pain (ketamine), orofacial pain (ketamine), surgical neuropathic pain (amantadine), diabetic neuropathy (dextromethorphan), and PHN (dextromethor-

phan), although effects on allodynia were not specifically evaluated.[52,108–110]

Sodium-channel blockers are the mainstay of treatment of chronic neuropathic pain syndromes arising from ectopic discharges in nociceptive fibers.

Treatment of Stimulus-Independent Pain

Sodium-channel blockers are the mainstay of treatment of chronic neuropathic pain syndromes arising from ectopic discharges in nociceptive fibers. Carbamazepine is traditionally the treatment of choice for the shooting, lancinating pain accompanying trigeminal neuralgia and was first proven effective in this condition in the early 1960s.[73,111–115] One of the most common side effects seen with carbamazepine is skin rash. When skin rash develops, some physicians have had good experience substituting oxcarbazepine for carbamazepine.[116] However, there is an estimated 25% cross-reactivity in patients who have had a rash with carbamazepine.[117] Alternatively, patients could be started initially on oxcarbazepine, which appears to have a lower incidence of skin rashes than carbamazepine.

Like carbamazepine, lamotrigine has been shown to be more effective than placebo in alleviating the sharp, shooting, or stabbing pain of trigeminal neuralgia when administered with phenytoin or carbamazepine to refractory patients.[75] However, in a separate placebo-controlled study, lamotrigine 200 mg daily was found to have no effect on pain in 100 patients with neuropathic pain of various etiologies.[90] In another placebo-controlled trial, a single dose of phenytoin (15 mg/kg infused intravenously over 2 hours) significantly relieved shooting pain in patients experiencing acute flares of neuropathic pain.[76] Additionally, tricyclic antidepressants may be effective for shooting pain, possibly because of their sodium channel–blocking properties.[118]

Several trials have demonstrated that tricyclic antidepressants are also effective in alleviating burning pain. Drugs evaluated include amitriptyline (2.5–150 mg/d), desipramine (12.5–250 mg/d), and imipramine (25–350 mg/d).[72,119–121] However, sedation and anticholinergic effects associated with the tricyclic antidepressants limit their usefulness. Gabapentin also produced a moderate but significant relief of both continuous burning pain and paroxysmal (lancinating/shooting) pain.[65]

Treatment of Complex Regional Pain Syndromes (CRPSs)

CRPS types I and II (formerly reflex sympathetic dystrophy and causalgia, respectively) represent a variety of painful conditions that typically follow injury. The resulting pain is greater than would be expected from the injury, may progress over time, and is often associated with significant motor impairment.[46] Clinical findings for type I include regional pain, sensory changes, abnormalities of temperature, abnormal sudomotor activity, edema, and abnormal skin color. Type II includes all of the above features, as well as a peripheral nerve lesion.[122] CRPS types I and II may be associated with sympathetically maintained pain. Probably, for this reason, some of these patients will respond to regional sympathetic blockade with guanethidine or ganglionic blockade with local anesthetics.[123] Intravenous regional guanethidine administration significantly reduced pain scores and increased skin temperature of the affected hand of patients with sympathetic dystrophy.[124] Guanethidine prevents pain transmission by blocking reuptake of norepinephrine at sympathetic nerve endings and further release in response to neuronal stimulation.[125] Intravenously administered regional bretylium combined with lidocaine has also been studied. Like guanethidine, bretylium inhibits pain transmission by blocking the release of norepinephrine from adrenergic nerve endings. In a study of 13 patients with CRPS, bretylium (1.5 mg/kg) and lidocaine (0.5%) provided 20 days of pain relief as compared with 2.7 days with lidocaine alone.[125]

Cancer-Related Neuropathic Pain

The treatment of cancer pain is complex because multiple nociceptive generators exist concurrently.[126] An international survey of over 1000 patients with cancer pain found that 72% of patients experienced nociceptive pain, 35% had pain considered to be visceral, and 40% had a neuropathic component to their pain.[127] Neuropathic pain related to cancer arises from compression or infiltration of nerves by tumor, nerve trauma, surgical procedures, and, significantly, treatments associated with nervous system injury such as chemotherapy or radiation.[128]

It has long been thought that neuropathic pain does not respond optimally to opioids.[129] However, a number of clinical trials demonstrate that neuropathic pain may respond to opioid doses higher than those used for nociceptive pain.[70,130] The pain response may also depend upon the quality of pain being treated.[128] A recent study in cancer patients with neuropathic pain inadequately controlled by opioids has demonstrated clinically significant reductions in burning-pain intensity, shooting-pain frequency, and allodynia 1 to 2 weeks following the addition of gabapentin.[131] Coadministration with opioids did not increase the incidence of adverse effects. The mechanism for gabapentin's potentiation of opioid analgesia is unknown but may be linked to an interaction

with the NMDA receptor system, which may be involved in the development of opioid tolerance.[131,132] This suggests that gabapentin might beneficially interfere with the mechanisms responsible for opioid resistance in patients with neuropathic pain.

The difficulty in achieving adequate control of neuropathic pain in cancer patients has led to the development of guidelines adapted from the World Health Organization (WHO) Analgesic Ladder.[133] Essentially, this algorithm suggests treatment according to the WHO recommendations. Step 1 of the ladder recommends treatment of mild pain: acetaminophen, aspirin, or other nonsteroidal antiinflammatory drugs. If pain persists or increases, the addition of opioids such as codeine, hydrocodone, and oxycodone is recommended as step 2. Step-2 opioids are frequently administered in fixed-dose combinations with acetaminophen or aspirin. Step-3 opioids are prescribed when moderate to severe pain control is needed. Step-3 opioids include morphine, oxycodone, hydromorphone, methadone, and fentanyl. Adjuvant agents such as tricyclic antidepressants, anticonvulsants, local anesthetics, and steroids may be added at any step to enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain, and produce analgesic activity for specific types of pain.[134] However, the adjuvant agent chosen should target specific neuropathic pain symptoms.

CONCLUSIONS

Effective treatment of chronic neuropathic pain continues to be a clinical challenge due to the variability in presentation across and within disease states and the underlying mechanisms of pain development. At present, therapeutic options are largely limited to drugs approved for other conditions, including anticonvulsants, antidepressants, antiarrhythmics, and opioids. Ongoing research continues to elucidate mechanisms linked to the presenting symptoms for chronic neuropathic pain, providing additional targets for drug activity. The traditional treatment approach, based on the underlying etiology for pain, is currently being supplemented by a more direct symptom- or sign-based, and perhaps ultimately a mechanism-based, approach. Neurologists must be cognizant of this shifting diagnostic focus to achieve more optimal therapeutic outcomes for their patients.

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