

NEUROPATHIC PAIN

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People usually think of pain as having some external physical cause that if removed would eliminate the pain. An unstable fracture, mass effect from tumor, and inflammation from underlying connective tissue disease are examples of mechanical or inflammatory stimuli that cause this type of pain (ie, nociceptive). However, the nervous system itself can also generate and perpetuate pain (ie, neuropathic), without any ongoing stimuli from injury. Examples of neuropathic pain include diabetic neuropathy, postherpetic neuralgia, phantom limb pain, trigeminal neuralgia, and sciatica. Neuropathic pain is often puzzling and frustrating for both patients and physicians because it seems to have no cause, responds poorly to standard pain therapies, can last indefinitely and even escalate over time, and often results in severe disability.

TYPES OF NEUROPATHIC PAIN

There are four common types of neuropathic pain;

- due to direct stimulation of pain-sensitive neurons
- automatic firing of damaged nerves,
- deafferentation, and
- sympathetically mediated pain.

DIRECT STIMULATION OF PAIN – SENSITIVE NEURONS

The primary sensory neurons that carry pain signals are called C-fiber nociceptors. They fire in response to mechanical stretching or compression and to certain chemicals (eg, prostaglandins, other mediators of inflammation).

A tumor compressing or stretching the brachial or lumbar plexus or spinal cord can produce pain that is perceived in the distribution area of those nerve structures. Lumbar disk herniation with its accompanying chemical irritants to the adjacent nerve root can produce sciatic nerve pain. Carpal tunnel syndrome is due to a combination of repetitive stretching of the median nerve, compression caused by edema, and inflammation producing chemical irritation of the median nerve.

Trigeminal neuralgia has been attributed to compression of a vascular structure on the trigeminal nerve near the brain stem.

In each of these examples, treatment is aimed at alleviating mechanical or chemical irritation through

- surgical decompression,
- chemical decompression (decompression with use of anticancer drugs or corticosteroids)
- or resting, (splinting) the affected body part.

AUTOMATIC FIRING OF DAMAGED NERVES

Nerve fibers that have been damaged by injury or disease can fire spontaneously at the site of injury or at ectopic foci along the damaged nerve. Resulting paroxysms of pain are often described as lancinating, stabbing, or shooting. When many nerve fibers are affected and fire asynchronously, neuropathic pain has a quality of continuous burning. This process of automatic firing can last indefinitely and represents one cause of persistent physiological pain. It also explains how pain can occur in a part of the body that is numb (anesthesia dolorosa). When large-diameter fibers are damaged, as in diabetic neuropathy, ectopic impulses can be generated in the small-diameter fibers (C-fiber nociceptors) that carry pain sensation (1).

DEAFFERENTATION

Under normal conditions, sensations are transmitted from peripheral tissues via a connected chain of neurons in the spinal cord, brain stem, and brain. Interruption of any portion of that chain provides the potential for increased irritability and firing of nerves further up the pathway. This phenomenon explains how phantom limb pain can occur: Loss of sensory input from a limb can produce spontaneous firing of second- and third-order neurons, resulting in pain and other sensory experiences in the missing limb.

Similarly, nerves damaged by diabetic neuropathy, post-herpetic neuropathy, or peripheral nerve trauma may generate firing in the higher-order nerves and, thus, ongoing pain. A stroke causing a strategic lesion in the pain pathway can result in ongoing deafferentation pain that is experienced at one body site but is generated at the infarct site or further along the pain transmission pathway.

SYMPATHETICALLY MEDIATED PAIN

Any painful stimulus can trigger autonomic activity at about the same dermatomal level of the spinal cord. Thus, injury often initiates regional changes in circulation and temperature. The first response often is warm-

ing and increased circulation, probably to aid the inflammatory response. However, the autonomic nervous system can continue to respond in a changing pattern of sympathetic hyperactivity. Vasomotor and sudomotor changes are usually seen as cooling of the skin, sweating, and circulatory dysregulation.

The sympathetic nerves release norepinephrine, which can stimulate the primary sensory nerve for pain (C-polymodal nociceptor [C-PMN]), causing pain and fueling further sympathetic activity. Thus, a repeating process, called sympathetically mediated pain, is put in motion. When the condition persists or progresses, the clinical syndrome is called complex regional pain (previously known as reflex sympathetic dystrophy or causalgia). Treatment is aimed at interrupting the cycle by blocking sympathetic nerve ganglia.

DIAGNOSIS OF NEUROPATHIC PAIN

The first step in managing neuropathic pain is recognizing it as part of the presenting problem. The clinical setting; quality, timing, and distribution of the pain; and accompanying physical signs can be valuable clues and should be carefully evaluated during history taking and physical examination.

CLINICAL SETTING

Certain medical conditions are associated with neuropathic pain, and when a patient with such a condition presents with pain, a neuropathic process should be considered. For example, up to half of patients with multiple sclerosis have pain related to the disease. HIV has a predilection for nerve tissue and thus causes neuropathy or myelopathy, often with resultant neuropathic pain, in a high percentage of patients. Diabetes can affect the peripheral nervous system at all levels and cause neuropathic pain that has an acute onset or progresses insidiously.

Condition	Type or distribution of pain
Diabetes	Peripheral neuropathy Mononeuropathy Radiculopathy
HIV infection or AIDS	Peripheral neuropathy Mononeuropathy Radiculopathy Myelopathy
Multiple sclerosis	Myelopathy Trigeminal neuralgia Scattered nerve pain
Cancer chemotherapy	Peripheral neuropathy
Spine surgery	Radiculopathy
Alcoholism with neuropathy	Peripheral neuropathy Mononeuropathy
Herpes zoster	Radiculopathy (dermatome)
Amputation	Neuroma Phantom limb

PAIN QUALITY AND TIMING

Although neuropathic pain can be described in almost any way, adjectives that patients are most likely to use include shooting, stabbing, lancinating, burning, and searing.

Neuropathic pain is often worse at night, which distinguishes it from many other types of pain. For example, muscular pain is usually worse during the day when activity is increased. Inflammatory pain is worse first thing in the morning and during activity. Mechanical pain is worse during activity and often eases at night with lying in bed in a special position. Patients are often perplexed by this phenomenon of heightened pain at night or when stimulation is reduced. The reason may be twofold. First, lack of competing stimuli can heighten neuropathic pain (gate mechanism). Second, circadian rhythms are known to affect pain thresholds.² It is conceivable that many chemicals modulate neuropathic pain and have circadian variations throughout the day and night.

PAIN DISTRIBUTION

Perhaps the most distinguishing feature of neuropathic pain is its anatomic pattern or distribution. Neuropathic pain follows nerve distributions, depending on whether it results from peripheral neuropathy (stocking-glove distribution), radiculopathy (dermatomal distribution), or myelopathy (spinal cord level). In contrast, inflammatory and muscular pain have very different patterns.

PHYSICAL SIGNS

Physical examination can often clinch a diagnosis of neuropathic pain that was suggested by history taking. Examination in a patient reporting pain should always include inspection of the painful body part and comparison with the contralateral side for colour, temperature, skin texture, sensation, and weakness. Documentation of a neurologic deficit in the distribution of pain helps build a case for neuropathic pain syndrome.

Sometimes physicians are as surprised as their patients to hear that severe pain is present at a site that is numb or even insensate. Anesthesia dolorosa is one of the hallmarks of neuropathic pain. It occurs either because of automatic firing of higher-order neurons in the pain transmission pathway or because larger-diameter sensory nerves are damaged (causing numbness) but C-fiber nociceptors are still able to send pain signals.

The presence of allodynia (ie, pain from a non-noxious stimulus, such as light touching or rubbing) also suggests a neuropathic process. Sympathetically mediated pain is associated with autonomic changes in tissues, including cooling of the skin, abnormalities of

vascular tone, increased sweating, and neurogenic edema. In a patient who presents with a swollen limb that is redder and also cooler than the contralateral limb, a neurogenic process (rather than inflammation) should be suspected.

TREATMENT OF NEUROPATHIC PAIN

A suggested organizational plan for treatment of neuropathic pain is discussed in the following text.

DISEASE-SPECIFIC MEASURES

Making a diagnosis is the first step toward developing a treatment plan for neuropathic pain. Treatment of the underlying disease and management of symptoms should be considered simultaneously. For example, in a patient with diabetes, tighter glucose control is a good investment in pain control for the future³. Disease-modifying drugs for multiple sclerosis should be considered. Surgery, chemotherapy, or radiation therapy for decompression of nerve structures that are compressed by tumors may be beneficial. Antibiotics should be prescribed for treatable infections (eg, HIV, herpes zoster, Lyme disease).

LOCAL OR REGIONAL TREATMENT

Symptom control can be divided into local or regional measures and systemic treatment. Giving consideration to whether neuropathic pain can be managed with topical or regional treatment is always worthwhile, because these methods are usually better tolerated than systemic therapies. Even if local or regional measures are insufficient, they may allow for less aggressive drug therapy.

One local measure is topical application of capsaicin cream to localized areas of chronic pain near the skin surface⁴. Capsaicin, the pungent ingredient in chili peppers, causes local release of substance P from the C-PMN and, if used repeatedly (three or four times a day), can deplete substance P and limit pain transmission. However, the patient must be prepared for a 4- to 6-week trial and some initial burning with application.

Regional-anesthetic measures (eg, sympathetic nerve blocks, use of epidural or intrathecal pumps) can also be beneficial in appropriate cases. A series of sympathetic blocks can break the cycle of sympathetically mediated pain. When combined with other treatments, it can result in long-term remission or partial remission of complex regional pain. Other regional-anesthetic procedures should be considered temporary measures for pain relief. Epidural injections of corticosteroids with or without local anesthetic can temporarily ease radicular pain while more definitive therapies are proceeding. Intercostal nerve blocks can reduce the pain of herpetic neuralgia in the thoracic dermatomes.

Stimulation-based therapies (eg, transcutaneous

electrical nerve stimulation, acupuncture, spinal stimulation, massage) can help in cases of neuropathic pain. However, occasionally these methods aggravate symptoms, especially when allodynia is present. In these cases, stimulation of adjacent uninvolved dermatomes may be effective.

Physical-rehabilitation techniques (eg, splinting, bracing) can sometimes ease symptoms. For example, an ankle-fixation orthotic device may help reduce leg neuropathic pain in footdrop, or a wrist splint may ease the discomfort of carpal tunnel syndrome. Physical therapy techniques (eg, range-of-motion exercises) can be therapeutic and preventive in such conditions as complex regional pain.

Ordinarily, one should avoid nerve-destructive procedures because of the risk of neuropathic pain from neuroma formation or through deafferentation. In addition, residual numbness or weakness may occur when larger or mixed nerves are cut or avulsed or chemically destroyed. In terminal illnesses, these risks may be less important. A dorsal root entry zone lesion or dorsal rhizotomy interrupts pain fibers as they enter the dorsal horn of the spinal cord. Pain can be substantially reduced in one or more segments or dermatomes. A lateral cordotomy destroys the spinothalamic tract and eliminates pain transmission from the opposite side of the body below where the lesion is made. Usually, the lesion is made in the cervical cord. Trigeminal nerve ganglion ablations are carried out using radiofrequency energy, chemical neurolysis, or radiation for management of trigeminal neuralgia refractory to medical therapy.

SYSTEMIC TREATMENT

Local and regional measures alone are usually insufficient for optimal control of neuropathic pain. In systemic pain management, pharmacotherapy is the cornerstone and the addition of behavioral therapy is often useful.

Table 2. Commonly used drugs in treatment of neuropathic pain

Drug	Class & Dose range (mg/day)	Comments
Gabapentin	900-3,600	First-choice agent; reduce dose in renal failure.
Anticonvulsant		
Carbamazepine	600-1,200	First-choice agent for trigeminal neuralgia
Valproic acid	750-2,000	Useful in migraine and some neuropathic pain
Amitriptyline	25-200	First-choice agent; promotes sleep, improves mood; dose-limiting side effects
Tricyclic antidepressant		
Nortriptyline	25-200	Same as amitriptyline

Tricyclic antidepressant		
Desipramine	25-200	Same as amitriptyline but fewer anticholinergic properties.
Tricyclic antidepressant		
Mexiletine HCl	450-900	Limited efficacy for diabetic neuropathy; dose-limiting side effects
Antiarrhythmic		
Clonazepam	0.5-3	Limited efficacy, mainly for nocturnal pain
Benzodiazepine		
Dexamethasone	6-100	High doses used for cord compression or widespread bone metastasis; mainly for short-term use or in terminal illness
Corticosteroid		
Methadone HCl	5-100	Has N-methyl-D-aspartate receptor antagonist properties
Opioid		
Tramadol HCl	50-400	Short-acting analgesic effect; higher doses can produce seizures; can be habit-forming
Mixed weak opioid and serotonin reuptake blocker		

DRUG THERAPY:

Among the many drugs used to manage neuropathic pain, gabapentin has become the first choice of many pain specialists. Gabapentin is effective for the greatest variety of neuropathic pain states^{6,7} and has a favorable side effect profile and low rate of adverse drug-drug interactions. Other anticonvulsants have been used for neuropathic pain with varying success. For example, carbamazepine is the first choice for trigeminal neuralgia, and valproic acid is beneficial in some cases of neuropathic pain and in migraine.

Tricyclic antidepressants, such as amitriptyline hydrochloride, nortriptyline hydrochloride, and desipramine hydrochloride are also effective for neuropathic pain, as well as for other types of chronic pain^{8,9}. These agents probably work by enhancing the descending inhibitory pathway for pain through inhibition of serotonin and norepinephrine reuptake. In addition, tricyclic antidepressants promote sleep and stabilize mood. The major drawback is dose-limiting side effects (eg, dry mouth, excessive sedation, urinary retention, orthostatic hypotension, cardiac arrhythmia). The combination of a tricyclic antidepressant and gabapentin may produce a better effect than either drug alone, probably because the drugs work by means of different pain-control mechanisms.

Agents from other drug classes also have been shown to be effective for neuropathic pain. The antiarrhythmic drug mexiletine hydrochloride has sodium chan-

nel blocker properties similar to those of lidocaine and has been shown to be effective in management of painful diabetic neuropathy¹⁰. However, mexiletine is prone to such dose-limiting side effects as gastrointestinal upset and dizziness¹¹. The benzodiazepine clonazepam may be useful in nocturnal pain, and corticosteroids (eg, dexamethasone) have a stabilizing effect on neuronal membranes along with their usual anti-inflammatory effects.

N-methyl-D-aspartate (NMDA) receptor antagonists, which include dextromethorphan and some experimental drugs, have also been found to be beneficial. The NMDA receptor in the dorsal horn of the spinal cord mediates neurogenic hyperalgesia, so agents that block this receptor may control neuropathic pain. Methadone hydrochloride may have some NMDA receptor antagonist activity and therefore may be more effective for neuropathic pain than other opioids.

Although most opioids are not specifically directed at neuropathic pain¹², they are potent analgesics. Therefore, when other measures fail to control intractable neuropathic pain, opioids may have a role in reliable patients. Careful patient selection is critical to success in opioid therapy.

Another option is use of tramadol hydrochloride, a combination opioid and serotonin reuptake blocker. However, analgesic effects are short-lived and there is the possibility of dependence with this agent, as with opioids.

BEHAVIORAL THERAPY:

As most patients acknowledge, stress amplifies pain especially neuropathic pain. Relaxation can reduce excitability of the autonomic nervous system and probably reduce irritable neuronal firing. However, relaxation does not come naturally to most people, so relaxation skills must be taught. Such techniques as biofeedback, hypnosis, guided imagery, progressive muscle relaxation, and meditative techniques may promote a calmer state and greater sense of control over biologic functions that have spiraled out of control.

ILLUSTRATIVE CASE REPORTS

The following three case reports of neuropathic pain are typical of patient presentation to primary care physicians and illustrate the approaches discussed in the preceding text.

CASE 1 A 63-year-old man with diabetes has had burning pain in both feet for several months. It is much worse at night but also somewhat limits walking during the day. His only other health problem is benign prostatic hypertrophy. On physical examination, he is found to have absent Achilles tendon reflexes, sensitivity to light rub-

bing of the feet, and loss of pinprick and vibratory sensation symmetrically from toes to mid-shin.

There is no doubt that this patient has neuropathic pain. The presence of diabetes suggests the diagnosis, and the burning quality and nocturnal worsening of the pain indicate a neuropathic process. Pain distribution is that of peripheral polyneuropathy, and examination reveals characteristic symmetric peripheral polyneuropathy.

Treatment should begin with optimization of glucose control. Next, local measures should be used if possible, but choices are limited in this patient. Capsaicin cream has had some success in similar cases, but applying it to both feet three or four times daily as directed may be awkward for this patient. In addition, he may be unable to tolerate the cream's initial burning because of his allodynia. Topical anesthetic cream is also impractical on the feet because it is greasy and has limited duration of effect. Comfortable footwear should be recommended, with an insole of silicon or similar gellike material if possible. Such seemingly simple rehabilitative measures can sometimes make a big difference in a patient's ability to function.

The mainstay of treatment in this patient should be pharmacologic methods. Gabapentin therapy should be started, usually at a dose of 100 mg three times daily with rapid increases up to a target dose of 300 mg three times daily. If pain relief is inadequate but therapy is well tolerated, the dose may be increased to 600 mg three times a day, with reassessment of tolerance. Most patients derive benefit at gabapentin doses between 900 and 2,700 mg/day, but occasionally patients require and tolerate up to twice that amount. In patients with renal insufficiency, the total daily dose of gabapentin should equal about 10 times the creatinine clearance rate.

Use of tricyclic antidepressants may be considered, but the potential for urinary retention is increased in this patient because he has prostatic hypertrophy. If tricyclic antidepressant therapy is chosen, the best agent is probably desipramine because it has fewer anticholinergic properties than do other agents in this class.

Acupuncture and relaxation therapies may be useful adjuncts if the patient is open to these approaches.

One month after initial evaluation, the patient presents with acute shooting and stabbing pain in a band around the midabdomen to the back, on the left side only. On examination, he is found to have numbness to light touch and pinprick in a T10 distribution on the left side. There are no signs of visceral disease.

The patient has acute diabetic truncal radiculopathy. When pancreatitis and other visceral diseases have been ruled out, the dose of gabapentin can be increased tem-

porarily, or an intercostal nerve block to help reduce the pain can be considered.

CASE 2 An 83-year-old woman has severe burning and stabbing pain across the left shoulder blade and under the left breast. It has been present ever since she had shingles in the same distribution 4 months previously. The skin is so sensitive that she cannot wear a bra, and she rarely leaves the house. Breathing is painful, and an accompanying cough aggravates the pain to an intolerable level. The patient is becoming increasingly depressed and isolated. Her relatives brought her in because they see significant deterioration in her overall status. Examination reveals healed hypopigmented patches in a T4 distribution typical of prior herpes zoster infection. The skin in the hypopigmented area is numb, yet light stroking is unbearable. Breath sounds are diminished on the left side, and chest film findings are consistent with pneumonia.

This is another clear case of neuropathic pain. The clinical setting (herpes zoster infection), distribution of pain (dermatomal), character of pain (burning, stabbing), and examination findings (dermatomal numbness with allodynia) all fit the diagnosis. This patient has the complication of pneumonia from splinting against chest expansion, which is adding an inflammatory component to her total pain.

Topical application of anesthetic cream or viscous lidocaine (Anestacon, Xylocaine) to the affected area may be temporarily soothing, or an intercostal block may give temporary relief at this crucial time and allow for deeper breathing. Ice massage or transcutaneous electrical nerve stimulation may give the patient more control over her pain if she is not too disabled to use such a technique.

It is too late to modify the herpes zoster infection, but identification and treatment of the pneumonia is critical and can reduce at least one element of the pain. Appropriate pharmacologic pain-control options include gabapentin and an opioid analgesic, at least at night because of the severity of pain and the substantial disability it is causing. Treating the cough with an antitussive agent is also an important comfort measure.

CASE 3 A 32-year-old woman has chronic pain in the right hip, leg, and foot, which she describes as a continuous aching or searing sensation. Two years previously, she had L5 to S1 fusion for disk herniation that was causing pain in the lower back and left leg. After surgery, these symptoms mostly resolved, but new residual pain in the right lower extremity has not improved. The patient says that sensation in the right leg "just seems different." She walks with a limp favoring the right leg.

Physical examination reveals that the skin on the right leg and foot has some subtle mottling, is sensitive to touch, and is cooler than on the left. Lumbar magnetic resonance imaging shows surgical changes and some epidural fibrosis on both sides; electromyographic findings are normal. The patient reports that low-potency opioids "just take the edge off the pain" and cause her to feel "goofy."

This patient's presentation is not too unusual, but the diagnosis is not as evident as in the other cases. The clinical setting does not distinguish neuropathic pain from muscular or inflammatory pain. The searing quality suggests neuropathic pain, but aching is nonspecific. Distribution of pain is also nonspecific. In this case, physical examination produces helpful findings. The coolness, mottled appearance, altered sensation, and allodynia of the right leg all suggest sympathetically mediated pain or complex regional pain.

Treatment should consist of a series of lumbar sympathetic nerve blocks in combination with physical therapy to mobilize and desensitize the leg.

Gabapentin or tricyclic antidepressant therapy should also be prescribed. Alternative therapy may include acupuncture or myofascial release for the muscular component of the pain that often accompanies complex regional pain.

SUMMARY

Neuropathic pain can seem enigmatic at first because it can last indefinitely and often a cause is not evident. However, heightened awareness of typical characteristics, such as the following, makes identification fairly easy:

The presence of certain accompanying conditions (eg, diabetes, HIV or herpes zoster infection, multiple sclerosis)

Pain described as shooting, stabbing, lancinating, burning, or searing

Pain worse at night

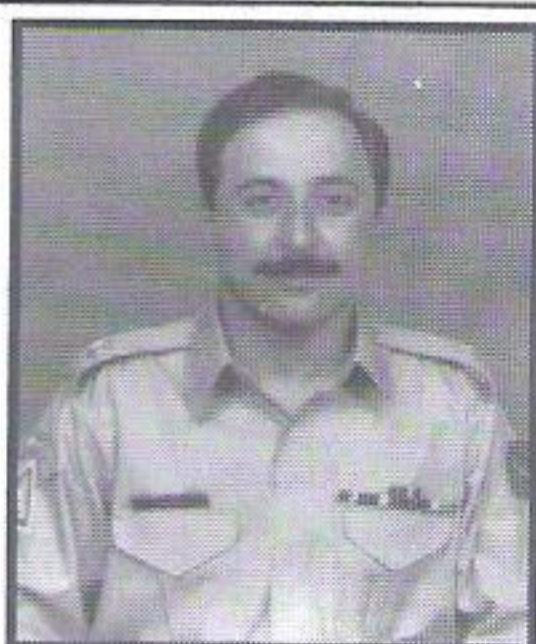
Pain following anatomic nerve distribution

Pain in a numb or insensate site

The presence of allodynia pain responds poorly to standard pain therapies and usually requires specialized medications (eg, anticonvulsants, tricyclic antidepressants, opioid analgesics) for optimal control. Successful pain control is enhanced with use of a systematic approach consisting of disease modification, local or regional measures, and systemic therapy.

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