INTRODUCTION

Neuropathic pain comprises a wide range of heterogeneous conditions. Various types of neuropathic pain may have distinct pathophysiologic causes and different clinical signs and symptoms. Despite the diversity of conditions classified as “neuropathic pain,” many potentially share common underlying mechanisms of nociception, including neuronal hyperexcitability, but others may not. This may in part explain why certain analgesic agents are relatively effective for a wide range of neuropathic pain states but why notable exceptions exist that appear to be resistant to conventional “neuropathic” pain therapy. A group has been assembled to address the inconclusive research on “neuropathic” pain and to operationalize and specify definitions and criteria for conditions that are to be referred to as neuropathic pain (Box 24.1).1 This work should lead to a more reductionist approach to the study of neuropathic pain and to effective therapies for specific disease processes.

In this chapter we focus on some of the more common states of “neuropathic” pain as defined by the sensitive but nonspecific definition of the International Association for the Study of Pain (IASP). These conditions include complex regional pain syndrome (CRPS), post-herpetic neuralgia (PHN), painful diabetic peripheral neuropathy (DPN), and human immunodeficiency virus (HIV) painful sensory neuropathy.

COMPLEX REGIONAL PAIN SYNDROME

The term complex regional pain syndrome, which denotes both types 1 and 2, originated from a history of different names appointed by individuals who made particular observations.

In 1864 Silas Weir Mitchell made an important observation of Civil War soldiers when he noticed that they suffered from burning pain and muscle atrophy at the sites of their injuries. He called this “causalgia,” which is derived from the Greek words kausis (burning) and algos (pain). In 1900 at a lecture in Germany, Paul Sudeck stated that this syndrome could not only extend from the initial insult but also had an inflammatory component. The name Sudeck’s dystrophy was applied in his honor. Half a century passed before the discovery that invasive procedures that block the sympathetic nervous system provide further relief of pain symptoms. Because of the success of these methods, Evans renamed the syndrome “reflex sympathetic dystrophy.” Over the years cases arose in which patients lacked a trophic component, sympathetic involvement was absent, or there was no evidence of reflex involvement. These exceptions led to a meeting in 1993 by the IASP at which the term “complex regional pain syndrome” was formulated and subsequently published the following year.2 The most commonly used clinical diagnostic criteria for CRPS types 1 and 2 are low in specificity but high in sensitivity, which has led to overdiagnosis of the pain syndrome.3 This in turn has made it difficult to obtain accurate epidemiologic data for CRPS or to perform rigorous studies of the pathologic state. In 2007, research criteria (also known as the Budapest criteria) were published that included objective signs of pathology characteristic of patients with CRPS4 (Box 24.2). These criteria had good specificity and sensitivity. Although they were initially intended for research use, many physicians prefer them to the less stringent original criteria.

PATHOPHYSIOLOGY

There are two types of CRPS, known as type 1 and type 2 (Box 24.3). They differ in that type 2 has evident nerve injury whereas type 1 assumes an injury to the nerve or nerves. A consistent finding in both types of CRPS is the discrepancy between the severity of the symptoms and the severity of the inciting injury. In addition, symptoms have the propensity to spread in the affected limb in a pattern not restricted to the specific nerve’s area of innervation. CRPS is characterized by intense burning pain with resultant hyperalgesia or allodynia. It may be associated with local edema and autonomic involvement, such as changes in skin color and sweating and increased or decreased skin temperature in the affected area. There may also be trophic changes in the skin, hair, and nails in the affected site (see Box 24.3). Although many questions concerning the pathophysiology

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**Box 24.1 Updated Definition of Neuropathic Pain**

**IASP Definition: 1994**

“pain initiated or caused by a primary lesion or dysfunction in the nervous system”

**Revised Research and Clinical Definition: 2007**

“pain arising as a direct consequence of a lesion or disease affecting the somatosensory system”

IASP, International Association for the Study of Pain.
of this syndrome are still unanswered, three main principles remain at the core of CRPS: abnormalities in both somatosensory and sensory pathways as well as sympathetic nervous system involvement.

**SOMATOSENSORY ABNORMALITIES**

Inciting injury to either the upper or lower extremity is an important trigger of CRPS. Studies have shown that changes in cutaneous innervation of the injured extremities take place even when no nerve injury is found. In one recent study, skin biopsy samples were obtained from the affected limbs of patients with CRPS type 1. A lower density of C and A fibers was found in the affected limbs than in the unaffected limbs, which led to sensory deficits in the affected limbs.\(^5\) Brain plasticity is another important factor found to be associated with somatosensory abnormalities. Data suggest that patients with CRPS have decreased activity in the somatosensory cortex of the affected side.\(^6\) These patients also tend to have tactile mislocation because of somatotopic reorganization, which was found to be directly correlated with hyperalgesia.\(^7\) Changes occurring within the primary somatosensory (SI) cortex are dependent on pain and have been shown to be reversible after recovery from the pain.\(^8\)

**SENSORY PATHWAYS (CENTRAL NERVOUS SYSTEM SENSITIZATION, PERIPHERAL SENSITIZATION, INFLAMMATION)**

Central sensitization occurs when pain perception increases because of constant firing of painful stimuli to the central nervous system. Neuropeptides such as substance P and bradykinin are released in response to nociceptive stimuli and activate N-methyl-D-aspartate (NMDA) receptors, which together lead to hyperalgesia and allodynia.\(^9\) Peripheral sensitization is the counterpart of central sensitization. When a nerve injury occurs, multiple proinflammatory factors such as glial cell activation, substance P, bradykinin, tumor necrosis factor-α, interleukin-1β, prostaglandin E\(_2\), and nerve growth factor are activated, which results in increased

<table>
<thead>
<tr>
<th>Box 24.2 Difference between the IASP Criteria and the Budapest Criteria for the Diagnosis of CRPS</th>
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<tbody>
<tr>
<td><strong>IASP Criteria for the Diagnosis of CRPS</strong>(^*)</td>
</tr>
<tr>
<td>1. Presence of an initiating noxious event or reason for immobilization</td>
</tr>
<tr>
<td>2. Disproportional pain, allodynia, or hyperalgesia from a known inciting event</td>
</tr>
<tr>
<td>3. Sign or symptom of any evidence showing edema, skin changes, blood flow, or abnormal sudomotor activity in the region of the pain</td>
</tr>
<tr>
<td>4. No other condition that would otherwise explain the degree of pain or dysfunction</td>
</tr>
<tr>
<td><strong>Budapest Criteria for Diagnosis of CRPS</strong>(^*)</td>
</tr>
<tr>
<td>1. Presence of continued disproportional pain from the known inciting event</td>
</tr>
<tr>
<td>2. Must report at least one symptom in three of the following categories:</td>
</tr>
<tr>
<td>• Sensory: hyperesthesia, allodynia</td>
</tr>
<tr>
<td>3. Must report at least one sign in two or more of the following categories at the time of evaluation:</td>
</tr>
<tr>
<td>• Sensory: hyperalgesia to pinprick, allodynia to touch or joint movement</td>
</tr>
<tr>
<td>• Vasomotor: temperature asymmetry, color asymmetry</td>
</tr>
<tr>
<td>• Sudomotor/edema: edema, asymmetrical sweating, sweating changes</td>
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<tr>
<td>• Motor/trophic: decreased range of motion, motor dysfunction, trophic changes</td>
</tr>
<tr>
<td>4. No other condition that would otherwise explain the degree of pain or dysfunction</td>
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</tbody>
</table>

\(^*\)If seen without any major nerve damage, the diagnosis is CRPS type 1; if seen with evidence of nerve damage, the diagnosis is CRPS type 2. CRPS, complex regional pain syndrome; IASP, International Association for the Study of Pain.

<table>
<thead>
<tr>
<th>Box 24.3 Difference between CRPS Type 1 and Type 2</th>
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</thead>
<tbody>
<tr>
<td><strong>CRPS Type 1 (Reflex Sympathetic Dystrophy)</strong>(^*)</td>
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<tr>
<td>1. The presence of an initiating noxious event or a cause of immobilization</td>
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<tr>
<td>2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event</td>
</tr>
<tr>
<td>3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain</td>
</tr>
<tr>
<td>4. This diagnosis is excluded by conditions that would otherwise account for the degree of pain and dysfunction</td>
</tr>
<tr>
<td><strong>CRPS Type 2 (Causalgia)</strong>(^†)</td>
</tr>
<tr>
<td>1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve</td>
</tr>
<tr>
<td>2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain</td>
</tr>
<tr>
<td>3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction</td>
</tr>
</tbody>
</table>

\(^*\)Criteria 2 to 4 must be satisfied. 
\(^†\)All three criteria must be satisfied. 
CRPS, complex regional pain syndrome.
nociceptive sensitivity and a decreased threshold for firing of nociceptive stimuli. Together, central and peripheral sensitization results in the allodynia and hyperesthesia seen in patients with CRPS. There are other important factors in the inflammatory pathway, such as the role of nuclear factor NFκB upstream in the proinflammatory pathway observed in animal studies.

ALTERED SYMPATHETIC NERVOUS SYSTEM FUNCTION

Involvement of the sympathetic nervous system is thought to be responsible for the limbs in patients with CRPS becoming cool, blue, and painful secondary to vasoconstriction as a result of excessive outflow from the sympathetic nervous system. In an animal study, rats with chronic postischemic pain that had norepinephrine injected into their hind paws experienced increased nociceptive firing, thus supporting the notion that pain can be sympathetically maintained. However, this provides little evidence in support of sympathetic maintenance of CRPS pain. Coupling of sympathetic neurons may occur not only to nociceptive afferents but also to non-nociceptive mechanosensitive or cold-sensitive neurons. Sympathetic afferent coupling, considered the cause of sympathetically maintained pain, occurs in cutaneous and deep somatic tissues, but during the acute event of CRPS, the deep somatic tissues are of greater importance.

Although coupling occurs in some patients with CRPS, a subset of patients with clinically identical CRPS have sympathetically independent pain. These patients exhibit little to no response to sympathetic blockade either pharmacologically with phenolamine or via interventional blockade of the sympathetic ganglia.

EPIDEMIOLOGY

Multiple studies of CRPS type 1 have shown that the male-to-female ratio ranges between 1:2 and 1:4, thus suggesting that females are at higher risk for development of the syndrome. However, the male-to-female ratio for most other pain syndromes is similar. A retrospective, cross-sectional analysis study showed that the male-to-female ratio was 1:4 and that the most common initiating events were bone fractures, sprains, and trauma. Outcomes of the disease tended to be worse in patients with upper extremity injuries than in those with lower extremity injuries, injuries other than fractures, and “cold” (commonly chronic) CRPS rather than “warm” (acute) CRPS. Other risk factors that contribute to the development of CRPS are age, workplace, and type of injury. The average age of patients ranges between 16 and 79 (median range, 41.6), with a higher incidence in the older population. Patients with motor nerve damage were found to be at higher risk for CRPS than those with sensory nerve damage. Fracture has been reported to be the most common initiating injury. The incidence of job-related injuries leading to CRPS was as high as 76%, which may indicate a psychosocial or secondary gain component in reporting of this pain. Studies report that CRPS develops in patients with a family history of CRPS at a higher incidence and younger age, thus suggesting that CRPS may have a genetic component. Another study showed that siblings of patients in whom CRPS developed before 50 years of age had a threefold increased risk for development of the syndrome. Psychological factors such as depression, personality disorders, and anxiety have no correlation with CRPS patients, which suggests that there is no specific type of CRPS personality.

CLINICAL FEATURES

The pain must be greater in proportion to the inciting event. There must be at least one symptom in three of the following four categories: sensory (hyperesthesia/allodynia), vasomotor (changes in temperature or sweating in the affected limb in comparison to the normal limb), sudomotor/edema, and motor/trophic (demonstration of weakness, decreased range of motion, or trophic changes in hair, nails, or skin). At least one sign must be present at the time of evaluation in two or more of the following four categories: sensory, vasomotor, sudomotor/edema, and motor/trophic. There must be no other diagnosis that better explains the patient’s signs and symptoms. This is different from the criteria proposed in 1993 by the IASP (see Box 24.3). A recent study in which the validity of CRPS was evaluated by comparing the Budapest criteria in patients with CRPS and in those with neuropathy showed that the IASP criteria had a sensitivity of 1.0 and a specificity of 0.4 and the Budapest criteria had a clinical sensitivity of 0.99 and a specificity of 0.68. The newly revised criteria are also divided into clinical and research. The research criteria contain more inclusions, which allows a specificity of 0.96.

The current IASP taxonomy also divides CRPS into CRPS 1 (formerly known as reflex sympathetic dystrophy) and CRPS 2 (formerly known as causalgia). The distinction between CRPS 1 and 2 is the presence of a definable nerve lesion in patients with CRPS 2. The signs and symptoms for both conditions are clinically indistinguishable and include sensory changes (allodynia, hyperalgesia, and hypoalgesia), edema, temperature abnormalities, and changes in sweating (see Box 24.3). Pain is the principal feature in both CRPS 1 and CRPS 2. In patients with CRPS the associated clinical signs are typically out of proportion to the inciting injury. Patients describe a burning, deep-seated ache that may be shooting in nature along with associated allodynia or hyperalgesia. Pain occurs in 81.1% of patients meeting the CRPS criteria. Patients also frequently complain of sensory abnormalities such as hyperesthesia in response to the typical mechanical stimuli encountered in day-to-day activities (such as dressing) involving the affected limb.

In CRPS 2 (i.e., CRPS with associated major nerve injury), patients often report hyperesthesia around the injured nerve in addition to electric shock–like sensations, shooting pain, and allodynia. Symptoms indicative of vasomotor autonomic abnormalities (including color changes) occurred in 86.9% of patients; temperature instability occurred in 78.7%. Sudomotor symptoms of hyperhidrosis and hypohidrosis were reported in 52.9%. Trophic changes in skin, nail, or hair pattern were reported in 24.4%, 21.1%, and 18%, respectively. Edema was reported in 79.7%, with decreased range of motion in 80.3% and motor weakness in 74.6%.

DIAGNOSIS

There is currently no “gold standard” test for the diagnosis of CRPS. A very thorough history and physical examination are essential for evaluation and diagnosis. Patients with this condition will have the signs and symptoms mentioned previously. Physical examination must be performed to establish the sensory, motor, trophic, sudomotor/edema, and autonomic
changes. Sensory changes such as allodynia may be evaluated by light touch and the application of warm/cold temperature to the affected area. Autonomic dysfunction may be confirmed by the presence of asymmetry in temperature and color. Trophic changes may be manifested as changes in skin, nails, and hair in the affected limb. Motor activity may be evaluated by examining motor strength and range of motion. Sudomotor/edema changes may be assessed by dragging a smooth object over the affected and unaffected limb, with the wetter limb allowing a smoother drag than the drier limb. Common diagnostic tools used for diagnosis of CRPS include quantitative sensory testing, tests of autonomic function, and imaging for trophic changes.

QUANTITATIVE SENSORY TESTING
Such testing includes the use of standardized psychophysical tests of the sensory and motor systems, thermal sensation, thermal pain, and vibratory thresholds to assess the function of large-fiber, myelinated small-fiber, and unmyelinated small-fiber afferents. Patients with CRPS may have impaired paradoxical heat sensations, mechanical detection thresholds, mechanical pain thresholds to pinprick stimuli and blunt pressure, allodynia, and pain summation with the use of continuous pinprick stimuli. There is currently no definitive diagnostic sensory pattern in patients with CRPS, but this test can aid in distinguishing other neuropathies from CRPS.

TESTS OF AUTONOMIC FUNCTION
Thermoregulation and sudomotor regulation are the main systems tested in patients with CRPS for disorders in autonomic function. Thermoregulation is tested by using the thermoregulatory sweat test (TST) and infrared thermography or thermometry. The TST assesses calorimetric precipitation from a specific region of the body by adding a solution that changes color when enough heat is generated to produce sweat. Infrared thermography is direct visualization of the change in temperature of the affected site, and in infrared thermometry, a device is used to measure temperature through detection of infrared energy. Changes in temperature in patients with CRPS versus those with other types of pain had a sensitivity of 76% and a specificity of 94%. Sudomotor regulation is tested by using the quantitative sudomotor axon reflex test (QSART), which measures sweat output from various regions of the skin.

TROPHIC CHANGES
Three-phase bone scintigraphy (TPBS) is a very valuable test for detection of CRPS. Although joint and bone alterations are not part of the IASP inclusion criteria, they are very important in the outcome of the syndrome. TPBS detects alterations in periarticular bone metabolism, particularly increased bone metabolism, by detecting increase uptake of a periarticular tracer, which occurs predominantly within the first year. TPBS is low in sensitivity but high in specificity. Magnetic resonance imaging of the affected limb has also been used for detection of CRPS but has high sensitivity (97%) and low specificity (17%).

TREATMENT
Management of CRPS has been complicated by scant knowledge of the etiology of the disease, which has resulted in few targeted therapies. Most of the medications initiated as first-line therapy have been investigated for other non-CRPS neuropathic pain conditions and then applied to the treatment of CRPS, with mixed success. The historical approach to therapy for CRPS still remains a multimodal, multidisciplinary methodology. The predominant therapeutic modalities for the care of CRPS patients include physical therapy, pharmacologic agents, and interventional procedures.

PHYSICAL AND OCCUPATIONAL THERAPY
Physical and occupational therapy for restoration of function and improvement of limbs affected by CRPS has been studied widely. Physical exercises such as isometric strengthening, active range of motion, myofascial release, and stress loading are all tools that aid in restoring functional capacity of the affected limb. Other methods of therapy are currently under study. In a large controlled study in which tactile acuity and pain on application of a tactile stimulus were measured in patients with CRPS and mirror images were used to show the reflection of the unaffected limb during the stimulus, a decreased two-point discrimination threshold and decreased pain acuity were observed. This suggests that therapies that improve functional restoration of the affected limb may improve the outcome of CRPS.

PHARMACOLOGIC THERAPY
Membrane Stabilizers
Medications such as gabapentin and pregabalin have been shown to be effective in relieving neuropathic pain. CRPS is considered neuropathic pain and gabapentin is presumed to be effective in treating it, yet there are very limited studies showing its specific efficacy for CRPS. In a randomized double-blind, placebo-controlled crossover study in which patients were treated for two 3-week periods with 2 weeks in between, gabapentin had minimal effect on pain but it significantly reduced patients’ sensory deficits. Although there is no clear evidence of efficacy for gabapentin, these neuroleptic medications are the first-line therapy for neuropathic pain and are thus considered first-line therapy for CRPS.

Corticosteroids
A large part of the pathophysiology in CRPS is the acute inflammatory process that occurs after an inciting event (see “Pathophysiology”). Because of this inflammatory course, corticosteroids have been used for treatment. In a recent randomized controlled trial comparing prednisolone with piroxicam, patients were given either medication for 1 month, and their shoulder-hand syndrome scores (measuring pain, distal edema, passive humeral abduction, and external rotation) were determined. In the prednisolone group, 83.3% showed improvement, and in the piroxicam group, only 16.7% improved. The shoulder-hand syndrome score in the steroid group was significantly lower than that in the piroxicam group.

Antidepressants
These drugs have not been studied for use specifically with CRPS, but they have been widely studied for the control of neuropathic pain, and because CRPS is considered neuropathic pain, they are used in pain management.
Antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs) have been used to control neuropathic pain effectively. In a recent Cochrane review, TCAs were found to be effective in treating neuropathy, with a number needed to treat (NNT) of 3.6 and a relative risk (RR) of 2.1. Venlafaxine, an SSNRI, was also found to be effective, with an NNT of 3.1 and RR of 2.2. Further studies to investigate the drugs’ ability to specifically target CRPS are warranted. A recent study showed that the combination of gabapentin and nortriptyline was a more effective therapy than either medication alone for neuropathic pain (including CRPS).

Opioids
Studies on the effects of opioids directly on CRPS are lacking, although some have shown opioids to improve neuropathic pain when used in high doses. However, a double-blind, placebo-controlled trial studying the efficacy of sustained-release morphine in CRPS patients for a total treatment of 8 days showed that it was ineffective in decreasing pain, but the study had many limitations. Substantial challenges to using opioid therapy for nonmalignant pain include nausea, constipation, cognitive impairment, tolerance, and hyperalgesia, and therefore it should be used only until other therapies can be initiated. Studies of these medications in the CRPS population are lacking, and more are needed to demonstrate the efficacy of opioids.

Ketamine
Ketamine is an NMDA receptor antagonist. The NMDA receptor is a major part of the central sensitization that occurs in patients with CRPS (see “Pathophysiology”). Ketamine can be administered topically, orally, intranasally, or parentally in subanesthetic (analgesic) doses or in high doses to produce ketamine coma. A double-blind, randomized, placebo-controlled, parallel-group trial studying the effects of subanesthetic intravenous dosing of ketamine for 4 days in CRPS patients showed decreased levels of pain, but the pain progressively increased from the 1st week after infusion to the 12th week. In patients undergoing ketamine infusion, minor and rare side effects such as nausea, vomiting, and psychomimetic effects developed. In another nonrandomized open-label trial in which chronic CRPS patients refractory to standard therapies were treated with anesthetic doses of ketamine for 5 days, the pain improved significantly for 6 months, but 79.3% relapsed back to baseline after the 6-month period. The topical form of ketamine has also been shown to decrease allodynia and hyperalgesia in response to pinprick stimuli, but this has not been well validated.

Bisphosphonates
Bone resorption at the site of inflammation in the affected limb contributes to the pain in CRPS. The use of bisphosphonates to decrease osteoclast overactivity has shown promise in its pain-reducing effects. In an 8-week randomized, double-blind, placebo-controlled study, alendronate was used in patients with post-traumatic CRPS type I. This drug improved spontaneous pain, tolerance to pressure, and extremity range of motion. However, other trials have shown no reduction in CRPS-related pain.

Interventional Treatment
Sympathetic Nerve Block
The most common sympathetic nerve blocks are the stellate ganglion and lumbar sympathetic blocks for treatment of CRPS of the upper and lower extremities, respectively. Multiple modalities have been studied for their ability to disrupt the sympathetic pathway through these nerve plexuses, including local anesthetics, chemical neurolysis, and radiofrequency ablation. In a study in which both stellate ganglion and lumbar sympathetic blocks were performed with local anesthetic and normal saline on each subject, it was observed that the decreased pain that each experienced was almost identical, but the duration of decreased pain was longer when patients received the local anesthetic block. In a small randomized study in which radiofrequency neurolysis was compared with chemical neurolysis, the pain decreased from baseline, but no significant difference was seen between the two methods. Although sympathetic blocks provide a significant reduction in pain by blocking the sympathetic pathway of the pathophysiologic stages in CRPS, their greatest limitation is that they provide only short-term relief in the vast majority of treated patients. This means that patients must continue to frequently undergo sympathetic blocks, which most often places them on maintenance therapy. This form of therapy should be performed to provide enough pain relief so that patients are able to perform physical therapy exercises for functional restoration and multidisciplinary therapy, but not as a sole therapeutic modality.

Spinal Cord Stimulation
A spinal cord stimulator is a generator containing leads that are placed in the dorsal aspect of the spinal cord within the level that innervates the area causing pain. Most patients have been managed with standard medical therapy and some treated surgically before undergoing spinal cord stimulation (SCS). In a randomized trial, patients with CRPS were separated into two groups: SCS with physical therapy and physical therapy only. This study showed that SCS provided significant improvement in pain for the first 2 years. Unfortunately, there was no amelioration in quality of life or functionality in the group undergoing SCS with physical therapy, although this study was seriously flawed because of excessive patient dropout. SCS has been used widely for the control of intractable pain, but further research is needed to verify its impact on CRPS.

Intrathecal Treatments
Baclofen and ziconotide administered intrathecally have been examined for the treatment of CRPS. Baclofen is a γ-aminobutyric acid receptor agonist. It is currently used as a muscle relaxant and has been indicated for muscle spasticity and dystonia. A single-blind, placebo run-in, dose escalation study of CRPS patients with dystonia showed that intrathecal baclofen was very effective in decreasing dystonia and pain, as well as in improving quality of life, as indicated in a 12-month follow-up. Ziconotide is a very potent drug made from the toxin of sea snail venom and works by blocking chemicals that transmit pain signals. Intrathecal administration of this drug has great potential in reducing edema, trophic changes, and pain in these patients. However, it is associated with a nearly 100% side effect profile.
PHN is neuropathic pain that arises from herpes zoster (HZ—shingles) in a dermatome distribution. This form of pain is very debilitating and leads to poor quality of life and poor functional status at home and in society. Control of pain is difficult, with multiple interventions being required. There are multiple risk factors for the development of HZ and subsequent PHN. It is essential to understand the risk factors, pathophysiology, and diagnostic approach to PHN to delve into the various pharmacologic and interventional treatments available.

EPIDEMIOLOGY AND RISK FACTORS

Varicella is a viral infection that may lead to varicella zoster (chicken pox) on first exposure and subsequently remains in a latent phase for the majority of lifetimes. HZ develops secondary to reactivation of varicella virus from its latent state. Varicella virus is kept in a latent state by the body’s cell-mediated immunity. When there is a decrease in cell-mediated immunity, the risk for reactivation and subsequent HZ increases. Cell-mediated immunity may decrease with age, HIV infection, cancer, and immunosuppressive therapy as used for transplant patients. The incidence of HZ in the United States is approximately 500,000 cases per year, or approximately 2 cases per 1000 persons. The lifetime risk for the development of HZ is 10% to 20%, but this number increases with age. Patients older than 75 years have an incidence of 10 cases per 1000 persons per year. In patients older than 85 years, 50% would have had at least one episode of HZ.

PHN pain that persists after the acute phase of the disease is seen in approximately 10% to 20% of patients infected with HZ. The incidence of PHN developing from HZ also increases with age. Patients older than 70 years with HZ have a 50% risk for the development of PHN, whereas it rarely develops in patients younger than 40 years. There are many risk factors for the development of PHN, and among them are increased age, greater severity of the rash during the acute phase, female gender, and greater acute pain severity. In an epidemiologic study of patients with PHN in the Ferrara University Dermatology Unit, Italy, from the years 2000 to 2008, males had an earlier age at onset than females did, and 72% of the patients were older than 45 years. The sites most commonly observed to have been affected were ophthalmic in 32%, thoracic in 16.5%, and facial in 16%. The correlation of PHN developing after the first episode of HZ was reviewed in a prospective study in which patients were monitored for 12 months. It was concluded that 3 months after appearance of the HZ rash, the risk for development of PHN was 1.8%. In patients older than 60 years, the risk for development of PHN and the severity of the pain were higher.

In recent years, administration of varicella vaccine has become very popular. However, some data suggest that these vaccines may lead to an increase in the incidence of HZ secondary to a reduced opportunity for subclinical boosting, which results in an extreme reduction in the incidence of varicella from the immunizations. In contrast, administration of zoster vaccine has been proven to decrease the incidence of HZ and PHN. In a randomized, double-blind, placebo-controlled trial of the zoster vaccine, the incidence of PHN decreased by 66.5% (P < 0.001) and the incidence of HZ decreased by 51.3% (P < 0.001). The zoster vaccine has shown great promise in preventing HZ and PHN in patients older than 60 years.

PATHOPHYSIOLOGY

Varicella zoster is the primary infection that leads to chicken pox. After the primary infection, the virus remains dormant within one of the sensory nerve ganglia, the most common of which are the trigeminal and thoracic ganglia; these are also the sites where most of the cutaneous dermatomes are involved. The cell-mediated immune system keeps the virus dormant in the latent phase. Progression from the latent phase to reactivation of the virus leads to the development of HZ and subsequently PHN in some patients. During the reactivation phase of varicella-zoster virus (VZV), destruction of neurons and satellite cells occurs because this is the site of replication for the virus. VZV traveling along the affected sensory nerves leads to evasion of the host immune system and spreads from cell to cell until its characteristic unilateral dermatome rash is produced. Spread of the virus and its destruction of neurons occurs before development of the rash. Studies in postmortem patients have led to the conclusion that reactivation and replication of VZV result in inflammatory changes within the sensory neurons that it disturbs, which causes pain. This mechanism may help explain the findings of loss of cells, myelin, and axons, fibrosis of the affected ganglion, and atrophy of the dorsal horn in postmortem patients.

The previously mentioned mechanism contributes to the two primary pathophysiologic mechanisms of PHN pain: sensitization (hyperexcitability) and deafferentation. These mechanisms describe not only peripheral nerve pain but also central nerve pain. Following nerve injury, nociceptive receptors in the peripheral and central nervous systems become sensitized, which means that the threshold for firing of action potentials after a certain stimulus is lowered. This causes the nerve to become hyperexcitable and leads to allodynia without sensory loss. Deafferentation pain arises from the neuronal destruction and loss of afferent neurons that occur after the virus reacts and subsequently produces the inflammatory response within the affected nerve. The loss of afferent neurons leads to spontaneous activity centrally, which results in pain in areas where there is sensory loss. Neural sprouting is initiated in an attempt to reconnect the former C-fiber receptors, a process that leads to hyperalgesia with allodynia. The sympathetic nervous system is also thought to play a role in PHN by stimulating a vasoconstrictive response during the inflammatory process that results in decreased intraneural blood flow, hypoxia, and endoneural edema.

DIAGNOSIS

Post-herpetic neuropathy is principally a clinical diagnosis. The typical clinical scenario involves a patient complaining of persistent pain that is within a certain dermatome and affects the region that the dermatome innervates in a unilateral fashion. The acute phase of HZ is characterized as a maculopapular vesicular rash that crusts over after 1 to 2 weeks and results in a burning sensation, hyperesthesia, itching, and severe pain. Prodromal symptoms that may occur 1 to 5 days before the rash include headache, fever, malaise, abnormal skin sensation, and photophobia.
PHN may occur 2 weeks after the presence of HZ and is the chronic form of the disease. This is a very debilitating pain that consists of burning, dysesthesia, pruritus, and allodynia or paresthesia of the affected dermatomal region. The pain usually decreases or resolves within 6 months after exposure, but in some cases it may last years.70

TREATMENT

Therapy for HZ can be separated into the acute phase (shingles) and the chronic phase (PHN). In the acute phase of the disease process, the first-line medications that have proved to significantly decrease the length of disease are antiviral medications such as acyclovir, famciclovir, and valacyclovir. Three randomized controlled trials that measured the efficacy of these agents when initiated within the first 72 hours of disease onset concluded that they were all effective in increasing the rate of healing and decreasing pain.71,73 Another study showed that valacyclovir resulted in faster complete resolution than acyclovir did (44 vs. 51 days, respectively).74 In addition, a study comparing famciclovir with valacyclovir showed no statistically significant difference.71 When deciding which agent to use, it is important to consider the amount of administration and cost (Table 24.1). Unfortunately, data on the administration of antiviral medications for prevention of PHN are inconsistent. Other medications that may be used to control the pain of acute HZ are acetaminophen, nonsteroidal anti-inflammatory agents, tramadol, and opioids.54 Studies and randomized trials comparing opioids, TCAs, and membrane stabilizers for treatment of the acute pain from HZ are lacking, but they are still recommended as adjunctive therapy for refractory severe pain.54 The addition of corticosteroids with antiviral medications has proved effective in relieving the intensity of the pain of shingles, but not the duration of the disease process.75 Furthermore, corticosteroid administration did not aid in preventing the development of PHN, as shown in a recent Cochrane review study.76 Interventional therapy for the treatment of acute HZ has proved effective in relieving the pain but not in preventing the development of PHN. A randomized trial in which patients older than 50 years with HZ were given standard therapy versus standard therapy and one epidural injection of methylprednisolone, 80 mg, with bupivacaine, 10 mg, showed that after 1 month, patients in the epidural injection group experienced a significant reduction in pain.77

ANALGESIC THERAPY

PHN is a neuropathic pain historically refractory to many forms of therapy. PHN therapies have been separated into analgesic medications (e.g., topical, membrane stabilizers, opioids), interventional procedures (such as sympathetic blocks, intrathecal injections, or surgical interventions), and preventive therapy with the zoster vaccine. Nontraditional PHN therapies such as cognitive and physical therapy have also proved beneficial. As with most other chronic pain disorders, a multimodal therapeutic plan leads to an optimal chance of success.

Medications such as gabapentin, pregabalin, tramadol, and topical lidocaine are considered first-line treatments because they have been shown to be most well tolerated by the (commonly elderly) patient population. Other medications shown to help in patients with PHN are TCAs and SNRIs, opioids, and topical capsaicin cream (Table 24.2).

<table>
<thead>
<tr>
<th>Table 24.1 Antiviral Medications for Acute Herpes Zoster</th>
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<td>Medications</td>
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<tr>
<td>Acyclovir</td>
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<td>Valacyclovir</td>
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<td>Famciclovir</td>
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<tr>
<th>Table 24.2 Efficacy and Side Effects of Analgesic Medications for Post-herpetic Neuropathy</th>
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<tr>
<td>Medications</td>
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<tr>
<td>Anticonvulsants</td>
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<td>Gabapentin</td>
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<td>Pregabalin</td>
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<td>Topical</td>
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<td>Lidocaine</td>
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<td>Capsaicin</td>
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<td>antidepressants</td>
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<td>Opioids</td>
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<td>Tramadol</td>
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<tr>
<td>Oxycodone</td>
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<td>Morphine</td>
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The therapeutic modality chosen is patient specific and depends on a thorough history and physical examination.

**Topical Medication**

A 5% lidocaine patch and 4% to 10% lidocaine cream are widely used topical forms. A randomized, two-treatment period, vehicle-controlled, crossover study showed that a lidocaine patch is effective in controlling PHN pain from allodynia. At the end of the study, 78.1% of subjects enjoyed the lidocaine patch treatment phase and only 9% liked the placebo patch treatment phase. The lidocaine patch is also very safe because of minimal systemic absorption. It is also used safely with other medications based on studies showing no significant drug-drug interaction. The most common side effect reported has been mild skin irritation.80

Topical capsaicin in cream or high-concentration patch form has shown promise in treating PHN pain. The first application of the cream leads to exacerbation of the burning sensation, but with time, application leads to desensitization of the nerve root endings and decreases the hyperalgesia. In a 4-week, double-blind study, patients were randomized to receive a high-concentration topical capsaicin patch or placebo. The study showed that the high-strength capsaicin patch relieved pain in 64% of patients at the 6-week mark as compared with 25% taking placebo.81

**Anticonvulsants**

Gabapentin has been used widely as a first-line therapeutic agent for PHN. A quantitative systematic review of randomized controlled trials indicated that the pooled NNT for gabapentin was approximately 4.4.82 Another study, a randomized, double-blind, parallel-group trial of 9 weeks' duration, showed that gabapentin was just as effective as nortriptyline but was tolerated better. The pain score after 9 weeks of gabapentin treatment declined by 43% and sleeping scores improved by 52%.83 The dosage may be titrated up to effect to 1800 mg/day to a maximum of 3600 mg/day.84 Pregabalin has an identical site of action as gabapentin and is as efficacious in the treatment of PHN. It has the drawback of being on patent (and therefore more expensive) but can be better tolerated by patients because of its greater bioavailability, which results in twice-a-day dosing in comparison to the three-times-daily dosing required for gabapentin.85

**Antidepressants**

TCA medications have been the first-line therapy for neuropathic pain. In a recent randomized, double-blind, parallel-group trial of 9 weeks’ duration, patients with PHN who received nortriptyline had a 47.6% reduction in pain with sleeping scores improved from baseline.83 A quantitative systematic review of analgesic therapy for PHN noted a significant analgesic benefit with TCAs for the treatment of PHN pain, with the pooled data showing an NNT of 2.6 (95% confidence interval = 2.1 to 3.5).82 The efficacy of amitriptyline in providing relief of pain in patients with PHN was studied by comparing nortriptyline with amitriptyline. The results showed that both these drugs provided adequate pain relief in 67% of patients. Although they are both equally effective, patients tolerated nortriptyline better because of its fewer side effects.86

Venlafaxine is another antidepressant medication with good potential. It is classified as an SSNRI and provides relief of neuropathic pain by increasing the amount of serotonin and norepinephrine and inhibiting their reuptake. This drug has been shown to have fewer side effects than TCAs.87 Venlafaxine has yielded improvements in neuropathic pain such that 56% of patients had greater than a 50% reduction in pain in comparison to a placebo group (34%; P <0.01) in a double-blind, randomized, placebo-controlled trial.88 Venlafaxine must be used in doses exceeding a total daily dose of 200 mg/day to inhibit norepinephrine reuptake; doses below this level will only inhibit serotonin reuptake and have no analgesic benefit.

**Opioid Medications**

Although opioids are considered effective in overall pain management, their efficacy in controlling neuropathic pain is still controversial. In a double-blind, crossover, 4-week study of sustained-release oxycodone, 20 to 60 mg, for moderate to severe pain in patients with PHN, the response rate for pain relief was 58% versus 18% for placebo.89 Another study reported that the administration of 10 mg oxycodone to a patient already taking pregabalin did not enhance the pain relief obtained, thus demonstrating that oxycodone at low doses is not as effective as administration at higher doses. Morphine was also found to be beneficial in managing the pain of PHN. It was shown that a combination of morphine and gabapentin improved neuropathic pain in patients with PHN more than did either one of them alone.90 These data suggest that opioids at high doses are of therapeutic value in relieving pain in patients with PHN.

**Tramadol**

Tramadol is a weak µ-receptor agonist medication with properties that increase release of serotonin and inhibition of norepinephrine reuptake. This medication has been effective in treating neuropathic pain with an NNT of 4.8.91 In a multicenter, randomized, double-blind, parallel-group study involving 127 outpatients treated with tramadol or placebo for 6 weeks, the tramadol group showed significantly reduced pain in compared to the placebo group. Quality of life in the tramadol group was also improved.91

**Combination Therapy**

Many studies have combined medications to achieve the greatest efficacy with the least dosage and increased tolerability of the medications. In a double-blind, double-dummy, crossover trial in which patients with neuropathic pain took gabapentin or nortriptyline as monotherapy or combination therapy, combination therapy was shown to be better than monotherapy, although each medication was effective in relieving neuropathic pain.39 The combination of gabapentin and morphine has also been widely researched. Gabapentin in combination with morphine was more effective than either medication alone.90

**INTERVENTIONAL THERAPY**

Interventional therapy for the pain of PHN includes nerve blocks, intrathecal injections, and SCS. Interventional therapies are not considered to be a first-line choice, but they should be considered in a multimodal management approach for the treatment of PHN.
Sympathetic Nerve Blocks

The role of sympathetic nerve blocks is to provide relief of pain during the development of HZ, provide relief of PHN pain, and prevent the development of PHN from HZ. Unfortunately, most of the data attempting to prove the efficacy of sympathetic nerve blocks in these three main roles come from retrospective studies and are consequently limited. Thus, the use of sympathetic nerve blocks remains controversial. In a small, randomized study based on retrospective data in which bupivacaine was compared with saline solution, there was evidence of reduced duration of acute HZ pain in patients with sympathetic nerve blocks. Another retrospective study concluded that sympathetic nerve blocks provided temporary short-term pain relief in 41% to 50% patients with PHN.

Neuraxial Blocks

Epidural injections, paravertebral injections, and intrathecal steroid injections have all been used for temporary relief of pain from PHN, with successful short-term results. Epidural steroid injections have been proved to effectively reduce pain in the acute phase of PHN, but most research has focused on its effects in preventing progression of HZ to PHN. In a study performed in Italy, 600 patients older than 55 years with HZ were administered bupivacaine and methylprednisolone through an epidural catheter versus intravenous administration of prednisolone and acyclovir until they were pain free. After 1 year, the incidence of PHN was 22% in patients receiving intravenous prednisolone and acyclovir as opposed to 1.6% in those receiving bupivacaine and methylprednisolone through an epidural catheter. The efficacy of paravertebral blocks in preventing PHN was assessed in a single-center randomized study of patients with HZ given either the standard therapy of oral antivirals and pain medications or a series of four paravertebral injections with bupivacaine and methylprednisolone in addition to standard therapy. The study concluded that after 12 months, the incidence of PHN with standard therapy alone was 16% as compared with 2% in the paravertebral block group. Although it seems that paravertebral blocks are effective in preventing PHN, larger multicenter trials are still required. Another promising procedure for the relief of PHN pain is intrathecal methylprednisolone. A study in which 279 patients with intractable PHN pain for more than 1 year were given either intrathecal methylprednisolone with lidocaine, lidocaine alone, or no therapy concluded that the group receiving methylprednisolone with lidocaine experienced a significant reduction in pain in comparison to the groups receiving lidocaine alone or no therapy. Unfortunately, these data have never been replicated and clinical experience has not corresponded to the positive results that the authors obtained. Although this method of management of intractable PHN may have been effective in this single study, its association with adhesive arachnoiditis has and should limit its application.

Spinal Cord Stimulation

A study followed 28 patients refractory to conservative therapies after placement of a spinal cord stimulator. Twenty-three of the 28 patients had significant improvement in pain, and many stopped using their adjuvant oral medications. The pain relief was long lasting. Further trials, including cost-effectiveness data, are needed to determine the role of SCS in the treatment of PHN pain.

DIABETIC NEUROPATHY

EPIDEMIOLOGY AND RISK FACTORS

The definition of diabetic neuropathy as proposed by the San Antonio Consensus Statement is “demonstrable disorder, either clinically evident or subclinical in the setting of diabetes without other causes of peripheral neuropathy.” The diabetic neuropathies are collectively considered a diverse, complex disease that affects many components of the nervous system and exhibits varied clinical manifestations. They can be classified into two main categories: generalized neuropathies versus focal or multifocal neuropathies. Generalized neuropathies include acute sensory neuropathy, chronic sensorimotor distal polyneuropathy (DPN), and autonomic neuropathy. Focal and multifocal neuropathies include cranial, truncal, focal limb, and proximal motor neuropathy (amyotrophy), as well as chronic inflammatory demyelinating polyneuropathy.

The prevalence and incidence of DPN have been very difficult to verify given the inconsistencies in clinical diagnostic criteria, variability in patient populations, and wide range of physiologic techniques. The World Health Organization estimated that 150 million people had diabetes in the year 2000, and this number was expected to increase to 366 million by the year 2030. It has been estimated that approximately 56% of patients with DPN will complain of pain that affects their quality of life. In earlier studies, the prevalence of lower limb pain ranged from 6% to 27%, and DPN affected men and women equally. A study conducted in the United Kingdom involved 356 diabetic patients, most of whom had type 2 diabetes, and included a structured questionnaire with physical examination. Chronic sensorineural diabetic peripheral neuropathy (CSDPN) was diagnosed in almost half the patients, but only a third of them complained of pain that had been present for at least 1 year. The prevalence rate for DPN in this study was 16% as opposed to 5% for chronic neuropathic pain in a similar population without diabetes. It is also important to note that in this study 12.5% of patients with DPN did not report symptoms to their physicians and the 39% who reported pain did not obtain treatment of their pain, which suggests that DPN is undertreated. A cross-sectional descriptive study reported the prevalence of DPN in patients with diabetes mellitus type 2 to be 26%. The prevalence of diabetic patients suffering from CSDPN was found to be 44%. A multicenter study recently conducted in Belgium included 1111 diabetic patients, types 1 and 2, and estimated the prevalence of CSDPN and DPN. The study was performed with the NeuroPEN device, which tests for pain and monofilament perception, and based on studies is able to identify CSDPN with confidence. The duration of diabetes in this population was greater in patients with type 1 than in those with type 2, 16 versus 11 years, respectively. The study concluded that the prevalence of CSDPN was 43% and was higher with type 2 (51%) than with type 1 (26%) diabetes. The prevalence of lower limb neuropathic pain was 14%, again higher with type 2 (18%) than with type 1 (6%). According to these
and other studies, the prevalence of DPN may be estimated to be 15% to 20% in type 2 diabetics and approximately 5% in type 1 diabetics with an incidence rate of 2% per year.106

Risk factors for DPN have been widely studied in an effort to prevent its development. The most commonly reported risk factors are age and duration of diabetes.107 Other risk factors associated with DPN are arterial hypertension91 and impaired glucose tolerance (IGT).108 In a study examining patients with neuropathy of unknown origin, 36% of patients had IGT, 77% of whom had painful neuropathy.109 Other risk factors shown to have a relationship with the presence of DPN are obesity with low high-density lipoprotein cholesterol and high plasma triglyceride levels.104 Genetic factors are also considered risk factors based on a study by Galer and colleagues90; 56% of patients with DPN also had first- or second-degree relatives suffering from DPN.

PATHOPHYSIOLOGY

Diabetic neuropathy is theorized to occur by three mechanisms: the polyol pathway, microvascular damage, and glycosylation end-product theories. These three models most likely act simultaneously, but there may also be some overlap between them.110 Neurotrophic factors and neuronal membrane ion channel dysfunction may likewise play a role in DPN.

The polyol pathway theory proposes that increased blood glucose leads to elevated glucose concentrations within nerve endings. Through a series of reactions, the glucose is converted into sorbitol via the polyol pathway involving aldose reductase and elevation of the fructose level. The high sorbitol and fructose levels subsequently lead to a decrease in sodium-potassium adenosine triphosphatase (Na+,K+-ATPase) activity. Activation of the aldose reductase–depleting cofactor NADPH (reduced nicotinamide adenine dinucleotide phosphate) leads to decreased nitric oxide and glutathione, which inhibits the buffer against oxidative injury and vasodilation and results in chronic ischemia.110 In the microvascular damage theory, thickening of the capillary basement membrane along with endothelial cell hyperplasia leads to neuronal ischemia and infarction.110 The glycosylation end-product theory proposes that interference in axonal transport results in decreased nerve conduction velocity because of chronic hyperglycemia, which results in deposition of advanced glycosylation end products around peripheral nerves. These end products may also produce NADPH (which activates NADPH oxidase) and thereby contribute to the formation of hydrogen peroxide and increased oxidative stress. Nerve growth factors are important in the repair of nerve structure and function after an injury. Low levels of these neurotrophic factors correlate with diabetic neuropathy in animal models. Other factors associated with diabetic neuropathy are abnormal calcium channel activity contributing to cellular injury and death and sodium channel dysfunction playing a role in the genesis of painful neuropathy.111

CLINICAL FEATURES

Acute sensorimotor neuropathy often occurs in association with periods of poor metabolic control such as uncontrolled glycemic levels or the development of ketoacidosis. This form of neuropathy is very rare.98 The most common form of peripheral neuropathy is CSDPN, as seen in more than 80% of patients with DPN. Patients with CSDPN typically complain of distal, symmetrical burning pain that usually involves the feet initially and gradually moves upward in a symmetrical fashion. This is due to damage to longer nerves, a phenomenon known as length-dependent diabetic polyneuropathy.112

DPN causes neuropathic pain as a result of the involvement of small nerve fibers,113 and diagnosis is achieved through a diligent history and physical examination. One study showed that clinical neurologic examination, including questionnaires, was 23% sensitive and 93% specific in diagnosing DPN.114 Another recent study concluded that development of the DN4 questionnaire has improved diagnostic performance, with a sensitivity of 83% and specificity of 90% in patients with a neuropathic pain score greater than 4 out of 10.115 The initial symptoms in up to 50% of patients with DPN are highly nociceptive and include burning pain, electric or stinging sensations, paresthesias, hyperesthesia, and deep aching pain, which are typically worse at night. Upper extremity involvement is rare.96 Physical examination of the lower limbs typically shows sensory loss of vibration, pressure, pain, and temperature perception and absent ankle reflexes. Loss of touch and pin sensation typically occurs before loss of proprioception and vibration and is caused by the involvement of large-diameter fibers.112 This is evaluated with 10-gauge monofilament and tuning fork tests.105 Gait ataxia may occur with severe neuropathy. In addition, signs of peripheral autonomic dysfunction can be observed, including a warm or cold foot, distended dorsal foot veins, dry skin, and calluses under pressure-bearing areas.98 It is important to note that the diagnosis of DPN is a diagnosis of exclusion and that multiple pathologies may mimic this form of neuropathy. The differential diagnosis should include peripheral vascular disease, restless legs syndrome, Morton’s neuroma, vitamin B12 deficiency, hypothyroidism, and uremia.98,112

Autonomic neuropathy is a common pathology that may occur in patients with chronic diabetes types 1 and 2. This form of neuropathy may be present at any stage of the disease, but it most often affects patients who have had the disease for more than 20 years.116 The parasympathetic, sympathetic, and enteric nerves are affected, and myelinated and unmyelinated nerves are affected and damaged. The condition is considered to be irreversible, but cardiac sympathetic dysinnervation has been shown to revert with tight glucose control.117 It affects multiple organ systems, including the cardiovascular, genitourinary, sudomotor, gastrointestinal, and endocrine systems. Some clinical manifestations include resting tachycardia, orthostatic hypotension, distal anhidrosis, bladder dysfunction, erectile dysfunction and female sexual dysfunction, severe constipation, diarrhea, and dysmotility syndrome.118 In addition, because of the loss of sympathetic tone, vasodilatation occurs and leads to pooling of blood in the lower extremities. This has been proposed to cause osteopenia and is related to the development of Charcot’s neuroarthropathy.119

Multifocal neuropathies comprise a wide spectrum of neuropathies, including diabetic amyotrophy, truncal neuropathies, cranial neuropathies, and mononeuropathies. Diabetic amyotrophy most often occurs in type 2 diabetics and is characterized by subacute pain and asymmetrical
weakness and atrophy of the proximal lower limb muscles. There may also be involvement of the upper limb muscles and distal end of the lower extremity, but this is rare. Mononeuropathies most commonly involve the ulnar, median, and common peroneal nerves secondary to nerve ischemia because these nerves are more susceptible to injury from compression. Cranial nerve involvement may be present but is extremely rare.

TREATMENT OPTIONS

Treatment of DPN has been widely studied and includes the use of TCAs and SSNRIs, anticonvulsants, opioids, and other modalities. Treatment options can be viewed as approaches either to prevent the development of DPN or to alleviate its symptoms. As is true for all chronic pain syndromes, a multimodal approach is the most effective therapy for DPN, with the primary aim often focusing on protecting the lower limbs from damage caused by sensory loss or on relieving pain to enhance the quality of life and functionality of each patient.

GLYCEMIC CONTROL

Hyperglycemia and insulin deficiency are associated with the pathogenesis of DPN. It appears that glycemic control is one of the most effective treatments to slow progression of the disease and delay its onset. In a study conducted by the Diabetes Control and Complications Trial Research Group, a total of 1441 patients with insulin-dependent diabetes mellitus (726 of whom had no retinopathy and 715 had mild retinopathy) were monitored for 6.5 years after random assignment to intensive external insulin pump therapy or three or more daily insulin injections. The study concluded that in the group without retinopathy, intensive therapy reduced the risk for development of DPN by 76% in comparison to conventional therapy. In the retinopathy group, intensive therapy decreased progression by 54%. The study also showed that progression of microalbuminuria in both groups was reduced by 39%, albuminuria by 54%, and clinical neuropathy by 60% with intensive insulin therapy. Thus, tight glycemic control contributes to a delayed onset and slowed progression of DPN.

ANTICONVULSANTS

Gabapentin has been used as first-line therapy for neuropathic pain and has been shown to provide mild relief of pain in patients with DPN. In a randomized, double-blind, placebo-controlled, 8-week trial comparing gabapentin and placebo, it was concluded that daily pain in the gabapentin-treated patients decreased from 6.4 to 3.9 versus a decrease in the placebo group from 6.5 to 5.1. Patients in the gabapentin treatment group also had improved sleep. Another trial comparing the efficacy of gabapentin for DPN used three different forms of recording pain, including the visual analog scale (VAS), present pain intensity (PPI), and McGill Pain Questionnaire (MPQ) completed before and after therapy. Only the MPQ showed statistical improvement in pain with gabapentin treatment versus placebo. Gabapentin has an NNT of 3 for overall neuropathic pain. Use of gabapentin for DPN had no effect on quality of life, but it did yield improvements in sleep and mental health. A systematic review of the literature on the treatment of DPN from 1960 to 2008 recommended that pregabalin be used if medically appropriate before gabapentin. Gabapentin and valproic acid should be considered as alternative therapies for DPN. A randomized controlled trial comparing pregabalin with placebo in patients with DPN for 1 to 3 years showed that 46% of the patients taking a dosage of 300 mg/day, 48% taking 600 mg/day, and 18% taking placebo had greater than a 50% reduction in pain. In a 12-week randomized, double-blind, multicenter, placebo-controlled trial using a fixed dose of 100 mg/day for 1 week and 600 mg/day for 11 weeks in one group and flexible doses of 150, 300, 450, and 600 mg/day in the other group concluded that both treatments were superior in reducing neuropathic pain in comparison to the group receiving placebo. The NNT is 4 for a 50% reduction in pain at a dosage of 600 mg/day. Thus, pregabalin has been shown to be effective in providing relief of neuropathic pain in patients with DPN.

ANTIDEPRESSANTS

Multiple antidepressant medications, including TCAs and SSNRIs, have been used for general neuropathic pain with positive results. In one study in which nortriptyline and fluoxetine were given in combination and compared with placebo, the group receiving combination therapy had 63% more patients with greater than a 50% reduction in VAS scores for pain. The NNT for TCAs in patients with DPN was 1.3, as recorded by five randomized trials that established its effectiveness in treating neuropathic pain in those with DPN. In addition, combination therapy with gabapentin has increased the effectiveness of treating PHN and DPN pain. In a multicenter, double-blind, randomized, placebo-controlled study in which patients were treated with venlafaxine, those patients taking low dose venlafaxine (75mg) had 32% reduction from their baseline VAS scores after 6 weeks, and those taking high dose venlafaxine (150-225mg) had 50% reduction after 6 weeks with an NNT of 4.5. Duloxetine is another SSNRI that has shown promise in relieving neuropathic pain from DPN. Multiple studies have demonstrated duloxetine to be more effective than placebo. In a randomized, double-blind, crossover clinical trial comparing duloxetine with amitriptyline after a 6-week treatment concluded that both were effective in treating DPN. The duloxetine group had a 59% reduction in VAS scores with good pain relief, a 21% reduction with moderate pain relief, and a 9% reduction with mild pain relief. Duloxetine was also better tolerated than amitriptyline.

OPIOIDS AND TRAMADOL

Many studies have shown that opioid medications decrease pain in patients with DPN. The fear of dependency on and addiction to these drugs warrants close observation; opioid medication should be administered only if the patient’s condition is unresponsive to nonopioid therapy (Fig. 24.1). Of these agents, tramadol, morphine sulfate, and oxycodone consistently decrease pain from DPN. An open, randomized comparative study of gabapentin versus tramadol and acetaminophen showed that the combination of tramadol and acetaminophen was just as effective in relieving DPN pain as gabapentin. In a randomized, double-blind, placebo-controlled crossover study using tramadol, the group receiving tramadol experienced relief from polyneuropathy symptoms such as pain, allodynia, and paresthesia (NNT of 4.3).
Oxycodone has also been shown to be effective in treating neuropathic pain in patients with DPN. In a multicenter, randomized, double-blind, placebo-controlled study comparing controlled-release oxycodone with placebo, it was concluded that pain scores in the groups receiving oxycodone and placebo were 4.1 and 5.3, respectively. This suggests that oxycodone is mildly effective in relieving neuropathic pain in patients with DPN. Another study that added oxycodone to the regimen of diabetic patients already taking gabapentin for neuropathic pain concluded that use of the combination of these drugs relieved pain more than when gabapentin was used alone. There are limited data on the use of morphine monotherapy in diabetic patients with neuropathy. A crossover study investigating morphine and gabapentin used as either monotherapy or combination therapy showed that the addition of morphine to gabapentin was more effective with lower doses of each medication.

**NMDA RECEPTOR ANTAGONISTS**

The NMDA receptor plays an important role in processing nociceptive and chronic pain. Thus, antagonizing its actions may reduce neuropathic pain. One of the most common NMDA receptor antagonists is dextromethorphan. This drug has been examined in past studies, and it was shown to be efficacious in providing relief of pain in diabetic patients suffering from neuropathy. One study demonstrated that the pain in DPN patients had been reduced by 33% and that 68% of patients receiving dextromethorphan had more than moderate pain relief. A study comparing dextromethorphan with placebo showed a 27% reduction in neuropathic pain in diabetic patients, with higher efficacy achieved with increased doses. Also, it is worthwhile to note that both these studies showed efficacy of dextromethorphan for DPN but not for PHN.

**OTHER INTERVENTIONS**

Topical anesthetics have been deemed safe to use because of their lack of drug interactions, decreased side effects, and lack of titration required. Capsaicin cream (0.075%) has been shown to decrease neuropathic pain with an NNT of 6.6. In addition, 5% lidocaine–medicated plaster has been demonstrated to be as effective as capsaicin, amitriptyline, gabapentin, and pregabalin, as shown in a systemic review study comparing the efficacy of each of these drugs in patients with DPN. Because oxidative stress may play an important role in the pathogenic mechanisms of diabetic neuropathy, the use of antioxidants such as α-lipoic acid may have some beneficial effect in the treatment of diabetic neuropathy. A meta-analysis showed that treatment with α-lipoic acid, 600 mg intravenously for a 3-week course, provided effective relief of neuropathic pain and improved neuropathic deficits. A more current study reported significant improvement in neuropathic pain with a 600-mg daily intravenous dose for 5 weeks (NTT of 2.7). Other treatment forms have been suggested for DPN based on its pathophysiology, such as glycation inhibitors, aldose reductase inhibitors, and growth factors, but further research in these areas is necessary.

**HIV-RELATED PAIN SYNDROMES**

**EPIDEMIOLOGY**

It is estimated that more than 65 million people worldwide are infected with HIV. With the development and widespread use of highly active antiretroviral therapy (HAART) and the resultant decrease in opportunistic infections of the central nervous system, polyneuropathy has become the most prevalent neurologic complication associated with HIV infection. This disease affects the patient’s immune and nervous systems. As the patient progresses through different stages of the disease, a variety of neurologic complications arise that are directly or indirectly related to HIV infection. Although symptomatic neuropathy occurs in 10% to 35% of individuals seropositive for HIV, pathologic abnormalities exist in almost all those with end-stage acquired immunodeficiency syndrome (AIDS). A systematic review in which multiple studies were compiled in the hope of determining the incidence and prevalence of neuropathy in HIV-infected patients found a high level of variation across all the studies. The prevalence of neuropathy ranged from 1.2% to 69.4%. The rate of development of neuropathy per 100 person-years in HIV patients ranged from 0.7 to 39.7, with a greater risk for neuropathy in older patients and those with more advanced disease.
Multiple neurologic deficits occur with HIV infection, but the two most common forms of HIV-related sensory neuropathy (HIV-SN) are distal sensory polyneuropathy (DSP) and antiretroviral toxic neuropathy (ATN). DSP is due to the viral infection itself, whereas ATN is due to medical treatment of the viral disease. The more common of the two disorders is DSP. The most common risk factors for the development of HIV-SN before the introduction of HAART were older age and advanced disease states (such as high plasma viral load and low CD4+ cell count). After initiation of HAART, risk factors for the development of neuropathy became more ambiguous and included older age, CD4+ count lower than 50 cells/mm, nutritional deficit, use of dideoxynucleoside reverse transcriptase inhibitors, and exposure to protease and alcohol.

**CLINICAL FEATURES**

Although these HIV-SN disorders may represent two distinct entities, the clinical syndrome and pathophysiologic manifestation of the two disorders are almost indistinguishable. The time course of the illness and, in the case of ATN, the temporal relationship to commencement of antiretroviral therapy represent the primary differentiating characteristic. The onset of DSP can occur in either the subacute or chronic phase or following the development of an AIDS-defining illness. The clinical manifestations of ATN can appear within the first week to 6 months after the initiation of antiretroviral therapy and may subside after its cessation.

The clinical features of HIV-SN are dominated by painful dysesthesia, alldynia, and hyperalgesia. Its onset is often gradual, and it most commonly begins with bilateral lower extremity involvement. The neuropathy progresses in a length-dependent fashion with a worsening gradient of disease from distal structures to those more proximal. The dysesthesia commonly involves the soles of the feet first and progresses proximally; when the symptoms encompass the dermatomes of the knee, the patient will frequently report finger involvement. The first symptoms noted are often numbness or burning sensations following a diurnal cycle, with the pain being worse at night. Shortly thereafter, patients will report alldynia (a stimulus previously not found to be noxious is perceived as painful) and hyperalgesia (a lower pain threshold) of the involved structures. As a result, wearing shoes and walking become painful and the patient’s gait becomes antalgic. There is minimal subjective or objective motor involvement, and pain is typically limited to the intrinsic muscles of the foot. In addition to the sensory findings, physical examination reveals a diminution or loss of ankle reflexes.

**DIAGNOSTIC STUDIES**

There is currently no gold standard for the diagnosis of DSP. In addition, the optimal combination of diagnostic studies has yet to be defined. The disease process remains primarily a clinical diagnosis. The neuropathy may be secondary to many other physiologic processes for which blood work must be obtained for exclusion, such as vitamin B12 deficiency, diabetes mellitus, hypothyroidism, IGT, and syphilis. In a nonrandomized, cross-sectional study, HIV patients with axonal peripheral neuropathy who were taking neurotoxic nucleoside analogues had their acetylcarnitine serum levels measured. Patients suffering from neuropathy while taking nucleoside analogue medications had a deficiency in acetylcarnitine and were nutritionally deficient. Although the level of acetylcarnitine may be used for the diagnosis of ATN, more studies are necessary. Nerve conduction studies are not necessary for the diagnosis of DSP and will show an axonal, length-dependent, sensory polyneuropathy. Needle electromyograms are of no great benefit because the findings are usually normal, but they may show chronic denervation and reinnervation. Punch skin biopsy specimens from the distal end of the calf and proximal part of the thigh may be used to detect small-fiber neuropathy by measuring intraepidermal nerve fiber density. The lower the intraepidermal density, the greater the likelihood of DSP symptoms developing and the greater the neuropathic pain level. Epidermal nerve fiber density may be used as a quantitative marker in clinical trials of neurodegenerative agents and also to predict the likelihood of symptoms developing in an asymptomatic patient. Dorsal root ganglion (DRG) neuronal loss has been reported, although the reduction is more modest than distal axon loss.

**PATHOPHYSIOLOGY**

DSP and ATN are clinically similar but have a distinct pathophysiology. The exact mechanism of the disease process is not fully understood, but it is hypothesized that there are multiple mechanisms at work that eventually cause axonal injury. The peripheral and central nerve toxicity related to HIV infection may be due to cytokine-mediated effects because HIV does not infect axons or Schwann cells. The gp120 protein is an HIV-associated protein thought to play a key role in pathogenesis by way of ligation of chemokine receptors located on glial cells and neurons. It may also play a role on chemokine receptors related to Schwann cell–to-neuron interaction. Damage to axons occurs secondary to the inflammatory reaction in the nerve and surrounding tissues, which eventually leads to the characteristic pain seen in DSP. This hypothesis has been supported by animal studies in which gp120 was found to produce pain in rats when administered epineurally into the sciatic nerve and intradermally into the paw. The indirect causes of DSP pain are thought to be mediated by inflammatory injury. They can be divided into peripheral and central mechanisms. The peripheral hypothesis proposes that the pain results from the spontaneous activity of uninjured pain-transmitting or C fibers after injury to adjacent fibers. Inflammatory mediators released by macrophages may further sensitize these fibers. The central hypothesis involves an alteration in ion channels in the DRG combined with changes in the spinal cord dorsal horn that result in “central sensitization.”

ATN primarily occurs as a result of the use of nucleoside reverse transcriptase inhibitors and typically ensues within a year of beginning treatment or in patients with preexisting peripheral neuropathy. The mechanism for ATN is currently unknown, but mitochondrial dysfunction as a result of abnormal mitochondria in Schwann cells and axons has been shown to play a role. Data have also shown that the depletion of mitochondrial DNA seen in AIDS patients treated with NRTIs leads to increased levels of serum lactate.
and increased cell death. In recent years, some of the protease inhibitor medications, more specifically, indinavir, ritonavir, and saquinavir, have led to an increased risk for mitochondrial toxicity that is partly due to their enhanced ability to penetrate within the neural compartments.

**TREATMENT**

No medication is currently approved by the Food and Drug Administration for the treatment of HIV-SN. Most of the therapeutic modalities available have been tested and approved for other neuropathic pain (PHN and DPN). The therapeutic approach for HIV-SN first involves removing or reducing the dosage of the antiretroviral medication whenever possible. Also, the patient’s metabolic and nutritional status must be optimized to exclude alternative explanations for the neurologic symptoms (see “Diagnostic Studies”) before initiating any other forms of therapy. Many different medications have been studied for the treatment of this form of neuropathic pain without any great success. Intranasal peptide T did not show any effectiveness in a randomized double-blind multicenter study in which patients with HIV-SN received either placebo or 6 mg/day of peptide T. One medication that has been proved to be effective in relieving pain is recombinant human nerve growth factor, was shown to prevent axonal degeneration in cells that had been exposed to HIV gp120 protein, but further studies are needed. Amitriptyline and mexiletine have proved effective in relieving neuropathic pain in patients with DPN and PHN. Unfortunately, they did not prove to be more beneficial for HIV-SN than placebo in a randomized, double-blind study. Other medications such as duloxetine and venlafaxine, both SSNRIs, have been approved for the treatment of DPN, but further research is required to demonstrate their efficacy in relieving pain in patients with HIV-SN. Gabapentin has been shown to be effective in treating all types of neuropathy, including HIV-SN pain. In a placebo-controlled trial in which patients were treated with gabapentin (1200 to 3600 mg/day) or placebo for 4 weeks and then an open trial for 2 weeks, the group receiving gabapentin experienced improvement in pain by 44% and improvement in sleep by 49% when compared with the placebo group, with the most statistically significant side effect being somnolence. Pregabalin is also very effective in relieving neuropathic pain. A recent randomized, double-blind, placebo-controlled, 14-week parallel-group trial testing the efficacy of pregabalin showed that there was no benefit in taking pregabalin over placebo. Lamotrigine, 300 mg/day, was found to significantly reduce pain in patients with DSP and ATN in a randomized controlled trial. Topical medication has also been studied in HIV-SN, including 5% lidocaine and high-dose capsaicin cream. In a randomized controlled trial, 5% lidocaine cream was shown to be ineffective in treating HIV-SN pain.

A double-blind, multicenter, randomized trial using high-dose capsaicin cream demonstrated pain relief in patients with HIV-SN.

**SUMMARY**

Despite the diversity of conditions and pathophysiology characterized by neuropathic pain, many of the underlying treatment options are comparable but not identical. Traditional systemic analgesic agents, such as antidepressants, anticonvulsants, local anesthetics, and opioids, are typically the mainstay of treatment of neuropathic pain, although the efficacy of individual classes of agents varies with the specific type of neuropathic pain. Few high-quality trials are available as interventional options for the treatment of neuropathic pain. Clinicians should be aware of the paucity and support the use of traditional interventional options in some cases.

**KEY POINTS**

- The most commonly used clinical diagnostic criteria for complex regional pain syndrome (CRPS) types 1 and 2 have low specificity but high sensitivity, which has led to overdiagnosis of this pain syndrome.
- In 2007, research criteria (also known as the Budapest criteria) were published that included objective signs of pathology characteristic of patients with CRPS (see Box 24.2).
- Psychological factors such as depression, personality disorders, and anxiety have no correlation with CRPS patients, which suggests that there is no specific type of CRPS personality.
- A double-blind, randomized, placebo-controlled, parallel-group trial studying the effects of subanesthetic intravenous dosing for 4 days in patients with CRPS showed decreased levels of pain but a progressive increase in pain from the 1st week after infusion to the 12th week. Minor and rare side effects such as nausea, vomiting, and psychomimetic effects developed in patients treated with ketamine infusion.
- In a randomized trial patients with CRPS were separated into two groups: spinal cord stimulation (SCS) with physical therapy and physical therapy only. This study showed that SCS provided significant improvement in pain for the first 2 years.
- The acute phase of herpes zoster is characterized by a maculopapular vesicular rash that crusts over after 1 to 2 weeks and leads to a burning sensation, hyperesthesia, itching, and severe pain. Prodromal symptoms that may occur 1 to 5 days before the rash include headache, fever, malaise, abnormal skin sensation, and photophobia. Post-herpetic neuralgia may occur 2 weeks after the presence of herpes zoster and is the chronic form of the disease.
- Medications such as gabapentin, pregabalin, tramadol, and topical lidocaine are considered first-line treatments because they have been shown to be most well tolerated by the (commonly elderly) patient population.
KEY POINTS—cont’d

Other medications shown to help in relieving the pain associated with post-herpetic neuralgia are tricyclic and serotonin-norepinephrine reuptake inhibitor antidepressants, opioids, and topical capsaicin cream (see Table 24.2).

- The initial symptoms in up to 50% of patients with painful diabetic peripheral neuropathy are highly nociceptive and include burning pain, electric or stabbing sensations, paresthesias, hyperesthesias, and deep aching pain, which are typically worse at night. Upper extremity involvement is rare.96

- The rate of development of neuropathy per 100 person-years in patients infected with human immunodeficiency virus (HIV) ranged from 0.7 to 39.7, with a greater risk for neuropathy in older patients and those with more advanced disease.144

- Lamotrigine, gabapentin, and topical capsaicin are effective in the treatment of HIV-associated neuropathic pain, but amitriptyline, topical lidocaine, and pregabalin are ineffective.

SUGGESTED READINGS


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