

Chronic Pain: Physiological, Diagnostic, and Management Considerations

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The following descriptions of pain by patients who suffer with chronic pain syndromes suggest the complexity of the conscious experience of chronic pain:

“I feel as if someone has pulled the skin off of my left leg, and is then constantly rubbing salt into my leg.”

“I feel as if my leg is on fire. My skin feels burnt, and it is as if someone is taking claws and tearing into my skin twenty-four hours a day.”

“I feel as if someone has taken a hot poker knife and is jabbing it deep in my right eye. If I could pull my eye out, only to remove this sensation, I would gladly do so.”

The suffering experienced by patients who have chronic pain is immense. Something distinguishes their perception of pain from the simpler sensory experience of acute pain: chronic pain is processed within the nervous system in a more complex manner than acute pain.

Acute pain is a universal experience and is biologically protective. Acute pain is generally short lived, although, when there is an ongoing component of tissue injury, the pain may persist for days or weeks as the body attempts to heal from the initial insult. Acute pain is an appropriate response to an inciting event associated with actual or potential tissue damage.

Chronic pain is pain that persists more than 1 month longer than might be reasonably expected following an inciting event and is sustained by aberrant somatosensory nervous system processing. Chronic pain can last for months, years, and even decades. Chronic pain may be considered a pain sensation that arises from within the nervous system rather than from an

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external source [1]. This salient feature of chronic pain becomes the basis for differentiating it from acute pain and for understanding that patients who suffer from chronic pain are suffering from dysfunction of the nervous system.

Pain processing and perception

The International Association for the Study of Pain has defined pain as “an unpleasant sensory and emotional experience which we primarily associate with tissue damage or describe in terms of such damage, or both” [2]. An analysis of this definition makes it clear that the experience of pain is multimodal, including physical, sensory, emotional, and cognitive experiences, as well as a perception that may or may not be related to actual tissue insult [3–5]. The quotations given above give evidence of this experience.

Acute pain essentially arises from activation of peripheral pain receptors called nociceptors. Activation of nociceptors alone is not sufficient for the experience of pain, because there are central nervous system modifiers for the processing of nociceptive pain [6]. Illustrative of this concept are the familiar wartime stories of soldiers who are severely injured, but who are also in imminent danger, and who experience no pain until they reach safety. Thus, pain is a subjective experience that depends on the state of the nervous system.

The normal processing of acute, nociceptive pain begins in the peripheral nervous system in primary afferent neurons. These neurons, known as nociceptors, distinguish noxious from innocuous events. The transmitting nerves may be lightly myelinated or unmyelinated and are specialized to respond to mechanical, heat, thermal, and chemical stimuli. Threshold activation of nociceptive afferent neurons leads to afferent transmission of signals into the spinal cord. Most afferent input occurs by way of the dorsal root (Fig. 1), although some fibers traverse the ventral route. Nociceptive input can be modified within the spinal cord. Both nociceptive-specific neurons and more nonspecific, wide-dynamic-range cells can be activated from these afferent sensory pathways [7]. In the most simplistic view of pain processing, nociceptive-specific cells in the spinal cord ascend to the contralateral thalamus by way of the neocorticospinal thalamic tract. From the thalamus, afferent pathways then activate both primary and secondary somatosensory cortices (Fig. 1).

Pain-processing pathways, however, are more complex than previously realized. Wide-dynamic-range cells, which are activated by innocuous and noxious stimuli, can amplify afferent stimuli. In addition, more widespread ascending pathways from the spinal cord to the brain activate multiple brainstem and subcortical regions, limbic pathways, and both ipsilateral and contralateral cortical brain regions (Fig. 1) [6]. These pathways intermingle with regions of the brain that mediate emotions, autonomic activity, attention and localization, motor planning, and cognition [8].

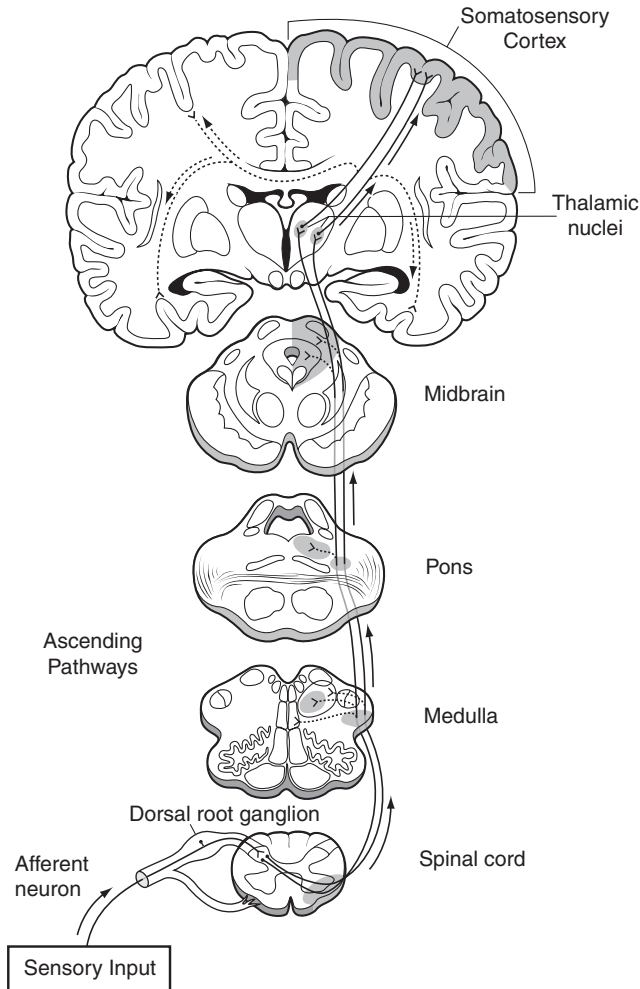


Fig. 1. Ascending pain pathways. Solid lines represent established pathways. Broken lines represent putative pathways.

Several descending pain pathways influence the perception of pain (Fig. 2). The best-studied descending pathway originates from the midbrain periaqueductal gray matter [6]. This brain region subserves the endogenous opiate system. The endogenous opioids comprise endorphins and enkephalins, which regulate the pain response, homeostasis, immune function, and the normal stress response. Activation of the periaqueductal gray matter leads to inhibition of dorsal horn neurons and subsequent analgesia, primarily through an excitatory connection with the dorsal raphe nucleus. The dorsal raphe nucleus (serotonergic) and locus ceruleus (noradrenergic) are two other brainstem centers that relay key descending pain-inhibitory

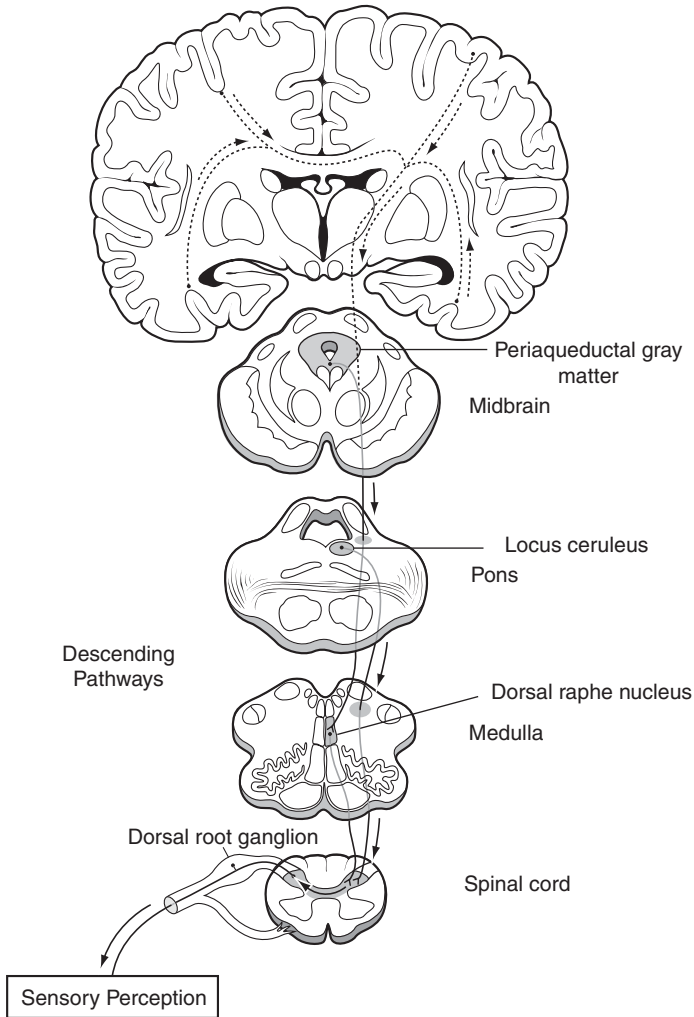


Fig. 2. Descending pain pathways. Solid lines represent established pathways. Broken lines represent putative pathways.

pathways (Fig. 2). These brainstem centers are modified by cortical, subcortical, and limbic pathways.

Additional brain regions are intimately involved in pain modulation through the activation of endogenous neurotransmitters, including acetylcholine, γ -aminobutyric acid (GABA), vasoactive intestinal peptide, oxytocin, somatostatin, cholecystokinin, vasopressin, histamine, prolactin, and cannabinoids [9–11]. Indeed, a host of endogenous neurotransmitters either inhibits or augments pain perception, but the manner in which these pathways become activated is poorly understood. These pain-modulating

pathways and their neurochemical substrate become one basis for the pharmacologic management of chronic pain.

Functional brain imaging studies have furthered the understanding of pain processing. In control situations, noxious stimuli lead to somatotopic activation of the contralateral primary and secondary somatosensory cortex. Additional activation occurs in the contralateral insular cortex, anterior cingulate and prefrontal cortices, and ipsilateral secondary somatosensory and parietal cortices [12]. These diverse but interlinked pathways demonstrate that simple physical pain processing is an outdated concept; pain perception is mediated by attentional, cognitive, emotional, and motor planning brain responses [8,12].

Neuropathic pain responses demonstrate recruitment of brain areas other than the control network. Whether or not an individual with neuropathic pain presents with a well-defined lesion, functional brain imaging studies consistently reveal abnormalities in the ipsilateral hemisphere, including the somatosensory cortex, the insular, motor, and premotor cortices, and the anterior cingulate cortex [12]. Activation of the contralateral posterior parietal cortex develops in patients who have mechanical allodynia [13], and left temporal and anterior cingulate cortex dysfunction is described in patients who experience chronic pain after thoracotomy when compared with surgical controls who heal uneventfully (H. Nemoto MD, personal communication, December 2004).

Such complex pain processing demonstrates that the central nervous system may reorganize after injury or perception of injury. Thus plasticity, which is the ability of the central nervous system to adapt to or to reorganize in response to new internal or external environmental requirements, may underlie the basis of neuropathic pain [14]. The cause of such reorganization is unclear, and the search for explanations must move beyond a simplistic lesion-oriented and single-pain pathway model to an appreciation of the conscious and nonconscious processing of pain.

There may be genetic predispositions to developing chronic pain involving the *N*-methyl-D-aspartic acid (NMDA) receptors within the spinal cord and brain [15], but such evidence is tentative. Psychologic maladaptations may be a significant factor for some individuals who develop chronic pain. Studies have demonstrated that patients who suffer with neuropathic pain have a statistically significantly increased incidence of childhood abuse [16–19]. Such statistics, however, do not lay a foundation for a causal relationship between childhood abuse and neuropathic pain and should not lead to an assumption that patients who have chronic pain have an underlying psychologic or psychosomatic illness. Ultimately, the dysfunction and misprocessing that occur in individuals who suffer from neuropathic pain need to be understood in terms of biologic predisposition and central processing of internal and external perception [8].

An understanding of the complexity of the central processing of pain, coupled with the clinical observation that patients who have chronic pain

are not experiencing pain as a result of simplistic processing of nociceptive input, leads to the acceptance of the definition of neuropathic pain. Understanding neuropathic pain is the cornerstone of effective diagnosis and management. Investigators have argued about the definitions of chronic pain versus central pain versus neuropathic pain [20]. In this article, chronic pain, central pain, and neuropathic pain are considered interchangeable terms.

The International Association for the Study of Pain defines neuropathic pain as “initiated or caused by a primary lesion or dysfunction in the nervous system” [2]. Although some argue that the term “dysfunction” makes this definition too vague, others believe that this term allows a better understanding that neuropathic pain is not simply the result of a localizable anatomic lesion [21,22]. For example, complex region pain syndrome is a well-defined clinical entity in which patients present with severe, unrelenting pain and autonomic dysfunction but with no lesion that accounts for the pain. Essentially, neuropathic pain represents a dysfunction in pain processing and perception and involves multiple nervous system sites.

Comorbidities

Neuropathic pain affects every aspect of a patient’s being. In many ways, the patient defines his or her life by pain rather than by a more soulful sense of being. In other words, the patient identifies himself primarily as one who has pain; virtually every aspect of life becomes associated with a maladaptive response. Whereas the purported initial injury or insult that leads to chronic pain may seem simplistic, the ultimate course, outcome, and cost of chronic pain are affected by a multitude of factors, including emotional, social, economic, and environmental factors [23].

Depression is the most common comorbidity between chronic pain and Axis I disorders in the *Diagnostic and Statistical Manual IV*. Indeed, some studies find a prevalence rate approaching 100% [24]. The relationship between depression and pain is complex. Although depression is not an independent risk factor for developing neuropathic pain, patients who have depression report higher levels of pain than do patients who do not have depression [25,26]. Depression augments the impairment associated with chronic pain, and there is a very low likelihood of successfully treating neuropathic pain if depression is not treated as well [23].

Anxiety similarly has a high comorbid association with chronic pain, and some postulate that chronic neuropathic pain may be an expression of chronic posttraumatic stress disorder [27–30]. Functional and metabolic similarities exist between neuropathic pain and posttraumatic stress disorder [31,32]. Some patients adapt to prior traumatic stress with chronic behavioral strategies and then develop complex regional pain syndrome after a seemingly innocuous inciting event years later. Thus, investigation must focus both on the injury or inciting event per se that leads to chronic

pain and on the meaning or perception of that event within the context of the individual's life experience [8].

Sleep deprivation is common among chronic pain patients, and sleep deprivation alone causes a hyperexcitability state that amplifies the pain response [23]. Social support systems for patients who have chronic pain may be dysfunctional both at home and at work, and self-esteem can be diminished considerably. Some patients believe that they deserve to suffer with pain and place such reasoning within a religious or metaphysical context. Patients who have chronic pain often develop several maladaptive physical responses that then predispose to perpetuating the cycle of chronic pain.

Examples of neuropathic pain syndromes

An exhaustive discussion of various chronic pain syndromes is beyond the scope of this article. Following is a brief discussion of some common chronic pain syndromes.

Low back pain

Although chronic low back pain is ubiquitous, there is no single satisfactory treatment regimen for this problem. Too often, back pain is viewed as a biomechanical problem that can be fixed by either local injections or surgical therapy. It is more useful, however, to view chronic low back pain as neuropathic pain. Chronic low back pain may comprise elements of acute biomechanical pain and active nerve root entrapment.

Patients who have chronic low back pain without active biomechanical symptomatology complain of essentially constant pain that is independent of position. Pain may be across the lower back and may radiate into one or both legs. The pain can have a burning quality but may also be described as stabbing or cramplike, as a deep pressure, or, less often, with other pain characteristics described later. Some patients describe position-dependent pain superimposed on chronic pain. For example, patients who have segmental lumbar instability complain of acute, severe pain occurring with sudden positional changes. Patients with lumbar stenosis develop progressively severe low back pain, with or without leg pain, upon walking greater than one block. Patients with active facet syndrome complain of sudden pain with back extension. It is important to distinguish these variations when obtaining a history. Treatment may combine interventions targeted at the acute, biomechanical pain while addressing the overall chronic pain syndrome.

The multitude of failed back surgeries is a testament that low back surgery, including laminectomy/discectomy, spinal fusion, and disc replacement, is not the answer for patients who suffer with chronic low back pain [33]. Similarly, to label all chronic low back pain as myofasciitis does not advance the scientific and clinical understanding of chronic low back

pain [34]. As with all neuropathic pain syndromes, chronic low back pain represents a transformation from acute pain into a chronic somatosensory processing disorder. The clinician's management should shift so that the chronic nature of the pain becomes the guiding principle for multidisciplinary management.

Postherpetic neuralgia

Postherpetic neuralgia is one of the better-studied chronic pain syndromes and is a clear example of how a peripheral nerve insult can lead to dysfunction of the central nervous system. Postherpetic neuralgia is caused by reactivation of the varicella zoster virus along a single dermatome related to either a spinal dorsal root ganglion or a brainstem cranial nerve ganglion. Pain develops along the same dermatome as the rash. The initial pain of postherpetic neuralgia is an appropriate, nociceptive response to irritation of the peripheral nerve. In a substantial number of individuals, however, postherpetic neuralgia becomes transformed into chronic pain. Such chronic pain, like other neuropathic pain syndromes, affects multiple aspects of life including affect, physical activities, social interactions, self-esteem, and sleep.

The transition from nociceptive pain to chronic neuropathic pain may result from deafferentation of the second-order neurons of the spinothalamic tract because of primary sensory neuronal death. This possibility has not been conclusively demonstrated, however, and pain transformation may involve other aspects of sensory processing, including an alteration in descending inhibitory signals. The key point in all neuropathic pain syndromes is that the transition from acute pain to chronic pain is probably multifactorial and differs from individual to individual. In terms of the final syndrome, it is irrelevant whether the transforming event is a lesion with subsequent deafferentation, in the classic lesion-oriented model of allopathic medicine, or the transforming event is one of processing, thus raising the possibility that the transformation is physiologically based. Ultimately, the central nervous system expression of chronic pain involves similar pathways, and the overlap between physiologic dysfunction and physical dysfunction becomes blurred, both causally and from a management viewpoint.

Patients who suffer with postherpetic neuralgia typically describe a burning, stabbing, or lancinating pain along the affected dermatome. Pain is unremitting and hypersensitive to touch, leading to considerable behavioral changes to protect this region of the body. As with all neuropathic pain states, treatment directed to the peripheral nerve alone is unrewarding; successful management involves a multidisciplinary approach.

Diabetic peripheral neuropathy

Approximately one quarter of the 17 million diabetic Americans develop a peripheral neuropathy. A substantial number of such patients experience

neuropathic pain, but there is no clear peripheral nerve feature distinguishing patients who have diabetic neuropathic pain from those who have nonpainful peripheral neuropathy [35]. Diabetic peripheral neuropathy is another example of a peripheral nerve lesion transforming into a chronic, sustaining pain mediated by dysfunction of the nervous system.

Patients with painful diabetic neuropathy and other painful peripheral neuropathies typically complain of pain in a stocking distribution. The pain is often burning and may be sharp or lancinating. Often, the pain is worse in a recumbent position and is somewhat better with weight bearing. There may be associated allodynia, thus leading to avoidance-type behavior. Patients often have severe interruption of sleep, because the pain typically is worse at nighttime. As with all neuropathic pain syndromes, other aspects of the patient's life can be affected in a cascade in the breakdown of affect, social support, and self-esteem. Treatment directed simply at the peripheral nerves is not successful.

Complex regional pain syndrome

Complex regional pain syndrome, formerly known as reflex sympathetic dystrophy, is a poorly understood chronic condition. Unlike low back pain, postherpetic neuralgia, and diabetic neuropathy, the initial inciting event of complex regional pain syndrome may not be evident. Often, the inciting event is a seemingly innocuous injury to the soft tissue, but the injury then becomes transformed into an unrelenting, debilitating pain syndrome. The term reflex sympathetic dystrophy, although still commonly in use, was changed to complex regional pain syndrome because it is not clear that the pain of complex regional pain syndrome is simply related to dysfunction of the sympathetic nervous system. Also, dystrophic changes are not universal, and the transformation from an inciting event into chronic pain is not reflexive. Complex regional pain syndrome is divided into type I (no evidence of peripheral nerve injury) and type II (documented peripheral nerve injury).

Complex regional pain syndrome illustrates the enormous complexity of neuropathic pain. Often, the inciting event is a seemingly trivial trauma. Indeed, the inciting event can be so trivial that patients often are led to believe they are fabricating the pain. Additionally, because there is no clear cut, satisfactory pathophysiologic explanation for the severe transformed pain, some authors have even doubted the neuropathic nature of this syndrome and have concluded that complex regional pain syndrome is a somatoform disorder [36]. Complex regional pain syndrome has been described as a peripheral nerve insult that results in one of the following: local peripheral nerve trauma with secondary ephaptic conduction and ectopic pacemaker activity; cross talk between unmyelinated C-fibers and interlinked sympathetic fibers; or wide-dynamic-range neuron hypersensitivity in the spinal cord from prolonged, intense nociceptive input [37].

Complex regional pain syndrome is diagnosed using the following four criteria [38]:

1. There has been an initiating noxious event for a cause of immobilization.
2. There is continuing pain, allodynia, or hyperalgesia that is disproportionate to any inciting event.
3. There is evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
4. The condition is excluded by the existence of a condition that otherwise would account for the degree of pain and dysfunction.

Thus, the diagnosis is made purely on clinical grounds, taking into account objective, autonomic nervous system pathophysiology. The changes in the autonomic nervous system led to sympathetic blockade becoming one of the hallmarks of treatment. Although pain relief from sympathetic blockade helps support the diagnosis of complex regional pain syndrome, sympathetically independent pain may develop early in the course of this condition and is unresponsive to peripheral sympathetic blockade [39,40].

Although there is unusual autonomic activity early in the course of complex regional pain syndrome, and this activity may be caused by dysregulation of the sympathetic nervous system, the condition quickly becomes transformed into neuropathic pain. In other words, the pain becomes sustained by dysfunction in somatosensory processing and is not simply secondary to sympathetic nervous system dysfunction. There is some controversy concerning this latter point: some authors have argued that complex regional pain syndrome has nothing to do with the sympathetic nervous system, confusing the difference between transient sympathetic nervous system dysfunction and long-lasting neuropathic pain [41,42].

The sometimes seemingly trivial inciting event of complex regional pain syndrome has led some to speculate that this condition is emotionally based. Whereas there may be truth in this supposition, it is likewise true that all neuropathic pain syndromes have a component of emotional dysfunction. On the one hand, depression and anxiety coexist almost universally with neuropathic pain syndromes. On the other hand, there may be a fundamentally important emotional processing component in the transformation from simple pain to more complex, chronic pain. It would be more useful to break down the arbitrary barriers between psychiatry and neurology, mind and body, and emotionality and physicality and to consider neuropathic pain as a neuropsychiatric disorder, instead of dividing chronic pain syndromes into emotionally based or physically based problems.

Pain secondary to central nervous system injury

A variety of chronic pain states have been described following well-documented central nervous system injury, including trauma, multiple

sclerosis, cerebrovascular accidents, infections, spinal cord syrinx, neoplasms, and others [43–47]. All have in common a well-documented lesion of the central nervous system. It is not clear, however, how some patients who have such lesions develop a transformed pain syndrome, whereas others with the same lesion develop a neurologic deficit without such pain. The only thing that is known with certainty is that the clinical manifestation of pain can become the overwhelming chronic presentation in such patients, and they develop the same comorbidities as individuals with other neuropathic pain syndromes. Pain usually develops weeks to months after the insult to the central nervous system, indicating that central nervous system reorganization may develop over time [45].

Diagnosis

History

Clinicians can make a diagnosis of neuropathic pain with confidence by taking a careful history, performing a focused physical examination, and judiciously using ancillary diagnostic studies. It is important, in taking a history, to understand the presenting characteristic of pain. The five most important characteristics are:

1. Temporal qualities, including acute, recurrent or chronic; daily variation; onset and duration.
2. Intensity, including average pain; pain at its worst; pain at its least; pain at the time of history taking.
3. Topography, including localized versus regional pain; superficial versus deep pain; focal versus radiating pain.
4. Quality, including descriptors such as burning, aching, freezing, stabbing, electric shock–like, tooth achy, cramping, or knifelike.
5. Palliative and precipitating factors, including physical activities, emotional stressors, nutritional triggers, and circadian rhythms.

It is beneficial for patients to use a rapid rating scale such as the Brief Pain Inventory or the Visual Analog Scale [48]. Patients rate temporal aspects of pain from zero (no pain) to 10 (the worst imaginable pain). Such rating scales are helpful in following patients and aid in understanding the relationship between the patient and pain. Some patients rate their pain as a constant “10” but seem to be in no acute distress, suggesting a disassociation between their perception of pain and their physical manifestations.

Clinicians should spend considerable time trying to understand the inciting event of pain, which may provide insight into a disease state or injury that has been undiagnosed. In addition, it is critical to understand the patient’s perception of the inciting event, which takes into account life experiences. Daily activities need to be considered, including physical

limitations caused by pain and the amount of daily exercise. Some patients are so debilitated by pain that they are essentially homebound, performing little in the way of even sedentary activities. The support system must be explored, including the immediate family and the patient's work environment, if appropriate. Often, patients suffering with neuropathic pain feel alone and abandoned and essentially become imprisoned by pain. Many patients have discontinued all sexual activity as a manifestation of depression, rejection, or fear that such activity will further exacerbate pain.

In addition to a general past medical history, careful attention must be paid to any prior psychiatric conditions or prior episodes of prolonged pain-related conditions. This investigation may provide important insight into the patient's adaptive responses over time. Childhood trauma must be considered, although probing into childhood trauma must be done in a delicate and noninvasive manner. Even though there is a high incidence of childhood trauma and abuse in chronic pain patients, one cannot suggest or assume that a patient with chronic pain has experienced such trauma. Alcohol and drug histories are critical, because one facet of chronic neuropathic pain treatment may be the use of narcotic analgesics.

A careful search for comorbid medical conditions is important. The three most common comorbid conditions are depression, anxiety, and sleep deprivation. If these conditions are not managed properly, successful pain management is unlikely. Simple questions may suffice. For example, asking if the patient has felt depressed or hopeless or has lost pleasure may uncover an otherwise undiagnosed depression. Pain centers often use more formal depression scales as part of an initial assessment. Family history may provide a clue to possible genetic predispositions to psychiatric disease, pain syndromes, or both.

The patient's expectations of treatment must be assessed [23]. It is unrealistic to expect that a simple procedure or medication will completely alleviate pain. Realistic goals must be set. Too often, patients arrive with an expectation of obtaining a simple anatomic explanation and subsequent treatment of pain. Once the clinician begins to discuss neuropathic pain, patients may fail to understand that their pain is a result of a somewhat ill-defined dysfunction of the nervous system. Patients can feel a lack of validation, which can undermine future treatments. It is frequently helpful to end a discussion by asking the patient something such as the following: "Just so that I can be certain I have explained myself well, please summarize for me your understanding of your condition." Such a statement does not assume that the patient is not intelligent or was not paying attention but places the burden on the clinician for having satisfactorily explained the condition.

Once the patient understands that the pain is a chronic condition, the foundation for multidisciplinary, long-term treatment begins. Patients need to understand that the ultimate goal of treatment is to reduce pain, increase function, and improve quality of life. The focus on complete cessation of pain alone will lead to treatment failure. Patients should feel that they are an

integral component of the treatment by actively participating in their pain management.

Physical examination

A careful physical examination should include vital signs, a focused musculoskeletal and extremity examination, and a neurologic examination. Patients with chronic pain generally do not present in acute distress, and vital signs should be stable. The musculoskeletal examination is important in many ways. First, some patients will demonstrate evidence of chronic maladaptation because of prolonged muscle spasm and avoidance-type behavior. Second, the musculoskeletal examination may reveal evidence of active mechanical signs of an entrapped nerve or of an irritated spinal segment. Third, the musculoskeletal examination may reveal evidence of psychologic maladaptation, in which patients claim pain when they are confronted directly with a musculoskeletal maneuver, but careful observation reveals that the patient is capable of such maneuvers when they are performing other tasks.

The extremity examination may demonstrate altered autonomic activity, for example a change in hair growth or nail bed pattern, a change in extremity color or temperature, or extremity swelling out of proportion to injury. Such changes are the hallmark of complex regional pain syndrome. Diabetic patients may present with diminution in peripheral blood flow, which can aggravate peripheral neuropathic pain. The findings in the neurologic examination may be normal in patients who have neuropathic pain but often point to dermatomal, regional, spinal, or brain dysfunction that correlates with the pain syndrome.

The sensory aspect of a neurologic examination is exceedingly important. In addition to testing for the presence or absence of primary sensory modality perception (vibration, proprioception, light touch, and pinprick), the examiner should test for alterations in sensory experience that are consistent with neuropathic pain. Allodynia is pain in response to a normally non-noxious mild stimulus. Hyperalgesia indicates an increased sensation of pain in response to a normally painful stimulus such as a pinprick. Hyperpathia is a prolonged painful experience following pinprick assessment.

Other findings of the neurologic examination may be abnormal, resulting either from a documented lesion or from a functional aberration caused by central nervous system dysfunction. For example, dystonia has been well described in complex regional pain syndrome or in patients who have a basal ganglia lesion [49]. Tremor may develop with peripheral neuropathy or may manifest as a physiologic aberration in patients who have chronic pain.

Ancillary studies

Ancillary studies should be used to exclude medical conditions that can either mimic or exacerbate the patient's clinical condition and to confirm or

to aid in understanding the origin of pain. For example, deep venous thrombosis presents as extremity swelling with abnormal temperature sensation and can either mimic complex regional pain syndrome or coexist with this condition. Chronic low back and lumbar radicular pain, rarely, can be caused by a cauda equina tumor. Chronic extremity pain can coexist with active denervation in a nerve dermatome. Ultimately, all diagnostic tests are taken in conjunction with the history and examination to secure a diagnosis that then becomes the springboard for effective management.

Management

As discussed previously, treatment for neuropathic pain should be multidisciplinary. Although many pain centers focus on anesthesiology-based procedures, such procedures are but one aspect of an important component of successful pain management. The following section presents a general discussion of the principles of multidisciplinary treatment. Such principles can be applied to any neuropathic pain state. Treatment must be individualized for the physical manifestation of pain and also for the patient's psychosocial adaptation.

Psychotherapies

Because of the high prevalence of depression and anxiety with chronic neuropathic pain, psychotherapy is an important component of successful management. Even in patients who are not depressed, learning effective coping strategies for chronic pain is helpful. Although patients may be resistant to psychotherapy, sensing that the clinician views their pain as "psychosomatic," clinicians must stress the importance of psychologic intervention, because this intervention will help manage depression and coping skills and may uncover a previously undiagnosed, repressed trauma or other significant life event.

Cognitive behavioral therapy helps patients understand the interplay of pain perception, affect, and daily thought patterns. The focus is on developing positive expectations in patients [1]. Patients who have chronic pain are often resistant to insight-oriented therapy. It is the author's experience that many patients who have chronic pain are sufficiently disassociated from their emotions that such therapy is not possible. Insight-oriented therapy should be recommended only when there is a trusting bond between the patient and clinician and the patient expresses a desire to explore a possible relationship between previously unrecognized emotions and chronic pain. Group therapy is extremely beneficial, especially for patients who feel they are uniquely alone in their experience of chronic pain. Family therapy becomes important in helping other family members understand that chronic neuropathic pain is a real medical condition. Patients need to be validated within the family, and they also need to understand that at times they isolate themselves from the family because of pain.

In some cases, acute psychiatric intervention becomes necessary for chronic pain management. Long-term treatment is sometimes associated with a sudden insight or flashback into previously unrecognized trauma, severe depression, or poorly managed anxiety, and a skilled psychiatrist is required to help manage such conditions.

Pharmacologic therapy

There are several pharmacologic strategies for treating chronic pain. No single drug effectively treats neuropathic pain. The following is a general discussion of various classes of drugs frequently used in chronic pain management. The best-studied conditions for using pharmacologic management are diabetic neuropathic pain and postherpetic neuralgia. The efficacy of pharmacologic therapy is less studied in other chronic neuropathic pain syndromes. Nonetheless, several generalizable treatment strategies exist.

Anticonvulsants

Anticonvulsants have become first-line treatment for neuropathic pain syndromes [50–52]. Carbamazepine, phenytoin, valproate, and clonazepam were the first anticonvulsants to be well studied in treating patients who have neuropathic pain, especially with such conditions as trigeminal neuralgia and diabetic peripheral neuropathy [51]. Many well-controlled studies have shown that gabapentin is effective in treating postherpetic neuralgia and other neuropathic pain conditions [51–53]. The list has extended to newer anticonvulsants including topiramate, oxcarbazepine, lamotrigine, zonisamide, and levetiracetam [54–58]. The mechanism by which such drugs work is not completely clear and generally has to do with reduction in a hyper-excitability state, either peripherally or centrally. Interaction with GABA and other neurotransmitters may also be important.

The initial choice of drugs should be based on clinician comfort and relative indications. Only gabapentin is approved by the Food and Drug Administration for treating neuropathic pain, and this approval is limited to treatment of postherpetic neuralgia. Thus, the majority of anticonvulsant usage in treating neuropathic pain is off-label, a common practice in good clinical medicine. One can take advantage of the side-effect profile of some medications, for example topiramate for weight loss and zonisamide for sedative side effects. Anticonvulsants are administered using the dosing schedules commonly employed for treating epilepsy. Generally, only one anticonvulsant should be prescribed at a time, and upward titration should be based on efficacy and tolerability. Anticonvulsants may be used in conjunction with other medications described below.

Antidepressants

Tricyclic antidepressants are much better studied in treating neuropathic pain than are the newer, more selective antidepressants [59–61]. Low-dose

amitriptyline, in particular, has been shown in many well-controlled studies to be efficacious in treating various neuropathic pain conditions, independent of depression. The sedative side effects of amitriptyline often provide a useful adjunct in treating patients who have comorbid sleep deprivation. Tricyclic antidepressant dosage should begin at 10 mg/night, with an upward weekly titration in 10-mg increments as tolerated and needed.

Serotonin selective reuptake inhibitors, combined serotonin and norepinephrine reuptake inhibitors, and dopaminergic-mediated antidepressants are less well studied as medication adjuncts in treating neuropathic pain, but several studies demonstrate efficacy [62–66]. These agents become particularly useful when patients manifest with comorbid depression, anxiety, or both. Antidepressants may be beneficial because of their influence on descending serotonergic, adrenergic, and other pain inhibitory pathways and because of interaction with common pathways in depression and pain [67–69].

Narcotic analgesics

Narcotic analgesics (opioids) are the most potent prescription analgesics. Although there is wide acceptance for prescribing narcotic analgesics in patients who have cancer, acceptance is not so universal in treating patients with pain from other causes. Problems arise because of a lack of acceptance in using such medication long-term in these patients, combined with a fear of causing drug addiction. Narcotic analgesics take advantage of the innate opioid receptor system in the central nervous system. These medications mimic the action of endogenous opioids, providing a powerful pain signal transmission [70].

It is common practice in pain medicine clinics for patients to sign a narcotic agreement if they are to begin chronic narcotic analgesic treatment. Such agreements help provide clarity with regard to intent of narcotic usage and the manner in which medications will be used. The agreement usually stipulates that patients may obtain narcotics from only one physician, may use only one pharmacy, and may take medication only in the manner prescribed. Patients must return for monthly visits and are subject to random drug screening. Although a contract may seem harsh, the medical literature supports the use of such contracts, which help to minimize narcotic abuse by drug-seeking patients [1].

Initially, short-acting narcotics should be prescribed. When a patient's daily narcotic need is discerned, clinicians should switch to a long-acting medication that allows the patient to obtain sustained pain relief and to eliminate the sometimes intrusive behavioral pattern of taking a pain medication every 3 to 4 hours. Once a long-acting medication has been prescribed, short-acting medications can be used for breakthrough pain.

Tramadol hydrochloride is a unique narcotic-like medication. Tramadol does have weak mu opioid receptor agonism and enhances the inhibitory effect of descending serotonergic and adrenergic systems. Tramadol is

efficacious in a variety of neuropathic pain conditions and can be used as a first-line medication before a more traditional narcotic analgesic is prescribed [1].

Topical analgesics

The best-studied topical analgesic is a 5% lidocaine patch [70]. This device may be especially useful in well-localized pain syndromes such as postherpetic neuralgia. Capsaicin may also be effective in relatively localized neuropathic pain conditions. Capsaicin leads to a depletion of substance P, a pain-generating neuropeptide in sensory afferent neurons. Capsaicin itself, however, may lead to a disquieting, burning pain, thus limiting its efficacy [71].

Other adjunctive medications

Tizanidine is a centrally acting alpha-2 adrenergic agonist with prominent antispasticity effects. This medication may be an important adjunct in patients who present with chronic muscle spasm or tension-type headache. Baclofen, a GABA agonist, may benefit patients who have chronic muscle spasm or paroxysmal pain. Mexiletine is an antiarrhythmic drug with demonstrable efficacy in treating some neuropathic pain conditions. Clonidine, another central alpha-2 adrenergic agonist, may be helpful in treating complex regional pain syndrome and related conditions when taken orally or transdermally [70].

Pulse therapy with corticosteroids or nonsteroidal anti-inflammatory drugs should be considered when patients develop acute musculoskeletal pain superimposed on chronic neuropathic pain. For example, some patients who have chronic back pain develop acute radicular pain with active, mechanical stretch signs on examination. In such patients, a 1- to 2-week course of nonsteroidal anti-inflammatory drugs or oral corticosteroids can help break the cycle of acute on chronic pain. Long-term corticosteroid and nonsteroidal anti-inflammatory drugs have little role in the treatment of chronic, neuropathic pain [70]. Neuroleptics and benzodiazepines are sometimes useful in and of themselves or in treating comorbid conditions [70,72].

There is some evidence that NMDA receptor antagonists ameliorate chronic neuropathic pain. Ketamine infusions have been studied, but the high rate of toxicity (causing hallucinations and anorexia) limits this medication's usefulness. Smaller doses of ketamine may be useful in select circumstances [73,74]. Oral NMDA receptor antagonist drugs have demonstrated little efficacy in treating chronic, neuropathic pain.

Interventional strategies

Several anesthesiology-based interventions are appropriate as one aspect of multidisciplinary pain management. It is a mistaken notion in some pain practices that management should be primarily intervention based. Indeed,

in some practices, the failure of one intervention leads to an escalation in intervention strategies, often to the detriment of the patient [20].

Nerve blocks may be helpful for diagnostic purposes and sometimes may provide an important break in the chronic cycle of pain [75]. Once a successful nerve block is obtained, physical therapy and other strategies should be used immediately to help the patient overcome maladaptive postures. Sympathetic blockade, which by definition does not include primary sensory or somatic block, has been used both diagnostically and therapeutically in complex regional pain syndrome and related conditions [76]. (The lack of benefit from sympathetic blockade does not preclude the diagnosis of complex regional pain syndrome, however.) As with other nerve blocks, a successful sympathetic blockade should be followed immediately by progressive physical therapy.

Epidural and transforaminal corticosteroid injections may benefit patients who suffer with back conditions that have a demonstrable mechanical component, such as lumbar disc herniation and lumbar stenosis. Similarly, facet blocks may be exceedingly useful in breaking the cycle of chronic facet locking or in providing transient relief in patients who have segmental lumbar instability. Such relief allows the patient to begin more progressive physical therapy strategies.

Spinal cord stimulation relies on the principle that a stimulator, placed in the dorsal spinal cord, blocks central pain processing from a peripheral pain generator. Spinal cord stimulators should be considered only in patients who have relatively well localized extremity pain and who have exhausted all other treatment strategies [77]. Too often, spinal cord stimulators are placed as part of a rapid escalation in interventional techniques, when other multidisciplinary strategies have been neglected.

Intrathecal administration of narcotic analgesics takes advantage of a very-low-dose narcotic coupled with strong binding to spinal cord receptors, with minimal systemic side effects. Such strategies are particularly useful in patients who have demonstrated a positive effect to narcotic analgesics but who cannot tolerate systemic side effects [70,77]. These medications may be combined with intrathecal clonidine, which also has independent pain-alleviating effects, and baclofen, which may be useful in alleviating spasticity.

Other surgical interventions, including spinal surgery, must be approached with caution. Other than for trigeminal neuralgia, placing a lesion in the nervous system or performing decompressive surgery in an attempt to alleviate chronic, neuropathic pain has yielded equivocal results [20].

Physical therapy

Most patients who have neuropathic pain—especially patients who have chronic low back pain but also patients who have severe extremity neuropathic pain—have developed several maladaptive physical manifes-

tations. Physical therapy should be an important consideration in treating chronic neuropathic pain [78].

Some physical therapy, such as craniosacral technique and myofascial release, is more intuitive and may help patients understand the link between physiology and the perception of physical pain. In these therapies, patients lie on a table, are extremely quiet, and the therapy is quite subtle. More conventional physical therapy includes the use of a transcutaneous electrical nerve stimulation unit, which may alleviate localized pain, as well as the employment of other modalities. In addition, range-of-motion, strengthening, and spine stabilization exercises help overcome chronic maladaptations.

Complementary strategies

Acupuncture is recognized by the World Health Organization as an effective treatment for pain. Several evidenced-based studies have demonstrated the efficacy of acupuncture in treating pain, although the difficulty of employing sham acupuncture leads to methodological flaws [79]. Acupuncture is not a stand-alone treatment but should be considered as part of a multidisciplinary approach, especially in patients who wish to explore nonpharmacologic strategies.

Nutritional counseling should be considered in patients who suffer with chronic neuropathic pain. Many such patients have poor eating habits, often because of chronic nausea or depression. In addition, many patients have a diet that is shifted toward high-carbohydrate and high-fat or junk foods. Such foods have an immediate gratifying effect, and poor eating habits often become part of a cycle of self-treatment underlying anxiety and depression [80].

Massage therapy can be used to desensitize areas of hyperalgesia and to help alleviate muscular and emotional stress. In some cases, massage therapy becomes a transition into developing greater insight into the interplay between physiology and physical pain perception [81].

Summary

Neuropathic pain is a neuropsychiatric condition in which pain is initiated or caused by a primary lesion or dysfunction in the nervous system. Understanding the complexity of neuropathic pain becomes the cornerstone for appropriate diagnosis and management. Diagnosis must take into account comorbid conditions. Successful management depends on realistic patient and physician expectations and an individualized, multidisciplinary approach.

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