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Clinical approach to patients with neuropathic pain

■ ABSTRACT

At long last, advances have been made in the field of neuropathic pain treatment, in large part due to a better understanding of the mechanisms underlying this type of pain. New antidepressants and anticonvulsants with novel mechanisms of action have spearheaded the way, and studies have finally shown that opioids are effective for treating chronic and breakthrough pain.

■ KEY POINTS

Often, no single drug relieves the pain completely: combination therapy with agents that work at different sites and by different mechanisms may be necessary.

Tricyclic antidepressants are a first-line therapy, especially for pain that disturbs sleep and contributes to depression.

Classic teaching holds that neuropathic pain is opioid-resistant, but recently, several carefully conducted trials have found opioid analgesics to be effective for neuropathic pain.

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are more effective than selective serotonin reuptake inhibitors (SSRIs) for neuropathic pain.

Lidocaine patches are useful for discrete areas of pain, especially for hypersensitivity.

Pregabalin, a new, rapidly acting antiepileptic drug, has been approved for treatment of painful diabetic neuropathy and postherpetic neuralgia.

Nonopioid analgesics such as acetaminophen can be used as adjuncts.

NEUROPATHIC PAIN SYNDROMES are challenging to treat. New drugs aim at the mechanisms of the pain, but results are still less than desirable.

Newer antidepressants and anticonvulsive drugs are becoming first-line treatments in many patients. And we now know that, contrary to conventional wisdom, opioids do have a role in treating neuropathic pain.

Still, there is no definitive algorithm for treatment. Rather, physicians often will have to combine agents in order to provide patients with relief from their pain.

This article reviews how to classify a patient's pain on the basis of the clinical picture, discusses the physiology of pain, and provides several approaches to managing common neuropathic pain syndromes, with two cases to illustrate the art and the science of treatment.

■ INTRODUCTION

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”¹

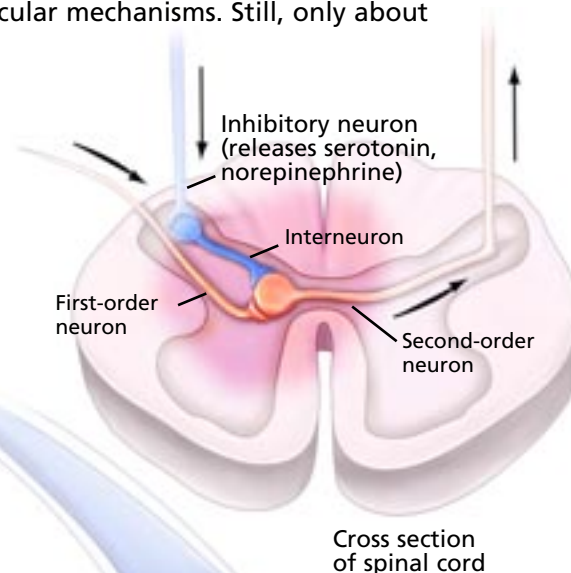
While any attempt to define such a complex phenomenon in succinct terms underestimates its significance, this definition makes several key points. Pain is not only a sensory event, but also a cause of suffering and even existential questioning. From the evolutionary standpoint, pain functions to protect us from harm, warning us of *pending* as well as *actual* tissue injury. But in actuality not all pain plays an adaptive or protective role, hence the difficult problem of neuropathic pain.

■ Toward rational therapy of neuropathic pain

Pain perception is a balanced process, with pain-conduction pathways (brown) opposed by pain-inhibiting pathways (blue). Damage anywhere in the system can lead to neuropathic pain. Current medical therapies target the putative molecular mechanisms. Still, only about half of patients obtain meaningful relief.

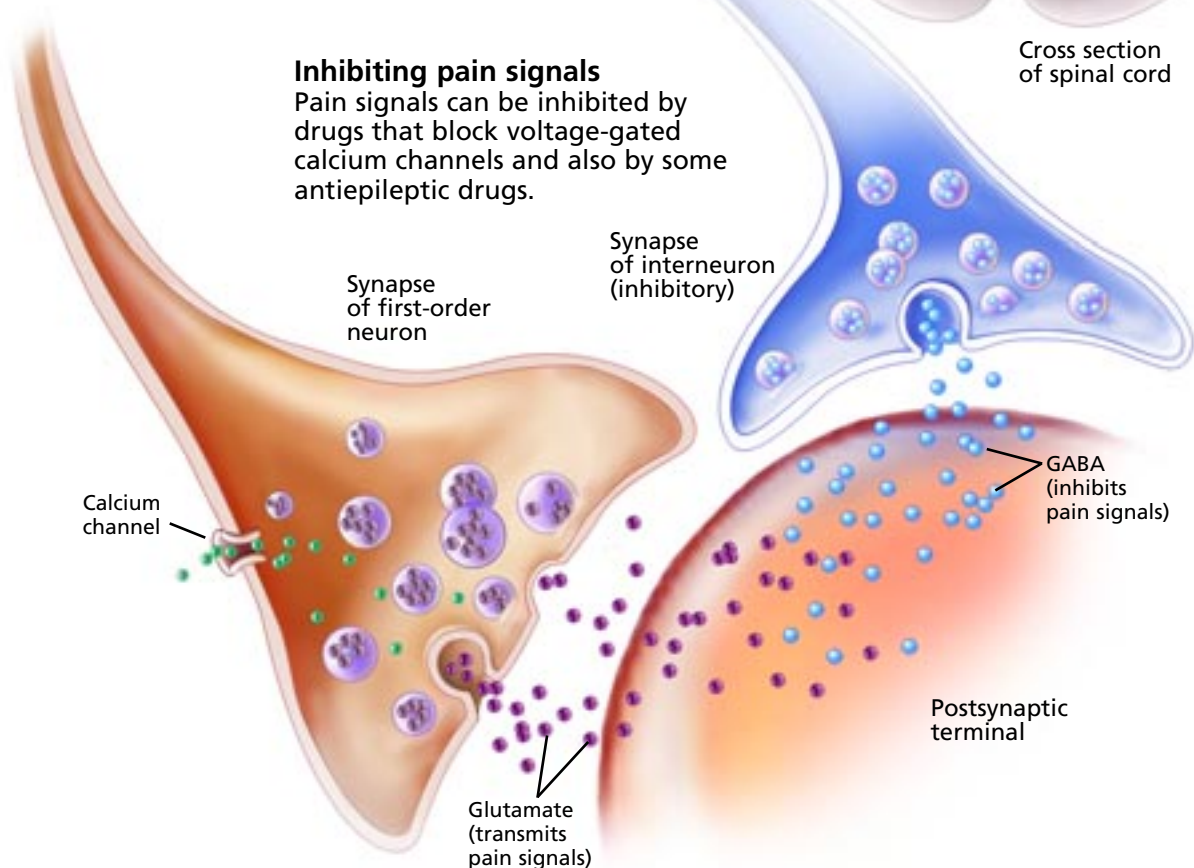
Enhancing the analgesic system

Inhibition of pain signals can be boosted by drugs that inhibit reuptake of serotonin and norepinephrine, such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, and promote gamma amino butyric acid (GABA), such as some antiepileptic drugs.



Inhibiting pain signals

Pain signals can be inhibited by drugs that block voltage-gated calcium channels and also by some antiepileptic drugs.



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FIGURE 1

TABLE 1

Clinical conditions associated with neuropathic pain

Central nervous system

Stroke—cortical and subcortical
 Traumatic spinal cord injury
 Demyelination
 Syringomyelia and syringobulbia
 Neoplastic and other space-occupying lesions
 Trigeminal and glossopharyngeal neuralgia
 Migraine*
 Fibromyalgia*

Peripheral nervous system

Nerve compression/entrapment neuropathy
 Traumatic nerve injury
 Ischemic neuropathy
 Peripheral polyneuropathy (hereditary, metabolic, toxic, inflammatory, paraneoplastic, nutritional, vasculitic, infectious)
 Plexopathy (neoplastic, autoimmune, radiation-induced, traumatic)
 Nerve root compression
 Post-amputation stump and phantom limb pain
 Postherpetic neuralgia
 Cancer-related neuropathy (infiltrative, chemotherapy-related, radiation-induced, post-surgical)

*Possible or theoretical neuropathic pain condition

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For the clinician, a useful adage is that pain is what the patient says it is, but because pain is subjective, its treatment is an inexact science. In other clinical fields, the “art of medicine” has yielded to rigorous, objective, evidence-based methods, but in pain medicine we must rely on patients’ subjective reporting, and this reliance has impeded the study of pain as a clinical science. Until recently, much of what practitioners were taught was based on a few scientifically rigorous studies and more often on anecdotal reports and consensus opinions.²

THE CLASSIFICATION OF PAIN

A useful clinical approach to the evaluation of patients is to classify pain as either somatic, visceral, or neuropathic (or a combination of these).^{1,3}

The first two classes, somatic (nociceptive) and visceral pain, can be further subclassified according to their mechanism. Both types refer to pain arising from stimulation of specialized nerve endings called nociceptors, which are located both in body tissues and in the viscera. The pain is classified according to which nociceptors are being stimulated.

This classification serves an important function: a patient’s “chief complaint” and “history of the present illness” can often tell us the diagnosis. Perhaps no clearer demonstration of the importance of clinical history-taking can be found than the classic monograph, *The Early Diagnosis of the Acute Abdomen* by Sir Zachary Cope.⁴

Somatic pain is usually due to an identifiable injury that stimulates nociceptors (see below). Patients describe the pain in recognizable terms, such as sharp, aching, or shooting, and they can easily tell where it hurts. Generally, the pain remits as the injury heals. Treatment is usually based on symptoms, using a variety of nonspecific but effective analgesics.

Visceral pain is caused by stimulation of nociceptors in the wall of the viscera, which are especially sensitive to mechanical distention. In contrast to somatic pain, visceral pain is diffuse, achy, cramping, or spasmodic, and generally poorly localized. It can be referred to distant sites, a characteristic that distinguishes it from somatic pain and that can be explained by the embryological development of the vertebrate nervous system.^{3,4}

Neuropathic pain results from damage to the nervous system anywhere along the neuraxis: peripheral nervous system, spinal or supraspinal nervous system, or brain. It differs considerably from somatic and visceral pain, both for the patient and for the physician listening to the patient’s story. In describing neuropathic pain, patients use words for both positive and negative sensations: burning, searing or scalding, cold, numb, tingling, shooting, stabbing, crushing, or vise-like. These sensations, which affect not only the sensory system but also the patient’s mood, thinking, and concentration, are due to disruption or abnormal function of the body’s normal pain-conducting circuitry.

Some of the symptoms are “negative” (eg,

numbness and sensory loss), as one would expect with nerve damage, while others are “positive” (eg, paresthesia, increased appreciation of pain, and spontaneous jolts of pain). These positive phenomena are of great interest to pain specialists and researchers, as they are observable at the bedside and in the clinical laboratory.

Allodynia is the experience of nonnoxious sensation as painful. It can occur after bodily injury, when stimulation of nociceptors causes regional stimulation of all nociceptors near the injury, exquisite pain, and hypersensitivity to all tactile and thermal stimuli. This widespread stimulation, known as primary sensitization, is commonly experienced as short-lived redness and tenderness (rubor and dolor). With healing, the hypersensitivity to all stimuli generally resolves.

Allodynia that persists after healing is presumed to be a residual effect of sensitization of the second-order neuron (central sensitization; see below) from nervous system damage.

Temporal summation of pain is an incremental increase in pain when a constant painful stimulus is applied repetitively to the same dermatome. It is related to allodynia and can be observed at the bedside.

Causalgia is a constant burning pain. It frequently occurs with nerve injury and can also occur spontaneously. Causalgia frequently accompanies allodynia and other spontaneous pains such as stabbing or tic-like pains.

TABLE 1 lists conditions frequently associated with neuropathic pain.⁵ Damage anywhere along the pain-conducting route (see below) can cause neuropathic pain, but the inciting damage may not be easy to determine.^{1–3,5}

■ MECHANISMS OF PAIN

Multiple pathophysiologic processes underlie neuropathic pain and serve as targets for medical pain management. These are discussed below and are outlined in FIGURE 1. A thorough discussion is beyond the scope of this article; interested readers are referred to reviews on the subject.^{6–11}

In response to a painful stimulus, nociceptors send a wave of depolarization up a first-order neuron, with sodium rushing in through sodium channels and potassium rushing out.

First-order neurons terminate in the dorsal horn of the spinal cord (or its counterpart in the brain stem, the trigeminal nucleus caudalis). There, the electrochemical impulse opens voltage-gated calcium channels in the presynaptic bouton, allowing calcium to enter. The entry of calcium allows the neurotransmitter glutamate to be released into the synaptic space. Glutamate binds to *N*-methyl-*D*-aspartate (NMDA) receptors on the second-order neuron, causing depolarization.

Second-order neurons cross over to the opposite side of the spinal cord and continue up to the thalamus, where they synapse with third-order neurons. Third-order neurons, in turn, connect to specific areas in the limbic system and cerebral cortex.

Another pathway inhibits the transmission of pain signals in the dorsal horn. Antinociceptive (analgesic) neurons start in the brain stem and travel down the spinal cord. They synapse with short interneurons in the dorsal horn by releasing serotonin and norepinephrine. These interneurons modulate the synapse between the first-order neuron and the second-order neuron by releasing an inhibitory neurotransmitter, gamma amino butyric acid (GABA). Inhibition of nociception occurs as a result of inhibition of synapses between first-order and second-order neurons, while enhancement may occur via inhibition of inhibitory synaptic connections.

■ PERCEPTION OF NEUROPATHIC PAIN

Although much has been discovered about nociception, relatively little is known about the mechanisms of neuropathic pain, and theories abound as to why it develops in some people and not in others. Several mechanisms are considered important; they have been studied in animals but may not necessarily apply to humans.

First-order neurons may increase their firing if they are partially damaged and increase the number of sodium channels. Depolarization is enhanced at certain sites in the fiber, such as neuromas, resulting in ectopic discharges.¹² This mechanism may cause tic-like spontaneous pain and movement-related pain.

Inhibitory (analgesic) circuits may be

Neuropathic pain differs considerably from somatic and visceral pain

Case 1: A man with painful diabetic neuropathy

A 63-year-old man who has had poorly controlled type 2 diabetes mellitus for 25 years (hemoglobin A_{1c} 8.8%) presents to the pain clinic reporting 6 months of sleep disturbance from symmetrical burning pain in his feet.

He first noticed the pain at night and found he could not stand to have anything touch his feet, including the sheets. It became increasingly difficult to walk unless he was wearing certain shoes or slippers, and his feet hurt with any movement. He feels like he is “walking on cotton.” He cannot navigate without watching his feet or the floor, and at night he must hold onto furniture and walls. He has been using a wheelchair since developing lancinating pain in his feet.

Physical examination. The patient is overweight, resting pulse 110, orthostatic. Reflexes are absent in his hands and feet, with distal wasting associated with intrinsic hand muscle weakness and bilateral foot drops.

He has loss of touch, joint position sense, and awareness of pinprick to just above the elbows and halfway between the knee and the groin symmetrically. There is a teardrop pattern of sensory loss over the abdominal wall. The Romberg test is grossly positive (the patient cannot maintain a standing position with feet together when he closes his eyes).

Ophthalmologic examination reveals background and proliferative retinopathy.

CASE MANAGEMENT

The patient is started on amitriptyline in small doses, but he cannot tolerate it because of severe constipation, hypotension, and urinary retention.

He is next started on gabapentin 100 mg a day. The dose is then increased, but because of renal insufficiency, it is only increased to 100 mg three times a day and maintained on that dosage. He reports that burning pain at rest has improved from a baseline level of 8 (out of 10) to between 3

and 4. However, allodynia in both feet remains problematic.

Mexiletine (an oral lidocaine analogue) is added to therapy but he cannot tolerate it because of nausea and vomiting.

Next, duloxetine (an SNRI antidepressant) is started at a dose of 20 mg at night and gradually increased to 60 mg at night. His chronic burning pain improves to between 1 and 2, his shooting pain is eliminated, and his mood improves. He still cannot walk because of proprioceptive loss.

COMMENTS

This case illustrates the all-too-common phenomenon of painful diabetic neuropathy in a patient with poorly controlled diabetes mellitus. He exhibited multiple sites of end-organ damage, and his axonal or length-dependent neuropathy (the longest fibers are most vulnerable) involved not only poorly myelinated and unmyelinated fibers, but also fast-conducting myelinated fibers subserving soft touch and joint position.

The clinician first chose amitriptyline, probably because the patient also had depression and trouble sleeping, and his pain was worse at bedtime. Not surprisingly, he could not tolerate even small doses because of autonomic neuropathy from poorly myelinated nerve fibers, making the resulting gastroparesis and orthostasis prohibitive.

Gabapentin was a better first choice, but the dosage had to be modified for his renal failure, as the drug is excreted renally. Because analgesia was incomplete, mexiletine was added but not tolerated because the patient was normally orthostatic. Next, duloxetine was added in the hope that it would control the allodynia and the increased pain sensitivity. The dosage should be only gradually increased for patients with renal failure. Although the patient's pain and mood improved, large-fiber neuropathy continued to impair his ability to walk.

impaired at the level of the dorsal horn, brain stem, or both, allowing pain impulses to come in unopposed. This mechanism might explain central (spinal cord or brainstem) neuropathic pain syndromes.

Alterations in central processing of pain may be functional rather than structural. With prolonged pain or use of certain drugs, the second-order and third-order neurons may develop a “memory” of pain and become cen-

trally (or secondarily) sensitized. Chronic pain states such as headache disorders or pain after failed back surgery may develop by this mechanism.^{13–15}

A combination of mechanisms can be involved in many chronic neuropathic or mixed neuropathic and somatic pain states.

For example, early in postherpetic neuralgia, patients may have hyperactive or irritable nociceptors amenable to treatment with local anesthetics and sodium channel blockers. More entrenched cases exhibit pain due to both loss of first-order neurons and disinhibition of pain-conducting pathways; patients may have complete loss of sensation yet can have spontaneous burning pain, spontaneous jabs of sharp pain, temporal summation of pain, and allodynia in the same dermatome. In refractory cases, severe pain can occur independently of any exogenous noxious stimuli, indicating a form of self-sustaining, central neuronal hyperexcitability.

■ MEDICATIONS FOR NEUROPATHIC PAIN

Currently used medications are aimed at the mechanisms of neuropathic pain. But drug and nondrug therapies provide complete or partial relief of pain in only about half of patients, leaving considerable room for improvement.²

A rational treatment approach

Several recent evidence-based reviews examined which agents offer the most objective benefit.^{9,11–17} All call for rational polypharmacy with combinations of medications targeted at many or all of the supposed mechanisms.

However, data are inconsistent among many studies: some used a 50% reduction in pain as the primary measure of efficacy while others used only 30%.¹⁸ Many drugs have not been studied using the rigorous scientific standards used today, and it is unlikely that those currently off-patent will ever be.

Another problem is that therapy has been extensively evaluated in only two conditions: postherpetic neuralgia and painful diabetic neuropathy. Most of the recommendations herein are based on studies of these two conditions, and extrapolating the results to other

neuropathic conditions such as reflex sympathetic dystrophy (complex regional pain syndrome I) or chronic pain due to failed back surgery may not be valid. Other neuropathic conditions such as poststroke pain and post-surgical states have also been studied, but not to the same extent.

Nonopioid analgesics

No randomized, double-blind studies of common nonopioid analgesics (nonsteroidal anti-inflammatory drugs [NSAIDs] and non-NSAIDs) for treating neuropathic pain have been done. But lack of hard data should not discount their potential usefulness: NSAIDs have demonstrated both a peripheral analgesic effect and a central one.^{19,20}

Common nonopioid analgesics such as acetaminophen have proven successful as adjuvants in treating cancer pain, which often is both nociceptive and neuropathic. They work synergistically with opioids and permit a lower dose of opioid to be used. However, their use comes with a higher risk of complications in medically fragile patients.¹⁹

Opioid analgesics

Opioid analgesics presumably inhibit central ascending pain impulses,¹⁴ but whether they should be used for treating neuropathic pain has been much debated. Classic teaching holds that neuropathic pain is opioid-resistant, and that opioids are best suited for visceral and somatic nociceptive pains.²¹ In addition, many physicians avoid using opioids to treat neuropathic pain, in large part because of concerns about regulatory scrutiny, drug abuse, and addiction.

But recently, several carefully conducted trials have found opioid analgesics to be effective for neuropathic pain.^{22–25} Controlled-release oxycodone was superior to placebo for relieving pain, allodynia, sleep disruption, and disability. Dosages were as high as 60 mg per day for postherpetic neuralgia and 120 mg per day for painful diabetic neuropathy.^{22,23} A similar placebo-controlled study found delayed-release morphine (as much as 300 mg/day) effective for phantom limb pain.²⁴

A unique study²² compared tricyclic antidepressants, opioids, and placebo and found that delayed-release morphine was better than

Therapy has been extensively evaluated only in postherpetic neuralgia and painful diabetic neuropathy

Case 2: A woman with postherpetic neuralgia

A 72-year-old woman who is otherwise healthy presents to the pain clinic accompanied by her daughter.

She reports pain in her right T8 dermatome 6 months after she developed a discrete, papular, pruritic rash in the same region. The original rash was painful and was diagnosed as shingles, which an anesthesiologist treated unsuccessfully with thoracic nerve blocks.

Although the rash healed with minimal scarring in 6 to 8 weeks, she is left with severe burning pain and exquisite sensitivity to touch in the area of numbness. She cannot wear anything but her pajamas, which she has worn to her appointment. She tried taking hydrocodone and acetaminophen but stopped because of extreme constipation and nausea.

Physical examination is normal except for scarring of the skin in the area of the healed rash. She grimaces in paroxysms from shooting pain during the examination. She has impaired sensitivity to pinprick and touch over the T8 dermatome on the right but still has sensation. Pinprick is more painful in the right T8 region than the left.

CASE MANAGEMENT

A 5% lidocaine patch is placed over the most painful areas of the skin daily and removed after 12

hours. This eliminates her burning pain, which she originally rated as 6 out of 10. For the shooting pain and constant aching pain, she is prescribed pregabalin 150 mg twice daily, which provides complete relief of the pain.

Eight months later she tapers off all medications. She is left only with a mild sensory disturbance in the right T8 dermatome.

COMMENTS

This is a typical presentation of postherpetic neuralgia in an otherwise healthy elderly woman. Thoracic nerve blocks failed to control or prevent its development. She had persistent allodynia in the involved dermatome: the positive response to dermal lidocaine suggests an element of nociceptor irritability or hyperexcitability.

Her spontaneous tic-like pain and residual aching pain did not completely respond to the local anesthetic. The physician looked for additional analgesics and considered using an antiepileptic drug or antidepressant. On the basis of published trials, he chose pregabalin, but a tricyclic antidepressant or SNRI would also have been an appropriate choice. Another option would have been to change the opioid analgesic to methadone, delayed-release morphine, or delayed-release oxycodone: nausea from one opioid does not preclude the use of another.

tricyclic agents against pain and sleep disruption. Opioids were, however, associated with more side effects.

Rowbotham et al²⁶ treated patients who had a variety of painful central and peripheral neuropathic conditions with levorphanol, a long-acting, potent opioid. Dose escalation resulted in greater analgesia without necessarily inducing greater sedation.

Protocols for prescribing opioid analgesics for cancer pain can provide guidance for treating patients with neuropathic pain. In general, controlled-release opioids given on a *scheduled* basis are recommended for patients with persistent or continuous pain to promote constant levels of analgesia, prevent fluctuations in blood levels, and avoid adverse events asso-

ciated with high peak opioid levels.¹⁹

Rescue doses of a short-acting version of the same medication, if available, should be provided for breakthrough pain. The recommended starting dose for rescue is approximately 10% to 15% of the total daily dosage of opioid used, every 3 to 4 hours as needed.

Oral preparations are recommended if the patient has a functioning gastrointestinal tract, owing to their greater ease of use and cost-effectiveness. Transdermal, rectal, sublingual, and parenteral preparations are commonly used in patients who cannot tolerate oral drugs.¹⁹

Tramadol has proven effective for neuropathic pain management. Although it is not classified as a schedule II opioid analgesic, it is

a mu-opioid agonist that also inhibits the reuptake of norepinephrine and serotonin.^{27,28} In studies, when doses were carefully titrated to a maximum of 400 mg per day in four divided doses, tramadol proved more effective than placebo for postherpetic neuralgia, painful diabetic neuropathy, and other neuropathic pains. Not surprisingly, it can cause central nervous system side effects, including amnesia in the elderly. It also has the potential for abuse.¹³

Antidepressants

Antidepressants increase synaptic serotonin and norepinephrine levels, thereby enhancing the effect of the descending analgesic system.^{9,13,25,29–33} They have been the mainstay of neuropathic pain therapy ever since the first studies of their analgesic potential were published nearly 2 decades ago.

Tricyclic antidepressants (eg, amitriptyline, imipramine, nortriptyline, doxepine) were the first antidepressants recognized as beneficial for postherpetic neuralgia, painful diabetic neuropathy, and other conditions such as central poststroke pain. They are also effective against steady burning or aching pain and tic-like spontaneous pain.³⁰

Tricyclic antidepressants have proven significantly more effective for neuropathic pain (including postherpetic neuralgia and painful diabetic neuropathy) than the newer selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline, and citalopram.^{29–33} The reason they are more effective may be that they inhibit reuptake of both serotonin and norepinephrine, while SSRIs inhibit only serotonin reuptake.

The “number needed to treat,” ie, the ratio of the total number of patients treated to those who obtained $\geq 50\%$ pain relief,⁹ was as low as 1.4 in placebo-controlled studies of tricyclic antidepressants, but as high as 7 in studies of SSRIs.^{9,30}

Tricyclic antidepressants can have problematic side effects, including sedation, confusion, constipation, and serious cardiovascular effects such as conduction blocks, tachycardia, and ventricular arrhythmias. They can also cause weight gain, lowering of the seizure threshold, and orthostatic hypotension. Recent reports in the lay press regarding sui-

cide among teenagers treated with SSRIs highlight a similar concern about tricyclic antidepressants.³⁴

Tricyclics must be used with special care in the elderly, who are especially prone to their serious side effects. The drug concentration in the blood should be monitored to avoid toxicity in patients who are slow drug metabolizers.⁹

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are a new class of balanced antidepressants. Like tricyclics, they seem to be more effective than SSRIs for treating neuropathic pain, because they also inhibit reuptake of both norepinephrine and serotonin.^{35–37}

Venlafaxine is as effective against painful polyneuropathy (including painful diabetic neuropathy) as imipramine (the standard reference tricyclic antidepressant), and both are significantly better than placebo.

Duloxetine, a newer SNRI, has received approval from the US Food and Drug Administration (FDA) for treating painful diabetic neuropathy on the basis of two large, randomized, double-blind, multicenter studies.³⁵

Duloxetine has also proven effective against fibromyalgia-related pain. Some researchers consider fibromyalgia to be a neuropathic or neurogenic condition involving a reduced pain threshold because of central nervous system nociceptive neuronal hyperexcitability (ie, central sensitization).³⁸

Like the tricyclic antidepressants, the SNRIs seem to confer benefits independent of their antidepressant effects.

Side effects include sedation, confusion, hypertension (from the rise in synaptic norepinephrine), and a perplexingly difficult withdrawal syndrome in some patients.

Local anesthetics

Local anesthetics stabilize sodium channels in the axons of peripheral first-order neurons, blocking spontaneous ectopic impulses in a dose-dependent manner.

These agents appear to work best when a nerve is only partially injured, a remnant of nociceptor function remains, and excess sodium channels have accumulated.¹⁵ Additional mechanisms may include modification of NMDA receptor activity and opioid-like

Nausea from one opioid does not preclude the use of another

effects.¹⁵ They suppress nociceptive impulses at concentrations below which they suppress normal sensorimotor impulses.

Topical lidocaine is the best-studied agent of this class for neuropathic pain. Randomized, double-blind, placebo-controlled studies support the use of the 5% lidocaine patch for postherpetic neuralgia and have led to its approval by the FDA.³⁹ The patch appears to work best when there is retained, but damaged, peripheral nervous system nociceptor function in the involved dermatome, manifesting as allodynia. The lidocaine patch does not appear to work when complete deafferentation has occurred.³⁹ It can be cut to fit a swath of involved dermatome and also functions as a physical barrier to protect allodynic skin. It should be placed directly on the symptomatic area for 12 hours and removed for the next 12 hours, and can be used for years in this manner. Aside from local skin reactions, it is well tolerated. Systemic blood levels are negligible, obviating concerns of systemic and cardiac toxicity.

Intravenous lidocaine in bolus doses of 5 mg/kg has been studied for patients with painful diabetic neuropathy and postherpetic neuralgia in a monitored unit, and it led to prolonged relief lasting 3 to 21 days. The successful results suggest that the oral preparations of tocainide and mexiletine may also be useful.^{15,40} No follow-up studies have been conducted, and the need for cardiac rhythm monitoring makes this approach prohibitive for many practitioners.

Antiepileptic drugs

The most impressive recent advances in neuropathic pain treatment involve antiepileptic drugs, which are now first-line therapy. They function in several ways:

- By modulating voltage-gated sodium and calcium channels
- By enhancing the inhibitory effects of GABA
- By inhibiting excitatory glutaminergic transmission.

Wiffen et al⁴¹ reviewed 23 trials of anti-convulsants, including carbamazepine, phenytoin, clonazepam, sodium valproate, and gabapentin. No evidence that antiepileptic drugs are effective for acute pain was found.

For chronic pain syndromes (defined as lasting 6 months or longer), little evidence supported the use of antiepileptic drugs as first-line drugs, except for the treatment of trigeminal neuralgia.

Carbamazepine was approved for the treatment of trigeminal neuralgia in the 1970s, and it is still routinely used for this condition and other neuropathic disorders involving acute tic-like or lancinating pains. However, at the time it was approved, clinical research was not as scientifically rigorous as it is now, and although carbamazepine may be effective, the trials were small. A Cochrane database systematic review included 12 valid trials for evaluation.⁴² For trigeminal neuralgia, the number needed to treat was 1.8; for diabetic neuropathic pain, the data were insufficient to determine carbamazepine's role.⁴²

Gabapentin was recognized as effective for neuropathic pain soon after it was introduced as an antiepileptic. A major advantage is that it does not interfere with other antiepileptic drugs. Gabapentin acts by inhibiting calcium channel function through agonist actions at the alpha-2 delta subunit of the calcium channel.

Studies of gabapentin for painful diabetic neuropathy and postherpetic neuralgia have led to its approval for the latter.^{43–47} Dosages between 1,800 mg and 3,600 mg per day in three divided doses significantly reduce pain compared with placebo, and mood, sleep, and other quality-of-life indices also improve.

Because it acts centrally, gabapentin can cause fatigue, confusion, and somnolence. To avoid these adverse effects the drug may need to be titrated upward slowly, starting at 100 to 300 mg a day and increasing by 100 to 300 mg a day until the target dose is reached. A full therapeutic effect may not occur for 8 weeks or longer. Gabapentin's pharmacokinetics are saturable, so larger doses do not necessarily lead to higher blood or tissue levels: 3,600 to 4,800 mg per day is generally recommended as a ceiling dose.

Pregabalin is similar to gabapentin and appears to be as effective. It offers several advantages: a faster onset of action (with benefits seen within 7 days), linear kinetics that allow a patient to start therapy at a clinically

Lidocaine patches should be worn for 12 hours on, 12 hours off

effective dose, and a rapid titration schedule for patients who need higher doses.

Like gabapentin, pregabalin is not a GABA agonist but rather binds a subunit of the voltage-gated calcium channel, where it reduces calcium influx and the release of neurotransmitters (glutamate, substance P, and calcitonin gene-related peptide) at the primary afferent nerve terminals.

Pregabalin has been approved for treating painful diabetic neuropathy and postherpetic neuralgia on the basis of large, multicenter, randomized, double-blind, placebo-controlled studies.^{48–51} Patients treated with pregabalin (≥ 150 mg per day) had mean reductions in their pain scores of at least 50% by the end of the first week and in some cases even earlier. Benefits were maintained throughout the studies, and other factors such as sleep, mood, and quality of life also improved. Side effects were similar to those seen with gabapentin.

Oxcarbazepine was recently evaluated in two trials. A small open-label trial suggested it was effective for postherpetic neuralgia in patients who got no relief from carbamazepine and gabapentin.⁵² In a larger placebo-controlled trial,⁵³ patients with painful diabetic neuropathy for at least 6 months had significantly better pain scores than at baseline after treatment with oxcarbazepine, suggesting it has a role as monotherapy in chronic painful diabetic neuropathy.

Topiramate was recently approved for preventing migraine headaches. It enhances GABAergic neurotransmission and blocks glutamate neurotransmission at voltage-gated calcium channels.

Several studies have found topiramate to be better than placebo and as effective as other agents for diabetic and nondiabetic neuropathic pain, but it is slower to act than pregabalin.^{54–56} A recent double-blind, placebo-controlled study found that by 8 weeks, half of the treated group achieved a 30% reduction in mean pain and one third achieved a 50% reduction. Side effects contributed to a high dropout rate and included paresthesia, confusion, forgetfulness, and anorexia. Most patients lost weight, which most considered a benefit.⁵³

Other antiepileptic drugs have not been studied as extensively.^{15,41}

■ MORE THAN ONE DRUG IS OFTEN NEEDED

No specific guidelines for neuropathic pain have yet been developed. As in other pain syndromes such as migraine headache, the initial treatment should be based on the patient's personal needs, concerns, and accompanying conditions such as depression, anxiety, insomnia, obesity, and anorexia. The choice also depends on the history and the characteristics of the pain, including whether it is intermittent or constant. As in cancer pain management, a key to success is to frequently reassess the analgesic effect and adverse events.¹⁹

The clinical approach to therapy must rely on available data and the practitioner's familiarity with the various classes of drugs. Often, no single drug relieves the pain completely²; combination therapy with agents that work at different sites and by different mechanisms may be necessary.

Antidepressants, antiepileptics, or both for intermittent or tic-like pain

Antiepileptic drugs have traditionally been used to treat intermittent or tic-like pain; carbamazepine is the standard for treating trigeminal neuralgia. However, there is little evidence to suggest that antiepileptic drugs are better than antidepressants or other drug classes in this regard.

If a patient has depression and frequent interruptions of sleep due to pain, one can start with a low dose of a tricyclic antidepressant at bedtime. The dosage can be increased every 4 to 7 days until treatment is effective or side effects develop. An adequate treatment trial requires 2 to 3 months.

SNRIs offer an alternative for patients who cannot tolerate the side effects of the tricyclics. They can be given in the morning, and more rapid benefits might be achieved than with the tricyclics. Some clinicians use both SNRIs and tricyclics together in some patients, but the growing body of literature on the treatment of neuropathic pain almost entirely neglects approaches involving combinations of drugs or drug classes (M. Backonja, MD, personal communication).

The most impressive recent advances in neuropathic pain involve antiepileptic drugs

An alternative approach is to use an antiepileptic drug as a first-line treatment for intermittent pain. Antiepileptic drugs can be added to antidepressants or vice versa. Gabapentin and pregabalin are the best-studied, and their benefits can occur within days to weeks. Especially with pregabalin, titration can be rapid compared with antidepressant analgesics.

In postherpetic neuralgia or painful diabetic neuropathy, pregabalin can be started at 50 mg three times a day and can be titrated over a matter of days to 600 mg a day. The benefit may be dose-dependent for both pregabalin and gabapentin. Alternatives to gabapentin and pregabalin are carbamazepine and oxcarbazepine: their effective dosages may be well below the doses used for seizure prevention.

Lidocaine, opioids may be needed for constant or persistent pain

Choosing the best treatment for constant or persistent pain can be challenging. There are few published reports to help as a guide other than the studies of intravenous infusions of lidocaine, a treatment impractical for many.

Lidocaine patches are effective for discrete areas of constant burning pain, especially if they are also allodynic.

For broad surface areas, more systemic approaches are necessary: if antiepileptic and antidepressant agents, used alone or in combination, do not suffice, opioid therapy becomes an important option.

Opioid analgesics remain among the most versatile drugs available for pain, notwithstanding concerns about adverse effects and physical and psychological dependence.¹⁹ They can be given by the oral, sublingual,

transdermal, rectal, intravenous, subcutaneous, intramuscular, or spinal routes. Some are long-acting (eg, methadone, levorphanol), while others have a shorter duration of action (eg, morphine, hydromorphone, oxycodone).

Novel delivery systems have significantly extended the pharmacokinetic profiles of individual short-acting agents. These technological advances have set the stage for the judicious use of opioids for pain that is persistent or intermittent, chronic or acute, or any mixture thereof.

Now that several carefully designed studies have demonstrated that opioid analgesics can play a role in various aspects of neuropathic pain treatment,^{22,23} rational polytherapy is possible.

The principles of therapy are similar to those in cancer pain management,¹⁹ with around-the-clock, scheduled dosing of delayed-release opioid analgesics for constant or persistent neuropathic pain. Rescue doses of short-acting opioids are reserved for short-lived, breakthrough pain, whether it is spontaneous and tic-like or incident-related ("incident pain"). The goal of therapy is to suppress any persistent pain with a minimum of adverse effects, at the same time anticipating and suppressing breakthrough pain.

Usually, opioids are used as add-on therapy when initial therapy with the combination of an antiepileptic drug and an antidepressant is insufficient. But for pain that is so disabling that a patient cannot wait for benefit from nonopioid therapy, an opioid may be chosen as first-line therapy. Nonopioid drugs may be started simultaneously, and when treatment has been successful, the opioids may be slowly tapered off.

Usually, opioids are added on when an antiepileptic drug and an antidepressant are insufficient

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