Chapter 10
Introduction to Central Pain Syndromes and Painful Peripheral Neuropathy

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Introduction

The International Association for the Study of Pain (IASP) describes neuropathic pain as pain caused by a lesion or disease of the somatosensory system. The types of neuropathic pain can be further segmented into pathways arising from the peripheral nervous system as well as those arising from the central nervous system depending on the location of interest. Neuropathic pain originating from the peripheral nervous system is more common. They can be further broken down into painful neuropathies originating from autoimmune/infectious diseases, systemic diseases, genetic conditions, or injury/acquired conditions [1]. Patients with peripheral neuropathy present with a wide range of issues and do not necessarily experience pain [1]. They may report with hyperalgesia (normally painful stimuli causing exaggerated pain), allodynia (normally non-painful stimuli causing pain), hyperpathia (repetitive stimulation causing prolonged persistent pain), paresthesia (atypical non painful sensations that is not unpleasant) and dysesthesia (atypical painful sensation that is unpleasant) [1].

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Painful neuropathies originating from the central nervous system (CNS) develop from diseases affecting the spinal cord, brainstem, or brain. These are deemed as Central Pain Syndromes (CPS) or Central Neuropathic Pain (CNP). There is a wide range of Central Pain-associated injuries that result from infectious, vascular, demyelinating, traumatic, or neoplastic etiologies. Some of the most common issues originate from stroke, and spinal cord injury (SCI) [1]. This chapter will first focus on neuropathic pain as a result of issues to the central nervous system and then later to the peripheral nervous system.

Central Pain Syndromes

History and Definitions

In the early nineteenth century, German neurologist Dr. Edinger first proposed the theory of a central pain in public literature [2]. Until that point, there had only been case reports detailing pain originating from the spinal cord or brain. This led to further case studies mentioning pain due to specific locations in the CNS (brainstem, thalamus, internal capsule, cortex, etc.). In the early twentieth century, Roussy and Dejerine found that thalamic lesions caused pain with other associated symptoms. This was later termed as "thalamic syndrome." [3]. Sometime later, Holmes and Head published literature further detailed the relationship between thalamic issues and central pain (CP) [4]. Holmes further found comparable pains that were associated with spinal cord injuries in WWI soldiers. Though it was becoming more known that CPs could arise from pain outside of the thalamus, the exact origin remained unknown. In the 1960s, however, Pagni and Cassinari published a monumental review that detailed the relationship between CP occurring as a result of a spinothalamic tract lesion [5].

Even with these findings, the terms "central pain syndrome" and "thalamic syndrome" remain synonymous. The increase in functional neurophysiologic testing and neuroimaging technology (MRI and CT scans) have led to increased evidence and literature supporting that lesions along anywhere in the CNS could lead to CP [2]. This has finally led to the term "Central Pain Syndrome" being increasingly adopted to indicate this change in thought.

Clinical Characteristics

CP can sometimes present similarly to neuropathies. Common presenting symptoms include tingling, burning, pins and needles, electrical, stabbing, itching, and many more feelings that can happen as an isolated instance or in various combinations.

The severity of pain is variable among patients, ranging from some mild discomfort to severe pain. The literature has pointed to several factors including psychological mood comorbidities, pain components, and scale of neurological deficits that possibly impact pain severity [2]. Specifically for neurological sensory deficits, literature indicates the thermal and pinprick sensations correlate with areas of greatest pain severity, and two-point discrimination, tactile sensation, and vibration were unaffected in areas of pain [2].

Furthermore, CP can present with varying traits in different combinations in the same person [3]. These traits can be broken down into continuous, intermittent, or evoked symptoms [6, 7]. Intermittent pain is often more severe and spontaneous when compared to continuous pain. Evoked pain is induced and often leads to hyperalgesia (normally painful stimuli causing increased pain), allodynia (normally non-painful stimuli causing pain), and hyperesthesia (normal stimuli causing increased sensitivity). Patients commonly present with a variation of severe intermittent pain and a dull continuous pain [8]. Generally, the more variations of pain present, the more severe the perceived pain. Patients with incomplete sensory deficits compared to those with complete sensory deficits will typically have an increased pain severity because they show extreme evoked pain in the impaired areas of sensory loss [3].

Aside from the intensity and descriptive characteristics, pain can negatively affect quality of life and function [9]. Pain and functional limitations often correlate with sleeping complications and depression 1 year after stroke [10]. Thus, it is vital to evaluate sleep and psychological mood impairments when diagnosing, evaluating, or treating CP. Challenges in either may alter the severity of pain perception.

Diagnosis

Diagnosing and classifying CP has been a continuous conversation between clinicians and researchers. Because CP is a type of neuropathic pain, the existence of typical neuropathy will often lead to further analysis.

Currently, there are several official neuropathic pain scales including the Neuropathic Pain Questionnaire [16], Douleur Neuropathique 4 (DN4) [17], and Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale [11]. These were created to assist in indicating the presence of neuropathic pain. These scales, however, are limited in defining CP. The Neuropathic pain System Inventory (NPSI) does break down neuropathic pain into further components which slightly helps classify CP [12]. However, it is limited in specificity and sensitivity [2]. As such, these scales are not intended to be used as a gold standard diagnostic tool, but rather in combination with a thorough history, physical examination, and other forms of additional testing [2].

The neuropathic pain grading system is used to determine, to a certain degree, the presence of neuropathic pain. It was created based on the definition detailed by

the IASP mentioning that "neuropathic pain caused by a lesion or disease of the somatosensory nervous system." For neuropathic pain to occur, history and distribution of pain, sensory deficits on physical examination, and lesion location confirmed on imaging must coincide [13].

Several limitations must be considered when diagnosing CP. The existence of neuropathic pain does not indicate whether it is a central nervous system (CNS) or peripheral nervous system (PNS) problem (i.e. burning sensations can be indicated in central poststroke pain [CPSP] and diabetic neuropathy). Further, CP can coexist with other pain manifestations, which can make the diagnosis inaccurate (i.e. patients with CPSP can exhibit coexistent pain affecting the same extremity). Lastly, patients with CP clinically present with a high degree of variability.

CP is a multifactorial issue because it shares many coinciding criteria with other pain conditions [2]. This further complicates the diagnosis, evaluation, and management. A common clinical scenario to see includes neurologically limited patients that have decreased mobility; thus, they are at an increased risk of musculoskeletal injuries. One study examined the relationship between stroke patients diagnosed with CP syndrome and the existence of myofascial pain (MP) [14]. It was concluded that for stroke patients, the existence of MP cannot be eliminated and can possibly be a comorbidity. As exemplified in the aforementioned example, other diagnoses of pain must be considered; otherwise, ineffective treatment plans could happen.

Because of the difficulties in diagnosing CP, the American Pain Society Pain Taxonomy published a multifactorial framework associated with multiple sclerosis, SCI, and stroke [15]. These suggestions include five factors: "(1) core diagnostic criteria, (2) common features, (3) common medical and psychiatric comorbidities, (4) neurobiological, psychosocial, and functional consequences, and (5) putative neurobiological and psychosocial mechanisms, risk factors, and protective factors."

Central Post Stroke Pain

Definition and Prevalence

Stroke often induces many complications such as chronic pain. Every year, approximately 795,000 strokes happen in the United States, and an incidence of 3.73 per 1000 person-years [2]. Literature shows that one-fifth to half of stroke patients experience some pain. Pain is further segmented into stroke-related and non-stroke-related. In the former, there are sub-conditions that typically happen as a result of stroke. These conditions include headaches, CP, complex regional pain syndrome, myofascial pain, and spasticity [16]. In the latter it tends to be explained by pre-comorbidities such as polyneuropathy.

Central post stroke pain (CPSP) syndrome is a sensory irregularity or pain that is localized to the area of cerebrovascular impact following a stroke [2]. As an example, an infarct in the right hemisphere of the brain can cause left-sided hemiplegia

may result in pain in those left-sided extremities. When considering all stroke types, the prevalence of CPSP is significantly variable; the incidence is typically 2–8% [9]. The variability can stem from variability in study design and definitions [7, 17]. Further, CPSP can often go undiagnosed by physicians as a result of the lack of a specific CP scale and as a result of patients not mentioning it; this often leads to differences in studies [18]. Studies suggest that risk factors for CPSP include tobacco use, depression comorbidities, and motor/sensory deficits [19, 20]. Some studies also suggest young age to be a risk factor, although this is highly variable [9]. Further, the progression is significantly correlated with depression and severity of stroke impairments, and other pain issues [17]. Specifically, in one of the biggest studies in thalamic CPSP, right-sided infarctions were more associated with CPSP than left-sided infarctions. This finding is significant because the right hemisphere is vital for pain control [9]. Screening and recognizing CPSP should include cognitive and functional deficits as well as emotional health.

Onset

Typically, CPSP onset is approximately 3–6 months. Although, there has been huge variability of up to 18 months [2]. This pain felt at a later onset, which can be both instant or gradual, is thought to be correlated with the sensory and motor improvements as time progresses [21]. Additionally, it can precede neurological improvements. As stated previously in the chapter, pain can be intermittent, continuous, or evoked. Continuous pain is most common and is typically dull, while evoked and intermittent pain are typically severe [3, 18].

The significant variability of CPSP symptoms presents challenges in diagnosing CPSP for clinicians. As such, there has been increased research to determine standard patterns and traits that clearly point to CP instead of other pain conditions [22]. Despite pain sensations such as shooting, tingling, and burning are not specific enough to CP, a vital trait is examining where the area of pain distribution is. For example, if there is pain that correlates with the area of a lesion in the CNS, these symptoms can be traced back to the CNS.

Diagnostic Standards

Diagnosis for CPSP includes a framework created by AAPT that is based on neuropathic pain [15]. Firstly, there should be a diagnostic test that confirms the stroke. Secondly, continuous or recurring pain after stroke after the onset for up to 1 year. Thirdly, pain that has a duration for a minimum of 3 months. Fourthly, pain will be distributed in the area affected by the stroke as mentioned earlier. Fifthly, sensory changes in the distribution of the insult, which can be either a positive or negative sign. Lastly, all other diagnoses must be ruled out that cannot explain the pain [15].

Location

Typically, stroke location is more critical to the risk for CPSP than stroke etiology. Thalamic and lateral medullary lesions have the highest incidence of CPSP [2]. The "thalamic pain syndrome" as coined by Dejerine and Roussy, is a common example of CPSP. With that said, further studies have indicated most patients with CPSP have non-thalamic strokes [2]. Studies suggest that insults in the cerebral cortex, medullary tract, and spinothalamic tract (which all regulate pain) are correlated with the etiology of CPSP.

Infarcts within the cerebral cortex are typically not associated with CPSP. Despite that, lesions in the cerebral structures involved in pain regulation, including the medial operculum posterior insular cortex, are partly responsible for the development of CP [23]. These specific brain areas are a receiving area for the spinothalamic tract and tightly intertwined with the sensory and limbic cortices, both of which are involved in pain processing [23]. The medullary tract includes the trigeminothalamic pathway, where one of its functions is to regulate pain within the face. Lesions involving this can lead to strokes such as the Lateral Medullary stroke or "Wallenberg" Syndrome. These patients have atypical pain and temperature sensations on the ipsilateral face and contralateral portion of the body [9]. Lastly, the spinothalamic tract is further responsible for both pain and temperature sensations.

Mechanism

The specific CPSP pathophysiology is still being studied today. There are several proposed working theories that include central disinhibition and sensitization.

In the early 1900s, insults to the lateral thalamus were proposed to affect CPSP. Specifically, the pain was suggested to be a result of insult to the GABAergic inhibitory pathway, which thus disinhibits the pathway from controlling pain. This theory was later confirmed by SPECT studies; now, it is the widely approved mechanism of CPSP [7, 34]. It was later found that spinothalamic pathway (which regulates pain and temperature) insults can lead to disinhibition and thus increased thalamic activity and pain sensations [2]. This is further supported by several studies that show decreased temperature and pinprick pain sensations in the progression of CP [7, 24].

Central sensitization is an abnormal condition resulting from chronic pain. It is not to be confused with central neuropathic pain. Central sensitization is where a loss of inhibition or increased neuron activity leads to allodynia and/or hyperalgesia [25]. In contrast, CP is more general and simply refers to pain that results from CNS injury. Central sensitization is one of the main driving factors for chronic pain. This is seen in several studies for post-stroke subjects, where an atypical thalamic burst firing caused further neuronal hyperexcitability and central sensitization [26]. Central sensitization can be tracked clinically by examining hypersensitive areas and measuring activity when applying stimuli.

Neuronal hyperexcitability is best examined through firing patterns in the thalamus. One study proposes two different neuronal firing patterns that are both controlled by neurotransmitters: (1) single-spike depolarization and (2) bursts during hyperpolarization [27]. Modulation of firing patterns is controlled by cholinergic, noradrenergic, and serotonergic variables and impact pain patterns [28]. For example, noradrenaline and serotonin increased GABAnergic transmission. This in turn explains why treating CPSP with antidepressants is a viable treatment. Studies involving pathways using opioid receptors suggest that decreased opioid receptor binding is correlated with CPSP [29]. Having said that, opioid use is often contraindicated in post stroke patients [30].

Spinal Cord Injury Central Pain

Definition and Prevalence

Patients with SCI can experience CP as well. In this patient population, this refers to neuropathic pain as a sequela of damage to the CNS, specifically the spinal cord. The International Spinal Cord Injury Pain Classification indicates that below-level neuropathic pain and some cases of at-level neuropathic pain can indicate central neuropathic pain. One important distinction in at-level neuropathic pain is that it can represent both peripheral (nerve root) and/or central (dorsal horn) pain depending on its specific location. The official prevalence of CP in SCI patients is highly variable. It was complicated by the lack of categorization by earlier literature and a latency in presentation in some post-SCI pain types such as below-level neuropathic pain [31, 32]. Despite that, studies indicate approximately 31% of patients with SCI had at-level lesions and 31% had below-level neuropathic pain 12 months after injury [33]. This CP significantly impacts function and quality of life in patients with SCI.

Localization

As stated before, SCI consists of both at-level lesions and below-level lesions. At-level CP is neuropathic pain that specifically involves the dorsal horn. It involves a segmental manifestation within the dermatome or up to three dermatomes below the lesion level [33]. As such, this is commonly mentioned as “transitional zone” or “segmental” pain. To reemphasize, this is not to be confused with at-level neuropathic pain that involves nerve roots ultimately leading to peripheral neuropathic pain [34]. This pain is either evoked or spontaneous. Evoked pain presents with common characteristics involving hyperalgesia, allodynia, wind-up pain, and after-sensations [33]. The pain can typically be traced with the dermatome of the lesion and can be unilateral or bilateral.

Below-level SCI neuropathic pain represents solely CP. It has previously been called "deafferentation central pain" [31]. In contrast to at-level CP in SCI patients, below-level CP involves pain manifestation more than three dermatomes below the lesion level [33]. Clinically, below-level CP presents similarly to at-level CP. However, below-level is commonly described as patch, asymmetric, and not typically dermatome. It can sometimes come from a specific body part.

Mechanism

The pathophysiology of at-level and below-level CP in SCI patients is not well defined. It is typically correlated with excitotoxic and neurochemical changes. Literature points to amino acids (glutamate) and post-inflammatory cytokines temporarily released at the site of the SCI lesion [35, 36]. This partly gives rise to many pathological alterations in the spinal cord. It involves "increased sensitivity due to loss of normal neuronal input, removal of inhibitory influences, increased efficacy of alternative synapses and deafferentation, hyperexcitability of spinal and/or thalamic neurons, and further alterations in cellular activity of neurochemical and excitatory amino acids due to changes in ion channels and transport activity" [36].

Recent literature also indicates that the neuroimmune system can contribute to chronic pain, specifically in the microglia. Microglia are known to be phagocytes that are activated after pathological causes such as infection, injury, disease, and seizures. The theory is that in SCI patients that have lesions in the spinothalamic tract, there is microglial activation that directly fires the surviving spinothalamic tract neurons [36]. When mobilized, microglial cells create nitric acid, proinflammatory cytokines, and excitatory amino acids which all regulate pain following neural injury create neuronal hyperexcitability in the dorsal horn [36]. Further, microglial insults are correlated with neuropathic and psychological pain-related behaviors (hyperalgesia, allodynia) and are theorized to contribute to the progression of chronic CP [36].

Lastly, there are structural changes in the gray/white matter at the lesion level. These anatomical changes modify the equilibrium the spinothalamic tract has with other tracts such as the dorsal column and spinoreticulothalamic tract; this can ultimately play a part in the progression of CP [34].

Treatment

Pharmacotherapy

The treatment options for CP are still being studied and are highly variable and challenging. There have been several studies that indicate effective treatments for CP. However, there are only a few and go against the general acknowledgement that pain resolution is unlikely. Certain pharmacological drugs have been proven to be effective solutions such as antidepressants, and anticonvulsants, and cannabinoids, opioids, and steroids. The pharmacotherapy treatment is summarized in Table 1.1 in Appendix.

Table 1.1 Pharmacotherapy information for central pain syndrome

Drug class	Agent	Mechanism	Effective dosage (mg QD)	Side effects/common notable adverse events and *precautions
Anticonvulsant	Gabapentin	Regulates Ca+ voltage-gated channels in neural synapses	1800 minimum	Sedation, confusion, edema, dizziness, tremor
	Pregabalin	Voltage-gated Ca+ channel (VGCC) antagonist	410–460	Sedation, confusion, edema, dizziness, tremor, euphoria
	Lamotrigine	Stabilizes Na+ channel blockade through neuronal membrane	200–400	Rash (Stevens-Johnson syndrome), abdominal pain, diarrhea, headache, dizziness
	Carbamazepine	Na+ membrane stabilizer and channel blocker	500–760	Stevens-Johnson syndrome, hematologic suppression, aplastic anemia, hepatic dysfunction, hyponatremia, nausea, dizziness, drowsiness
				*Monitor CBC and LFTs
Antidepressants	Amitriptyline	Inhibiting the reuptake of serotonin and norepinephrine (SNRI)	75 minimum	Sedation, blurred vision, dry mouth, orthostatic hypotension, confusion, weight gain, constipation, urinary retention
				*Risk of suicidal tendencies
				*Risk of serotonin syndrome
				*Risk of cardiac arrhythmias
	Duloxetine	SNRI and adrenergic agonist	60	Sedation, fatigue, nausea, dizziness, hyperhidrosis
				*Risk of suicidal tendencies
				*Risk of serotonin syndrome
				*Risk of cardiac arrhythmias
				*Risk of increased bleeding
				*Risk of withdrawal symptoms with abrupt discontinuation

(continued)

Table 1.1 (continued)

Drug class	Agent	Mechanism	Effective dosage (mg QD)	Side effects/common notable adverse events and *precautions
NMDA antagonist	Ketamine	Blocks the NMDA excitatory receptor	Highly variable in RCTs	Hypertension, respiratory depressions, hallucinations
				*Risk of cardiac issues
Opioid	Tramadol	Inhibition of the pre- and postsynaptic CNS and PNS neurons		Sedation, dizziness, nausea, confusion, respiratory depression, constipation, urinary retention
	Morphine			
	Oxycodone			
Steroid	Methylprednisolone	Not officially established		Confusion, nausea, restlessness, abdominal pain, weight gain, hyperglycemia
Cannabinoids	Tetrahydrocannabinol			Hypotension, palpitations, dry mouth, hallucinations, paranoia
	Cannabinol			

QD once a day, *CBC* complete blood cell count, *LFT* liver function test, *RCT* randomized control trial

Neuropathic Pain Meds

Randomized control trial data supports the use of anticonvulsants and antidepressants as first-line therapy for CP [37]. Anticonvulsants such as gabapentin and pregabalin have been well supported as the treatment for neuropathic pain due to the tolerability and price [34, 35]. Pregabalin has been tested more in CP disorders such as CPSP and SCI pain. For example, Gabapentin was effective for SCI-related central pain [38] and two trials showed pregabalin was effective for SCI central pain [39, 40]. Several studies have also pointed to show that pregabalin improves anxiety and sleep in patients with post-stroke CP.

Antidepressants such as amitriptyline and duloxetine are also used as first-line therapy for treating CP. The mechanism occurs through blocking reuptake of norepinephrine and serotonin reuptake inhibitors. In one study, amitriptyline (goal of minimum 75 mg/day) was effective for CPSP [41]. For SCI, studies show mixed results for amitriptyline [42]. Duloxetine (60 mg/day) was shown to be clinically effective for Multiple Sclerosis-related neuropathic pain. However, these antidepressant agents are shown to have side effects such as serotonin syndrome and emerging suicidality [9].

Some studies support the use of other neuropathic agents as second-line therapy. These agents can often include lamotrigine and carbamazepine. Studies on carbamazepine for CP are mixed. One study shows positive results; however, the study design was poorly powered and thus the conclusions were limited [34, 35, 43].

Given in certain doses (200-400 mg/day), Lamotrigine is effective for CPSP and for incomplete lesions of SCI for below-level and at-level CP [9]. However, both of these agents are used after first-line therapy because of a higher rate of adverse events and side effects [41, 44].

Nonneuropathic Pain Medications

Ketamine , an *N*-methyl-D-aspartate (NDMA) antagonist, is thought to have an antinociceptive effect in many disorders including CP. The proposed mechanism is that it "resets the CNS" because it blocks the excitation of the NMDA receptor [45]. Additionally, ketamine is thought to have an effect on the Hyperpolarization Activated Cyclic Nucleotide Gated Potassium Channel 1 (HCN1) on neurons involved in nociception as well as microglia, which are both involved in pain [46]. Intravenous (IV) fusion of ketamine has also been studied in patients with SCI-related CP and has been shown to temporarily reduce pain according to the Visual Analogue Scale (VAS) scores [45, 47].

Methylprednisolone was also proposed as a possible treatment option for CPSP. In one study, a group of stroke patients with CPSP were treated with methylprednisolone and showed a large decrease in pain, specifically numerical rating scale score, and a minor decrease in as-needed pain medications [52]. The treatment involved a taper scheduling starting from a 6-day taper at 24 mg, and eventual decrease of dosing by 4 mg on each subsequent and consecutive day.

Opioids are proposed as a therapeutic option for patients with unmanageable and uncompromising CP. In one study, a group of patients were treated with oxycodone, morphine, and tramadol, eventually leading to better management of the CP. Nonetheless, the potential for adverse events and side effects are widely known, specifically drug abuse. This can limit long-term use. It is worth noting that clinicians should follow proper clinical practice guidelines and appropriate recommendations to protect patients from the negative effects of opioids [56, 57].

Non-pharmacotherapy

Medical cannabinoids and cannabis have gained extreme popularity as alternative or adjunct therapy to conventional pharmacologic therapy. There have been mixed outcomes in the use of cannabinoids in neuropathic pain, specifically central spinal cord pain [35]. However, there have been positive results as well [48]. Because of the nature of how new this treatment is, current research is limited, and thus more is needed to develop a larger sample size and determine efficacy. Of note, cannabis is still classified as a Schedule 1 medication. Patients with CNS impairments have a critically increased risk of adverse effects secondary to neural impairments such as impaired judgement and motor coordination [48].

Central Pain can take a large mental toll on patients. It is a complex stressor, specifically in patients with neurological impairments. Thus, there are several

studies that indicate that behavioral and psychological therapy and treatments are effective in the management of pain disorders, especially CP [35, 49]. Other treatments not from the aforementioned studies include biofeedback, cognitive behavioral techniques, and hypnosis. These methods focus on other aspects of pain such as emotional and occupational functions. They can be utilized in combination with pharmacologic medical treatment.

Some alternative medical therapies such as acupuncture and transcutaneous electrical stimulation (TENS) are utilized to treat CP. In several studies, acupuncture has been shown to treat neuropathic pain and CP in patients with SCI [50]. However, it should be noted that there are a limited number of consistent studies on acupuncture for CP. The design and methods of each study vary widely. TENS is a treatment modality where electrical impulses are sent through electrodes placed where pain is located at or trigger points. One theory for how TENS works is that it activates large afferent nerve fibers, which then activates descending inhibitory fibers within the CNS [51]. This ultimately modifies the perception of pain through blocking the transmission of pain signals. Another theory is that the nerve stimulation increases the number of endorphins, which is the body's natural chemical that is used to decrease and block the perception of pain [51]. However, just like acupuncture therapy, it is worth noting that research on TENS therapy is limited. Of the studies that are available, TENS may be beneficial in the treatment of CP.

There are various current studies that are utilizing interventions for the management of CP. Some of these include botulinum toxin injections for central neuropathic pain and caloric vestibular stimulation for CPSP. Recently, studies on botulinum toxin (BTX) and its effects sensory nerves and on central neuropathic pain have been conducted. Several studies have shown that the effects of BTX on neuropathic pain after SCI, MS, and stroke show that it can be considered as a treatment option for CP [9]. One study had two patients with spinal cord lesions who had at-level CP and oral medications were not effective [52, 53]. The patients were given BTX-A treatment and there was a significant decrease in pain perception. There are many other studies with at-level CP in patients with SCI that corroborate this. Additionally, caloric vestibular stimulation has been shown to have beneficial effects for the treatment of CP. In several cases, it significantly reduced pain with a benefit of at least 7 weeks [54]. Additionally, another study showed improved motor skills and reduced pain and somatosensory delusions in a CPSP female patient [55]. The author postulated that the reflex activates the posterior insula which in turn inhibits the sensation of pain arising from the anterior cingulate, which was backed by behavioral and imaging evidence. However, like the previously mentioned studies, more research is needed to increase sample size and determine efficacy of the treatments.

Interventional/Surgical

Given the refractory nature of CP states, various interventional procedures and forms of surgery have been proposed to either impair afferent nociceptive signaling or regulate the signaling (neuromodulation) to ultimately treat patients with

refractory CP [2]. Lesioning, which is surgically creating a destructive lesion, is often most commonly applied to the spinal cord and includes various methods. Given a successful procedure, lesioning is most effective for treating allodynia and paroxysmal shooting pain [9]. However, pain usually returns after a number of years. Combined with the surgical risks, lesioning is now done infrequently [56].

Neuromodulation has also been studied for the treatment of CP states and includes repetitive transcranial magnetic stimulation (rTMS), spinal cord stimulation, motor cortex stipulation (MCS), and deep brain stimulation (DBS). The former is a method is a noninvasive procedure that utilizes magnetic fields that delivers impulses to stimulate nerve cells in the brain to improve symptoms of depression. One study treated patients with CPSP and trigeminal neuralgia with rTMS for 5 days. Fifteen days later at a follow-up visit, the patients expressed long-lasting pain improvement [2].

Spinal cord stimulation (or also called dorsal column stimulation) involves placing several stimulating electrical contacts in the epidural space in the spine near the region that supplies the nerves to the painful areas, specifically parallel to the posterior sensory columns of the spinal cord [9]. However, there is minimal literature on this approach to treat pain in patients with both SCI-related CP. Further, the neuromodulation signal needs to impair the afferent nociceptive signaling or activate descending inhibitory pathways above the central lesion. Thus, spinal cord stimulation is ineffective for CPSP and is more effective for thoracic spinal lesions where it can be applied to the early thoracic or cervical spine [9]. However, incomplete SCI injuries are more likely to be treatable because there is incomplete or no Wallerian degeneration of ascending sensory pathways, unlike complete SCI [9]. Additionally, patients with SCI often undergo surgical fixation. The resulting surgical hardware often impairs the patient's original anatomy and renders the patient unable to have spinal cord stimulation. Having said this, there is minimal backing of interventional approaches to treat CP permanently; the efficacy of the procedure for CP states tends to decrease as time progresses [9].

Motor cortex stimulation involves placing electrodes on the surface of the brain to regulate pain signals. Imaging has shown that epidural MCS can possibly activate structures involved in the evaluation of pain rather than the regulation of pain intensity [9]. The theory is that by activating fourth-order neurons in the precentral gyrus (motor function), nociceptive inputs from the cortex were blocked, ultimately decreasing pain. Further, evidence shows that pain decrease is associated with an increase in blood flow in the cingulate gyrus. This may indicate that motor cortex stimulation may also have a mechanism through decreasing the emotional aspect of pain (suffering) [57]. This treatment modality is most appropriate for arm- and face-predominant CP-related disorders. This aligns with the fact that the superficial portions of the homunculus are the hand and face. Almost two-thirds of patients with CPSP have clinically significant improvement with MCS [58]. In some studies, this treatment also shows promise in atypical facial CP [58].

Lastly, deep brain stimulation is where a surgically implanted device with electrodes is implanted in deep structures of the brain involving the supratentorial nuclei, often near the thalamus, periaqueductal gray matter, and globus pallidus [9].

It regulates sensory inputs and outputs through unclear mechanisms of action. Classically, the periventricular and periaqueductal gray matter have been the targets to ultimately release endogenous opioids [57]. The nucleus accumbens and ventral thalamus also are promising targets for the treatment of CP through activating inhibitory pathways [57]. The efficacy also varies widely based on the CP type, but positive results have been achieved. As mentioned before, DBS is generally less effective for patients with SCI-related CP [59]. However, for patients with CPSP, several studies show that DBS can be anywhere from 50 to 80% effective in pain relief [58]. One study further showed that slightly over half of the patients were able to taper down their pain medications [60, 61].

A multifactorial treatment approach involving the conventional pharmacotherapy treatment as first-line, as well as non-pharmacotherapy approaches and interventions should be employed simultaneously. The ultimate goal is to provide the appropriate medical treatment while achieving an optimal function and quality of life for the patient.

Conclusion

Chronic pain syndrome is a clinical state that is still very challenging to treat even with the many efforts to understand this condition. Some of these difficulties include diagnosis difficulty due to the various presentations in diagnosis and many mechanisms of action and pathophysiology as well as the wide spectrum of treatment outcomes. It is often difficult to recognize due to the delay (up to years) in onset and sensory inabilities from the CNS lesion. Theoretically, CP should be seriously considered when the pain is associated with spinothalamic tract sensory loss and is localized to the region of neurological impairment.

However, one thing is certain: early screening and recognition of CP syndrome is critical and is a vital component in the treatment of patients. It is most common in patients with functional deterioration from CNS conditions. The ideal treatment approach is a multifactorial pain plan that includes pharmacotherapy and non-pharmacotherapy medications, and interventional/surgical modalities if needed. Specifically, DBS has shown to be effective in several studies.

Incomplete management of pain, especially as it relates to CP syndrome, can ultimately lead to significant decrease in function and quality of life. Further direction could include creating a proactive approach or method of identifying patients who are at “high-risk” for developing CP. This would theoretically lead to better clinical outcomes. Additionally, more research into the mechanisms of action and pathophysiology may aid in the overall treatment of CP. Current treatments need to be looked at more deeply to understand pathophysiology as well. Specifically, patients may benefit from looking more into advanced neuromodulation techniques.

Painful Neuropathies (PNS)

Definitions and Prevalence

As mentioned before in the introduction to CP, according to the IASP, neuropathic pain is defined as pain caused by a lesion or disease involving the somatosensory nervous system. Neuropathic pain can be further segmented into peripheral vs. central neuropathies depending on the lesion location. The rest of this chapter will be focused on neuropathic pain as a result of issues to the peripheral nervous system.

Unlike patients with central neuropathy pain, patients with peripheral neuropathic pain have a lesser chance of experiencing pain [62]. In one study with patients with diabetic neuropathy, the prevalence of peripheral pain was approximately one-fifth of the cohort. These types of neuropathies can affect multiple nerves (peripheral neuropathy) or only one nerve or nerve group (mononeuropathy) at a time. Specifically, mononeuropathy is typically the result of damage to a single nerve or nerve group by inflammation, local compression, prolonged pressure, or trauma [63]. Most patients, however, suffer from polyneuropathy. Both types of insults cause similar changes in sensations of pain. This pain can be induced and often leads to hyperalgesia (normally painful stimuli causing exaggerated pain), allodynia (normally non-painful stimuli causing pain), hyperpathia (repetitive stimulation causing prolonged persistent pain), paresthesia (atypical non painful sensations that is not unpleasant) and dysesthesia (atypical painful sensation that is unpleasant) [62]. There is also a type of neuropathy called neuritis, where a nerve can undergo inflammation. Neuritis is typically caused by a bacterial or viral infection. One typical example is acute inflammatory demyelinating polyneuropathy (AIDP). This is an autoimmune process that is characterized by progressive areflexic weakness and mild sensory changes [62].

Describing the incidence and prevalence of neuropathic pain is particularly difficult to estimate given the diversity of related clinical entities and lack of validated diagnostic tools. However, there has been recent development of basic screening-tools based on symptoms and validation of a number of assessment tools. These have facilitated an estimation of the prevalence of neuropathic pain to range from 7% to 10% in the general population [64]. Further, some quality-of-life studies show that it can be associated with sleep conditions, depression, and physical function impairments. It is also more commonly seen in females and in patients older than 50 years of age [65].

Mechanisms/Pathophysiology

Various mechanisms of pain due to peripheral nerve injury have been proposed and have been under investigation. Acquiring a fundamental understanding of the mechanisms of neuropathic pain can lead to finding optimal therapeutic options. Several

small sensory fibers, which include myelinated Aβ, and Aδ fibers and unmyelinated C fibers, are involved with neuropathic pain. Once nerve insults occur, voltage-gated sodium channels build up around the impaired site and along the axon. This leads to hyperexcitability and action potential activation [66]. Specific membrane stabilizers and sodium channel blockers act on this mechanism to treat patients with neuropathic pain [67]. Additionally, transient receptor potential vanilloid type 1 (TRPV1) channels are a factor in neuropathic pain. Nerve insults cause a decrease in TRPV1 receptor activation on that nerve and an increase in C fibers. The valladolid firing rate increases with heat. This results in overactive nerve activity which can present as burning pain and heat hyperalgesia [67]. Capsaicin is a TRPV1 agonist that results in an influx and buildup of intracellular calcium resulting in permanent dysfunctionalities of nociceptive nerve fibers [68].

Atypical ectopic neuronal activity in primary afferent fibers and in the dorsal root ganglion (DRG) can lead to dysregulation of the synthesis and function of sodium channel, specifically the tetrodotoxin-resistance channel [69]. Fiber cross-excitation and ephaptic interactions, sympathetic sensory coupling, and nociceptor sensitization can also be involved [69]. Additionally, Nerve insults can cause sprouting of sympathetic postganglionic fibers in the dorsal root ganglion (DRG) and the peripheral nerves. More specifically, sympathetic innervation of the DRG may impact the development and maintenance of sympathetically maintained neuropathic pain. After nerve insult, the axons upregulate α-adrenoreceptors and increase uptake of many neurotransmitters from postganglionic sympathetic terminals. This can be treated therapeutically with sympathetic blocks or α1-antagonists [69].

Additionally, CNS alterations can happen after a peripheral nerve insult. Changes include fluctuations in the inhibitory regulation in the spinal cord. The disinhibition is regulated through multiple pathways. Research has shown that gamma-aminobutyric acid (GABA) and opioid receptors have been downregulated [66]. Cholecystokinin, an opioid receptor inhibitor, is increased in expression while GABA, an inhibitory neurotransmitter, is decreased in the dorsal horn [66]. Ultimately, these alterations in disinhibition lead to a heightened perception of pain. Thus, pharmacotherapy targeting GABA receptors or simulating descending inhibition such as clonidine can treat patients with neuropathic pain. Overall, further study into the pathophysiology of peripheral nerve injury is needed.

Diagnosis

Patients with peripheral neuropathic pain can present differently from those with nociceptive pain. As mentioned in the beginning of this section, the patient with peripheral pain can experience hyperalgesia, allodynia, hyperpathia, paresthesia and dysesthesia. Questionnaires have been developed as screening tools and first-line treatment to find patients with neuropathic pain and require active participation from patients to describe their symptoms. Some of these screening questionnaires include ID-Pain, Douleur-Neuropathique 4 (DN4), Neuropathic pain Questionnaire

(NPQ), and painDETECT [70]. Although there are multiple screening questionnaires and they are used as first-line, their accuracy and efficacy remain largely undetermined.

As part of the diagnosis of peripheral neuropathic pain, a thorough physical examination should be done. This should include a complete sensory examination involving temperature, pinprick, vibration, light touch, and temporal summation. Temperature can be tested by applying cold and hot stimuli; pinprick sensations can be tested with a sharp tool such as a sharp pin; light touch can be tested by applying a low-density object to skin such as cotton wool; vibration can be tested using a tuning fork; and temporal summation can be tested with repeated and equal-intensity noxious stimuli [71]. If a patient has peripheral neuropathic pain and is undergoing physical exam testing, it is often described in a pattern of a stock glove distribution of changed sensory perception.

Diagnostic testing involving electrodiagnostic testing (EDX) may be useful in patients with peripheral neuropathic pain. This specific testing is one of the most common and involves two components: nerve conduction studies (NCS) and electromyography (EMG). The former, also called a nerve conduction velocity (NCV) test, measures the velocity of an electrical impulse that is applied to the targeted nerve through electrode patches on the skin. The latter identifies electrical activity of muscle tissue as a visual display or audible signal through electrodes attached to the skin. Together, EDX is used to support confirmation of nerve damage and possible neuropathy. Further, it helps to determine whether the pathology is due to axonal or demyelinating and if it is a polyneuropathy or mononeuropathy [62]. However, since EDX tests primary large fibers, EDX can present as clinically normal if the painful peripheral neuropathy only affects small fibers, resulting in a pseudo-false negative outcome [72]. As such, skin biopsy is one way to test for small fibers in patients with peripheral neuropathy. However, its outcomes are minimally accurate at best and there is generally not much support between pain and abnormal atypical skin biopsy findings [73].

Another way to test for both small and large sensory nerve fiber function in peripheral neuropathies is through quantitative sensory testing (QST). This is vital since as mentioned before, conventional sensory EDX only assesses for large fibers. The tool involves patient psychological involvement and lacks the objectivity of EDX, specifically NCS [62]. Thus, the results can change and have high variability due to extraneous factors such as boredom, drowsiness, confusion, and distraction [62]. Because QST has many limitations, it is not meant to be an isolated diagnostic tool, but rather as a supplement to aid in the interpretation of the patient's clinical presentation [74]. Further, the results of QST do not influence or alter the therapeutic plan for patients with neuropathic pain. Laboratory testing can further aid in determining causes of neuropathic pain stemming from bacterial or viral infections, genetic, metabolic, and toxic causes.

Since the IASP redefined neuropathic pain in 2008, the redefinition has been widely accepted. The proposed grading system of possible, probably, and definite neuropathic pain from 2008 was intended to determine the chances of neuropathic pain. "Possible" neuropathic pain involves a history of relevant neurological lesion

or disease and pain distribution that is neuroanatomically plausible [13]. "Probably" neuropathic pain has the history mentioned in possible neuropathic pain as well as a physical examination that indicates the pain is associated with sensory signs in the same neuroanatomically plausible distribution. "Definitive" neuropathic pain has both the history and examination findings mentioned in probably neuropathic pain as well as confirmatory tests that verify a lesion or disease of the somatosensory nervous system that explains the pain [13]. Having said that, there have been several reviews that indicate that although the redefinition has widely been accepted, the adoption of the grading system has been used to a lesser extent.

Painful Neuropathies

To reiterate, this latter half of the chapter will hone in on peripheral neuropathies. These peripheral neuropathies that have painful peripheral presentations can be segmented into autoimmune and infectious, resulting from systemic disease, injury/acquired, and genetics. Painful peripheral neuropathies (PPNs) have a wide spectrum of pathophysiology. Because the PPNs origins can be very different, a complete history and physical exam is vital in order to use the appropriate supplemental diagnostic testing (such as EDX) and therapeutic treatments. Reviewing all PPNs in-depth is outside the scope of this introductory chapter to CP and PPN. Thus, the rest of this chapter will highlight some, not all, of the PPNs that present. The painful neuropathies are briefly organized in Table 1.2 in Appendix.

Table 1.2 Brief list of causes of painful peripheral neuropathies

Cause	Type of neuropathy
Infectious and autoimmune	Guillain-Barre syndrome/acute inflammatory demyelinating polyneuropathy (AIDP)
	Chronic inflammatory demyelinating polyneuropathy (CIDP)
Systemic diseases	Diabetic painful polyneuropathy
Injury and acquired	Complex regional pain syndrome
	Nutritional deficiency-induced peripheral neuropathy
	Chemotherapy-induced peripheral neuropathy (CIPN)
Hereditary	Charcot-Marie-tooth disease
	Hereditary sensory autonomic neuropathy
	Painful channelopathies
Drug-induced	Chemotherapeutics
	Antibiotics
	Cardiovascular agents
	NRTIs

Infectious and Autoimmune Painful Peripheral Neuropathies

Guillain-Barre Syndrome (GBS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIPD)

Acute Inflammatory demyelinating polyneuropathy (AIDP), also known as Guillain-Barre Syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIDP) are among the most acquired immune-mediated polyneuropathies. GBS can have PPN such as paresthesia and numbness in their extremities. However, the main hallmark is extensive motor muscle weakness and cramping in an ascending pattern from legs to arms. Difficulty breathing may also occur and call for a neurological emergency in case of respiratory arrest. GBS can have many causes, but one of the most frequent is campylobacter jejuni infections which lead to complement and antibodies against nerve ganglions to attack the nodes of Ranvier [62].

GBS is the leading cause of acute flaccid paralysis in developed countries such as the United States with an annual incidence of 0.6–2.7 per 100,000 persons [75]. Around 33% of patients diagnosed with GBS present with pain, and approximately 89% of patients with GBS are eventually affected with pain [62]. Mechanisms of pain in GBS are inflammation and compression of the nerve roots resulting from segmental demyelination in large and small motor and sensory nerves and spiral roots with secondary axonal degeneration. Other than treating the underlying cause of GBS, pain is typically treated with pharmacotherapy involving anti-epileptics such as carbamazepine and gabapentin, antidepressants, analgesics including opiate drugs. Steroids have also been shown to be effective but come with risks and complications with long-term use [76].

CIDP is a chronic form of GBS and may present with slowly progressive and diffuse sensory and motor symptoms after approximately 8 weeks. The peak incidence of CIDP happens in middle age (40s–60s). There are two patterns that predominate: relapsing-remitting (20–65%) and progressive [77]. The relapsing and remitting form, unlike GBS, occurs more often in young adults in their 20s, whereas older patients may present with more chronic progressive polyneuropathy. Prevalence largely varies because of changing adherence to diagnostic criteria, from 1 to 9 per 100,000 persons [77]. Of those, 13–17% have severe pain [77]. Some diagnostic criteria include the well-known Asbury and Cornblath electrodiagnostic criteria for demyelination and the American Academy of Neurology research criteria for, which is known for its high specificity [75]. The most frequently used diagnostic criteria tool used is published by the European Federation of Neurological Societies, which balances specificity and sensitivity [75]. Some common treatments CIDP involve intravenous immunoglobulins (IVIG), plasma exchange, and corticosteroids. Further, neuropathic pain may also be treated with pharmacotherapy involving anti-epileptics, antidepressants, and analgesics.

Post-herpetic Neuralgia

Post-herpetic neuralgia (PHN) is the most common long-term sequelae of varicella-zoster virus (VZV) reactivation, also known as herpes zoster or shingles . VZV is the viral cause of the formerly common childhood condition, varicella, classically known as chickenpox . Before vaccinations, approximately 90% of American adults tested positive for VZV. Although the number may start to decrease in the future, there is still an annual incidence of one million cases in the United States and manifests itself in approximately 20% of patients with shingles [62].

The hallmark of PHN is a lancinating, burning, and/or electrical pain in a unilateral dermatomal pattern for three or more months. Some widely accepted risk factors include immunosuppression and increasing age [78]. The American Academy of Neurology recommends that the treatment should include neuropathic pharmacotherapy and lidocaine patch 5% (approved by FDA for PHN). However, like most treatments, the most successful are multi-modal. In fact, some physicians will focus more on the prevention in high-risk populations such as elderly and infirm because of the often refractory and crippling nature of PHN in already delicate patient populations. Additionally, the VZV vaccine is recommended for patients over 60 years of age and may help prevent PHN. Interventional procedures can be used as a last line of defense which include nerve blocks to the impacted dermatome and neuromodulation [78].

Painful Peripheral Neuropathies Resulting from Systemic Diseases

Diabetic Painful Polyneuropathy

Diabetic painful polyneuropathy (PPN) is the most common and serious peripheral painful neuropathy with a known cause [79]. Studies have reported a large range of prevalence, with 8–30% of patients that diabetic polyneuropathy reporting pain. The variation may be attributed to varying study designs and definitions of DPN. Although the specific pathophysiology of hyperglycemia-induced PPN is yet to be described, neurovascular and nerve insults are likely causes. Axonal degeneration and atrophy, peripheral sensitization, and changed peripheral neurovascular flow, all lead to diabetic PPN. However, increasing evidence has shown that not only hyperglycemia, but also factors such as type 2 vs. type 1 diabetes, obesity, smoking, female sex, and diabetes duration may be linked to painful DPN. Diabetic PPN affects multiple peripheral sensory and motor nerves that branch out from the spinal cord into the upper and lower extremities in the classic “stocking and glove” distribution. They typically affect the longest nerves, those that extend from the spine to the feet. This can present classically present as paresthesia such as tingling, burning, or stabbing, and electric sensations [79].

Treatment of diabetic PPN, like most PPNs, requires a multifactorial approach. Hyperglycemic regulation is critical in a preventative manner in type 1 diabetes but not as much in type 2 diabetes [79]. Other approaches include pain medications,

anti-epileptics such as gabapentin, tricyclic antidepressants (TCAs), topical creams, TENS therapy, hypnosis, relaxation training, biofeedback training, and acupuncture [80].

Injury and Acquired Painful Peripheral Neuropathies

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a neuropathic painful condition that is defined by symptoms such as allodynia, trophic changes, hyperalgesia, and motor dysfunction. It typically occurs as a result of varying degrees of trauma, with fracture being the most common occurring in >40% of CRPS cases [81]. Some other common inciting events include surgery, crush injuries, sprains, and contusions.

There are two types of CRPS: type l, formerly known as reflex sympathetic dystrophy and occurs in the absence of nerve trauma, and type II, formerly known as causalgia and occurs in the presence of nerve trauma. They are clinically indistinguishable and follow a regional pattern (hence the name) rather than a nerve distribution or dermatome pattern. It presents initially most commonly the distal extremities and spread proximally or to the contralateral extremity. It is further broken down into sympathetically maintained (SMP) versus sympathetically independent (SIP) and "cold" versus "warm."

Using the IASP diagnostic criteria, the incidence in the United States is 5.46 per 100,000 person-years and 0.82 per 100,000 person-years for CRPS type I and type II, respectively. It is found to have peaks between ages 50 and 70 years, to be three to four times more common in women than in men, and to be found more in the upper limbs.

Currently, CRPS is diagnosed clinically by a set of decision rules for proposed clinical criteria developed by the Budapest consensus pane (sensitivity 85% and specificity 70%) [81]. The criteria, illustrated in Table 1.3 in Appendix, consists of four categories: sensory, vasomotor, sudomotor/edema, and motor/trophic. The first category, sensory, reports hyperalgesia and/or allodynia, which is when a normally non-painful stimulus causes pain. Patients may report wind, shoes, and gloves may cause pain in a distal extremity such as hands and feet. The second category, vasomotor, involves temperature and/or skin color asymmetry and/or changes. The third category, sudomotor/edema, involves edema and/or sweating changes and/or asymmetry. The fourth and final category, motor/trophic, involves decreased range of motion, motor dysfunction (weakness, dystonia, tremor), and/or trophic changes (hair, skin, nails). For this specific criterion, the patient must report at least one symptom in three of the categories and at least two of the categories at the time of evaluation. Lastly, one final criterion is that there should be no other condition that can better explain the signs and symptoms presented by the patient.

Developing a treatment plan in a prudent and aggressive manner is vital to delay an unfavorable outcome such as spread to different limbs peripherally and to the spinal cord and brain centrally. Patients should seek a treatment plan from a pain

Table 1.3 Budapest diagnostic criteria for CRPS

Requirement #	Criteria details
1	Continuing pain, which is disproportionate to any inciting event
2	Must report at least one symptom in three of the four following categories:
	1. *Sensory*: Reports of hyperalgesia and/or allodynia
	2. *Vasomotor*: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
	3. *Sudomotor/edema*: Reports of edema and/or sweating changes and/or sweating asymmetry
	4. *Motor/trophic*: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nails)
3	Must display at least one sign at the time of evaluation in two or more of the following categories:
	1. *Sensory*: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch or deep somatic pressure)
	2. *Vasomotor*: Evidence of temperature asymmetry and/or skin color changes and/or asymmetry
	3. *Sudomotor/edema*: Edema and/or sweating changes and/or sweating asymmetry
	4. *Motor/trophic*: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, skin, nails)
4	No other diagnosis that better explains the signs and symptoms.

clinician who has experience treating this disorder. Further, comprehensive treatment involves a multimodal strategy with a rehabilitation program driving the treatment. Treatments can involve oral corticosteroids (for warm CRP), anti-epileptics (gabapentin), analgesics (duloxetine), transdermal lidocaine, and opioids. Nonpharmacologic therapy including physical therapy, psychological therapy is also vital. Lastly, more interventional techniques may be used if pain is severe, such as spinal cord stimulation (SCS), DRG stimulation, ketamine infusions, and intrathecal drug pumps [82].

Nutritional Deficiency-Induced Peripheral Neuropathy

Malnutrition can affect all areas of the nervous system and can thus lead to PPNs. Pain is also one of many symptoms that can present for the patient. General risk factors for malnutrition can include eating disorders, alcohol abuse, older age, pregnancy, lower socioeconomic status (SES), and homelessness [83]. Thiamine deficiency can commonly lead to two conditions: beriberi and Wernicke-Korsakoff's syndrome . Beriberi has two subtypes: dry, which does not include heart failure, and wet, which includes heart failure. Additionally, thiamine deficiency due to chronic alcoholism can typically lead to Wernicke-Korsakoff's syndrome. Both of these

Table 1.4 Summary of nutritional-induced neuropathies

System	Sub-system	Nutritional toxicity or deficiency
Cardiovascular	Cardiac	Thiamine deficiency (wet beriberi)
Central nervous system	Cognitive	Lead toxicity, arsenic toxicity, mercury toxicity, disulfiram toxicity, vitamin B12 deficiency (pellagra), thiamine deficiency (Wernicke-Korsakoff syndrome)
	Corticospinal	Vitamin B12 deficiency, copper deficiency
	Cerebellum	Vitamin E deficiency, mercury toxicity
	Posterior column	Vitamin B12 deficiency, copper deficiency
Gastrointestinal	Intestinal	Vitamin E deficiency, thallium toxicity, lead toxicity, arsenic toxicity
	Liver	Vitamin E deficiency, arsenic toxicity
Hematologic	Anemia	Vitamin B12 deficiency, copper deficiency, lead toxicity
	Pancytopenia	Arsenic toxicity
Integument	Skin	Thiamine deficiency (beriberi), lead toxicity, thallium toxicity (alopecia), arsenic toxicity (alopecia)
	Nails	Thallium toxicity (Mees lines), arsenic toxicity (Mees lines)
Musculoskeletal	Muscle	Vitamin E deficiency (myopathy)
Renal	Kidneys	Mercury toxicity

conditions can manifest themselves with PPN that act similarly to Guillain Barre Syndrome which can include burning pain, paresthesia, muscle weakness and fatigue. If left untreated, it can eventually lead to ascending paralysis and weakness in the legs and sensorimotor neuropathy in the hands [83].

Cobalamin deficiency can also lead to PPN. It is absorbed in the terminal ileum. Thus, deficiency can be caused by pernicious anemia, gastrointestinal surgeries, malabsorption, and weight reduction surgery. Additionally, as cobalamin is only found in animals , vegetarians who follow a strict vegan diet must supplement with cobalamin. When cobalamin is deficient, this leads to altered metabolism of homocysteine and lack of tetrafolate and the creation of succinyl coenzyme A. Without these reactions, this can lead to deficient purine and pyrimidine synthesis and myelin sheath formation, respectively [83]. A summary of some nutritional deficiencies and their associated pathologies are listed in Table 1.4 in Appendix.

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent side effect of chemotherapeutic agents with a prevalence from 19% to over 85% [84]. This specific neuropathy is mostly sensory in nature that may also present with a wide spectrum of motor changes. Because of its high occurrence in cancer patients, CIPN presents a major challenge for both current patients, survivors, and their clinicians; there is no clear-cut defined solution to treating CIPN. Traditional antineoplastic

agents that cause CIPN include platinum-based chemotherapies, vinca alkaloids, taxanes, epothilones (ixabepilone), proteasome inhibitors (bortezomib,), and immunomodulatory drugs (thalidomide). The most potent are the platinum-based therapeutics, taxanes, ixabepilone, and thalidomide; the relatively less toxic are vinca alkaloids and bortezomib [84].

The platinum-based antineoplastic agents (i.e. cisplatin, oxaliplatin, carboplatin) have many discussed mechanisms. The PPN is most likely initiated by the buildup of platinum adducts in the trigeminal ganglion (TG) and dorsal root ganglion (DRG) neurons [84]. Additionally, some patients experience paradoxical intensification of symptoms despite cessation of the platinum drug. This phenomenon is called "coasting" and presents a particular challenge for clinicians since there are no indications that point to a reduction in the dosage to mitigate the symptoms [84]. Vinca alkaloids (i.e. vincristine, vinblastine, vinorelbine, vindesine) inhibit the assembly of microtubules and induce sensorimotor neuropathy that is dose-dependent, often in a stocking-glove distribution. Taxanes (i.e. paclitaxel, docetaxel, cabazitaxel) typically present as a sensory dominant neuropathy that is proportional to the dose and length. Thus, symptoms tend to improve after stopping the treatment. Epothilones are a relatively new class of antineoplastic agents and thus research on the mechanisms of epothilone-induced CIPN is minimal. However, it is postulated that the mechanism is somewhat similar to that of taxanes due to preventing the disassembly of microtubule. Proteasome inhibitors (bortezomib) are dose-dependent and cause distal and symmetrical sensory PN accompanied by neuropathic pain syndrome after drug termination. Thalidomide-induced PPN is proposed to be dose dependent and may be from its antiangiogenic effect, which is postulated to be responsible for the ischemia and hypoxia of nerve fibers followed by damage of the sensory neurons [84].

Hereditary Painful Peripheral Neuropathies

Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth disease (CMT), also known as hereditary motor and sensory neuropathy (HMSN), is the most common hereditary neuromuscular disease and occurs with a prevalence of 1 in 2500. It is a group of diseases with approximately 4 genes (PMP22, GJB1, MPZ, MFN2) that account for 8–90% of CMT-causing mutations that are detectable [85]. There are two main types: the demyelinating form CMT1, and the axonal type, CMT2. The CMT1 primarily affects Schwann cells and the myelin-forming glial cells in the peripheral nerves [85]. The CMT2 directly affects the axons of peripheral neurons. Autosomal dominant CMT (AD-CMT) is the most common pattern, followed by X-linked CMT. Autosomal recessive forms are rare. Because of these inheritance statistics, people with CMTs will have a 50% chance of transmission to further generations by the affected parent

[85]. In addition to PPN, patients will exhibit slowly progressive distal extremity atrophy and weakness, starting in the feet and legs. Deep tendon reflexes can be decreased or absent and foot deformities (most often pes cavus) can be an early sign.

Hereditary Sensory Autonomic Neuropathy

Hereditary sensory autonomic neuropathy (HSAN) has a much lower prevalence than CMT disease. It primarily causes a loss of large unmyelinated and myelinated sensory fibers. There are several subtypes and classifications. HSAN I (also known as hereditary sensory radicular neuropathy and hereditary sensory neuropathy type I) is the most common form of HSAN [86]. It typically shows progressive degeneration of DRG and motor neurons. This leads to distal sensory loss and eventually distal muscle atrophy and weakness and a certain degree of deafness. Brief sharp leg pain is typically the initial symptom followed by some foot ulcers and reduced sensation in the legs. It is inherited in an autosomal dominant pattern. At least thus far have been found in this disorder (HSANIA-HSANIE). Symptom onset is typically during early adulthood. HSAN II is caused by a loss of touch, pressure, pain, and temperature sensations [86]. Fractures in the digits often occur in early childhood and eventually lead to mutilation of the fingers and toes. It is inherited in an autosomal recessive pattern. HSAN III, also known as Riley-Day Syndrome or familial dysautonomia, is inherited in an autosomal recessive pattern [87]. It is a progressive sensorimotor neuropathy, but sympathetic autonomic dysfunction causes most of the clinical symptoms. HSAN IV, also known as congenital insensitivity to pain with anhidrosis (CIPA), is inherited in an autosomal recessive pattern. It typically presents in infancy and has a profound loss of pain sensitivity and thermoregulation [86]. Lastly, HSAN V has a loss of pain and temperature, but most other sensations are preserved.

Painful Channelopathies

Channelopathies are a group of disorders that involve genetic mutations affecting pain receptors. Voltage-gated sodium channels are responsible for conducting action potentials in the peripheral nociceptive pathway where Nav1.8, Na1.7, and Na1.9 sodium channels (encoded by *SCN9A*, *SCN9B*, *SCN9C*) are expressed [88]. Clinical pathologies that result from mutations in these genes include erythromelalgia, and paroxysmal extreme pain disorder, small-fiber neuropathy (SFN), and dysautonomia, and acromesomelic. The onset is variable and can occur early from birth to later in life in adulthood. There are currently no cures for the conditions. Treatment only consists of symptom regulation. Of note, genetic mutations in the SCN9A and SCN11A genes which affect the Na1.7 and Na1.9 voltage-gated channels, respectively, cause a loss of pain perception [88].

Drug-Induced Painful Neuropathy (DIPN)

In general, drug-induced peripheral neuropathy (DIPN) is most often seen in chemotherapeutic agents, antibiotics, cardiovascular agents, immunosuppressants, and NRTIs. Most of these neuropathies involve damaging the dorsal root ganglia. Some groups follow certain trends more so than others. Chemotherapeutics, for example, often show consistent side effects while others are prescribed more frequently such as statins [89]. Additionally, DIPN occurs more in patients with comorbidities such as diabetes. It is relatively difficult to treat, but drugs such as gabapentin and duloxetine have been used to aid in pain symptoms. Additionally, neuromodulation has been promising and is growing through further randomized control trials and studies [89]. The drug-induced painful neuropathies are summarized in Table 1.5 in Appendix.

Table 1.5 Drug-induced painful peripheral neuropathy

Group	Agents	Incidence	Pathophysiology	Neuropathy
Chemotherapeutics	Vinca alkaloids	All grade: up to 96%; severe (grades 3–4): up to 37%	Microtubule-mediated axonal and cellular transport dysfunction	Sensory; distal lower extremities and ascends proximally
	Platinum	30–40%	Irreversible DNA cross-linking and neuronal apoptosis	Chronic sensory neuropathy
	Bortezomib and thalidomide	Bortezomib: 37–64%, severe up to 33%; thalidomide: 23–70%, severe up to 13%	Mitochondrial calcium release leading to apoptosis cascade activation	Bortezomib: Small fiber sensory neuropathy with burning pain, distal lower extremities; thalidomide: sensory neuropathy, primarily in distal extremities
	Epothilones	15–64%	Microtubule dysfunction	Primarily sensory deficits
	Arsenic trioxides	2–42%	Demyelination and acute axonal damage	Sensory and chronic motor polyneuropathy
	Taxanes	Monotherapy: up to 30?%; combined therapy with platinum: 70%	Interfere with calcium signaling; interfere with tubulin depolymerization in axonal transport	Primarily sensory deficits; motor deficits if severe

Table 1.5 (continued)

Group	Agents	Incidence	Pathophysiology	Neuropathy
Antibiotics	Isoniazid	2–44%	Disruption of vitamin B6 synthesis	Sensory peripheral neuropathy
	Ethambutol	1–18%	Unclear; possibly due to protein inhibition and mitochondrial toxicity	Optic neuritis and neuropathy
	Linezolid	13–20%	Axonal degeneration, binds to neuronal rNA	Sensory peripheral neuropathy and optic neuropathy
Immunosuppressants	Interferon-α inhibitors—adalimumab, etanercept, infliximab	Rare	Immune-mediated myelin degeneration, vessel occlusion leading to nerve ischemia, induction of anti-GM antibodies	Acute axonal polyneuropathy, demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy, vasculitic neuropathy

Chemotherapeutics

Some of the chemotherapeutics that can cause DIPN include vinca alkaloids, platinum, bortezomib and thalidomide, epothilones, arsenic trioxides, and taxanes. Vinca alkaloids (i.e. vincristine, etc.) are used to treat gynecologic, lymphatic, and hematologic malignancies and solid tumors. They can cause distal lower extremity DIPN and it progresses proximally through microtubule-mediated axonal and cellular transport dysfunction [90]. Platinum drugs, such as cisplatin, irreversibly cross-links to DNA eventually causing apoptosis. This leads to chronic sensory neuropathy via accumulation in the dorsal root ganglia. Bortezomib and thalidomide, which are used to treat multiple myeloma, cause mitochondrial dysfunction in axons and calcium release leading to activation of the apoptosis cascade. Bortezomib can cause small fiber sensory neuropathy (i.e. c-fibers) leading to a burning sensation in the distal lower extremities [89]. Thalidomide can cause sensory neuropathy often leading to paresthesia in the distal extremities and mild numbness and motor dysfunction. Epothilones (i.e. ixabepilone), which are used to treat breast cancer, also cause microtubule dysfunction and cause predominantly sensory neuropathies but are also reversible. Arsenic trioxides (ATO) are frequently used to treat Acute Promyelocytic leukemia (APL). They can cause acute axonal damage and demyelination eventually leading to chronic motor and sensory polyneuropathy [90]. Taxanes (i.e. paclitaxel and docetaxel) have been frequently used to treat breast and ovarian cancer and interfere with metabolic calcium signaling which causes disruption of tubulin depolymerization in axonal transport [89]. This leads to predominantly sensory neuropathy but can also lead to motor loss if it is severe.

Antibiotics

Many antibiotics have been shown to cause peripheral neuropathy thus this is not an all-inclusive list, but rather a few select antimycobacterials that were chosen to highlight below [62]. A few of the drugs that are used to treat Tuberculosis and can cause DIPN include Isoniazid (INH), Ethambutol , and linezolid. INH interferes with vitamin B6 synthesis, which is the suspected pathophysiology for why INH and can cause sensory peripheral neuropathy. Ethambutol is suspected to chelate zinc, which affects metal-containing enzymes in mitochondria in the retinal ganglion neurons and excitotoxic pathway [91]. This leads to optic neuropathy. Linezolid is a bacterial protein synthesis inhibitor used to treat both MRSA and multi-drug resistant TB (MDR-TB). It is still unclear where linezolid alone can cause DIPN due to varying studies but is hypothesized to be related to mitochondrial toxicity and protein inhibition which can lead to sensory PN and optic neuropathy.

Cardiovascular Agents

Some cardiovascular agents that have been associated with DIPN include amiodarone and statins. Amiodarone is a class III anti-arrhythmic used to treat atrial and ventricular pathologies. Statins are universally given to reduce cardiovascular mortality and disease. Both of these drugs are not traditionally known to cause DIPN, but a growing number of studies indicate some type of association [89]. Amiodarone is theorized to cause demyelination and large axonal loss with lysosomal inclusions and degenerative processes, suggesting oxidative stress and impaired lysosomal degradation [89]. Further research into how both these drugs can possibly cause DIPN is needed to better understand the pathogenesis and clinical manifestations.

Immunosuppressants

Various immunosuppressants have been shown to induce DIPN but TNF-α inhibitors will be highlighted. TNF-α inhibitors such as adalimumab, etanercept, and infliximab are typically used to treat rheumatoid arthritis, inflammatory bowel disease, and other inflammatory conditions. However, they can cause immunosuppression and thus T-cell and humoral immune attacks on peripheral myelin, inhibition of axon signaling, and vasculitis-induced nerve ischemia [89]. This can lead to Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Miller fisher syndrome, and a whole host of other neuropathies. Interferons can also inhibit T-cell proliferation, decrease TNF-α, and increase anti-inflammatory cytokines. This can also cause a wide array of neuropathies including chronic inflammatory demyelinating polyneuropathy, acute axonal polyneuropathy, vasculitic neuropathy, and demyelinating polyneuropathy [89].

NRTIs

NRTIs (i.e. zalcitabine, didanosine, stavudine, lamivudine) can also cause PN. The incidence varies based on the specific drug and is often cited as one of the reasons for discontinuing use of NRTIs in therapy. The pathophysiology is still being studied, but it is commonly theorized to be due to inhibition of γ-DNA polymerase. This enzyme is responsible for replication of mitochondrial DNA and thus disruption can lead to mitochondrial dysfunction, increased lactate production, and accumulation of toxic metabolite [92]. This leads to a distal axonal-type sensory neuropathy that is difficult to distinguish from HIV-induced neuropathy [89].

Treatments of Painful Peripheral Neuropathies

As stated previously, treatment of PPNs and CPs should generally follow a multifactorial treatment plan to deliver optimal results for the patient and maximize function and quality of life. Thus, ideally less invasive and interventional techniques are preferred. However, since each patient's clinical presentation is unique, each treatment plan should be individually created for each patient's symptoms. General treatment includes pharmacotherapy and non-pharmacotherapy modalities, and interventional techniques.

Medications

Certain pharmacological medications are first-line treatment options and have been proven to be effective as listed in Table 1.6. The European Federation of Neurological Societies Task Force (EFNS) created a list of recommendations that guide treatment of PPNs. These include gabapentin, pregabalin, and TCAs as first-line, tramadol as second-line, and opioids as third-line treatments [93]. However, like most of the painful neuropathies whether central or peripheral, treatment varies and is individualized based on the neuropathic condition and specific patient presentation.

Table 1.6 Pharmacotherapy for painful peripheral neuropathy

Chemical regulator	Agent
Na+ channel antagonist	Gabapentin, carbamazepine, valproic acid, phenytoin
Alpha 2 agonist	Clonidine
Glutamate antagonist	Gabapentin
NE reuptake inhibitors	TCAs (i.e. duloxetine)
NDMA Ca channel antagonist	Ketamine, amantadine dextromethorphan
Non-NMDA Ca channel blocker	Nifedipine
GABA agonist	Baclofen

Anticonvulsants

As mentioned in CP disorders, anticonvulsants such as gabapentin and pregabalin are well supported for their tolerability and cost-effectiveness. They impact the voltage-gated calcium channels thereby reducing the release of the neurotransmitters and increasing the function of inhibitory GABA receptors [94]. They have been proven to treat many various forms of painful neuropathy. Typically, the number needed to treat is 7 and 8–9 for gabapentin and pregabalin, respectively [95]. Their primary adverse events include sedation, cerebellar symptoms (incoordination, tremor), nystagmus and some less common adverse events include cardiac arrhythmias and hematological changes [96]. Some key differences involve the pharmacokinetic profiles, saturability, and systems involved, and absorption rate. For example, pregabalin follows a linear pharmacokinetic profile and is unsaturable, whereas gabapentin follows a non-linear pharmacokinetic profile and is saturable [97].

Neuropathic agents such as carbamazepine and oxcarbazepine are used as first-line therapy for trigeminal neuralgia. Both block the voltage-gated sodium channels. Carbamazepine specifically only needs an NNT of 1.7, which renders it very effective. However, due to its effects on cardiac, liver, and renal systems, labs and EKG should be initially and periodically done to avoid adverse events [62]. Contraindications involve atrioventricular block, hypersensitivity, tricyclic antidepressants, bone marrow depression, and many others [62]. Side effects include rashes, nausea, diplopia, hyponatremia, hyperhydration edema, and memory issues. Some more severe side effects include teratogenicity during the first semester, Stevens-Johnson syndrome, hepatotoxicity, agranulocytosis, and aplastic anemia [98]. Initial dosing for acute treatment is 100–400 mg/day with a dosing recommendation of 2–4 divided doses per day depending on the preparation and is increased in increments of 200 mg/day every 1–4 days. Oxcarbazepine is given in 300–600 mg/day in 2 divided doses [98, 99].

Antidepressants

Tricyclic antidepressants (TCAs) such as amitriptyline and nortriptyline are the most studied antidepressants for neuropathic pain [100]. They are used as therapy for treating PPNs. However, their use is limited by adverse events and side effects. Their mechanism works by inhibiting the reuptake of norepinephrine and serotonin at the synapse. However, it differs based on chemical structure. The secondary amines (i.e. nortriptyline, desipramine) have inhibited norepinephrine more so than serotonin. In contrast, the tertiary amines (i.e. amitriptyline, imipramine, doxepin) have a greater effect on serotonin. Some argue that the two subclasses of TCAs have equal effects, while others say that tertiary amines are more effective [100]. Pain relief is uniquely not correlated with the primary antidepressant effects of the drugs and can be achieved at a lower clinical dose than that used in the therapeutic plan for depression. Despite this, their use is typically complicated by side effects such as

weight gain, orthostatic hypotension, cardiovascular effects, anticholinergic effects, and lethality in overdose [100].

Other classes of antidepressants used include selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and duloxetine. The mechanism of action for SSRIs and the others involves the reuptake inhibition of serotonin and norepinephrine, similar to that of TCAs. They have significantly lower affinity for other receptors though, leading to milder side effects. Venlafaxine is a unique mixed-action antidepressant that inhibits norepinephrine reuptake at high doses and serotonin reuptake at low dose doses. Thus, unlike SSRIs and like TCAs, they affect both neurotransmitters used in the regulation of PPNs. Duloxetine is also a dual-action drug (i.e. inhibits reuptake of serotonin and norepinephrine) that seems to have a higher binding affinity than venlafaxine. Side effects of these drugs can include constipation, somnolence, dry mouth, and decreased appetite [100].

Mirtazapine acts central alpha-2 adrenergic autoreceptors and heteroreceptors, resulting in increased norepinephrine and serotonin release while also blocking 5-HT2 and 5HT-3 receptors [101]. It has been studied in the treatment of phantom limb neuropathic pain and fibromyalgia. A case series suggests it may have some partial relief on postamputation limb pain, but the study was very limited and inconclusive [102]. No efficacy was found for the treatment of fibromyalgia because it had the same effect as that of the placebo [101]. Lastly, recent literature shows a partially beneficial effect in diabetes-induced hyperalgesia [102]. However, further research is needed to establish more conclusive evidence.

Cannabinoids

As mentioned before, medical cannabinoids and cannabis have increased in availability and popularity dramatically. Cannabidiol is the ligand in the cannabinoid receptors. It is present in both the CNS and PNS pain pathways. A numerous number of research studies have found the reduction of pain from use of medical cannabis [62]. Specifically, PPN induced from HIV-associated neuropathy has shown the greatest statistical benefit [62]. Classic side effects of cannabis include dry mouth, paranoid delusions, euphoria, anxiety, increase in appetite, hallucinations, conjunctival injection, impaired judgement, social withdrawal, tachycardia, and perception of slowed time. As more research is done, more information will be released to details the exact benefits and risks of using medical cannabis in the treatment of PPN.

Topical Medications

Local anesthetics (i.e. lidocaine), capsaicin, menthol products, and compounded topical medications are commonly used for PPN. Lidocaine is used as a medical patch or spreadable cream ointment. It is a sodium channel blocker which in turn blocks the increase in discharge threshold and reduces pain transduction [103]. In terms of

treating localized neuropathic pain (LNP), it is Nav 1.7 and 1.8 are thought to be most important for inducing pain and have atypical and sensitized functions after nerve insults [103]. When applied as a 5% medical plaster, lidocaine has been shown to be effective in treating post-herpetic neuralgia and diabetic polyneuropathy.

Capsaicin is a natural vanilloid from the capsicum plant. It binds to the transient potential vanilloid receptor 1 (TRPV1) channels, which is a receptor expressed on Aδ and C-nerve fibers involved in pain. The mechanisms are not fully understood, but it is thought to release substance P and cause transient depolarization through sodium and calcium influx. Thus, it is counterintuitive, since, when initially applied, it causes pain. However, after repeated administration, chronic exposure will overstimulate and eventually desensitize its receptors causing defunctionalization and decrease in pain [104]. It has been used as both low concentration patches of 0.025 and 0.075% as well as 8%, which have been not particularly effective and much more efficacious, respectively [103]. In fact, the topical use of the 8% patch showed a 30–50% improvement in pain for patients with PHN and HIV-distal sensory polyneuropathy, which is an efficacy not achieved by the low-dose capsaicin patch [62].

Topical medications in combination have a large variety and are given based on a specific patient presentation and context. Some of these medications include ketamine, gabapentin, clonidine, baclofen, and clonidine. However, one study showed that compounded medications did not provide any additional benefit as compared to placebo [62]. To further complicate it these specific medications are often not included in health insurance coverage and are expensive. As such, other treatment options should be considered.

As mentioned before, cannabinoids are also increasing in extreme popularity. Topical cannabidiol (CBD) oils, specifically, are becoming much more widespread in pain management for not only patients experiencing PPN, but also for athletes. One group found a large reduction in pain with a 4-week application of CBD oil for lower extremity neuropathy. However, this was a small study with only 29 patients. Symptoms were looked at using a neuropathic pain scale [62]. Because there is still a lack of clinical studies, further research is needed to understand its true efficacy.

Infusion Medications

Intravenous (IV) administration of medications including ketamine and lidocaine have been used to treat many forms of neuropathic pain. IV ketamine is the most commonly used to treat patients with chronic pain [47]. It is an anesthetic induction agent that ranges in dosing levels from 1 to 4.5 mg kg [62]. As mentioned in the treatments for CP, ketamine is an NMDA-antagonist. At higher doses, ketamine acts at the opioid receptors. It is a phenylpiperidine derivative structure related to phencyclidine (PCP), which is colloquially known as “angel dust” and is a drug of abuse [62]. It was first synthesized in the early 1960s and was used during the Vietnam War because of its anesthetic effects and preservation of respiratory and hematological function. Of unique note, ketamine also impairs semantic memory, unlike other drugs. As noted earlier, ketamine has been extensively studied in treatment for

CRPS [105]. Typical literature shows the pain relief and benefits are achieved using doses at 100 mg over 4 h for 10 consecutive days [62]. Now, it varies widely and the optimal dose is not known. However, the efficacious pain relief found in most studies' follow-up time frames were 9–12 weeks [105].

There are many potential side effects, adverse events, and contraindications that accompany IV ketamine therapy. Side effects from clinical ketamine can generally be divided into CNS-related, cardiovascular, and hepatic. Some of the primary side effects can include psychedelic symptoms (panic attacks, hallucinations, memory defects), nausea/vomiting, somnolence, and cardiovascular stimulation. Further, the recreational use of ketamine is becoming increasingly popular and comes with additional risks such as bladder and renal complications, and persistent memory defects and psychotic behavior [105]. In clinical settings, ketamine can be well-tolerated if used with benzodiazepines to regulate the psychotropic side effects [105]. Further, clonidine may be used to counteract the increase in blood pressure of IV ketamine [62]. As with all levels of anesthesia, close monitoring of patients is critical to avoid unfavorable circumstances. They should be targeted toward CNS, hemodynamic, renal, and hepatic symptoms. This can include monitoring of blood pressure, electrocardiogram, pulse oximetry, respirations, and heart rate.

Intravenous lidocaine has also has also been used to treat PPN and chronic pain. It has been increased as an alternative to opioid use. As mentioned before, it is used to block sodium channels and reduce pain transduction. Literature indicates that it treats PPN conditions such as trigeminal neuralgia, PHN, and CRPS [106]. Some studies have shown that the effect of lidocaine on neuropathic pain is dose-related [106]. For example, one study shows doses comparing 1, 3, and 5 mg/kg suggest that doses less than 5 mg/kg is the same as placebo. Main side effects can include light-headedness, dizziness/vertigo, perioral numbness, speech disturbance, and nausea/vomiting [62].

Therapeutic Modalities

Many non-pharmacotherapy options are commonly used for treatment of PPN. These can include electrotherapeutic and physical agent modalities that use heat, cold, electricity, electromagnetic, water, and sound waves [107]. They are typically used in conjunction with other modes of treatment for neuropathic pain disorders. Transcutaneous electrical nerve stimulation (TENS), as previously mentioned in the treatments for CP, is one of the most commonly used treatments for neuropathic pain. One study by the Cochrane Library compared TENS to sham TENS in patients with neuropathic pain. It showed a mean postintervention difference in effect size favoring TENS of −1.58 (during TENS of −1.58, 95% confidence interval (CI) −2.08 to −1.09, $P < 0.00001$, $n = 207$) [108]. There were six comparisons from five studies and indicated very low-quality evidence. Despite meeting the pre-specified criteria, there was very low-quality evidence and thus the authors found this quality inconclusive. In fact, they mentioned that "the true effect is likely to be substantially different" from reported in the study [108]. As

mentioned before, TENS has a theorized mechanism of activating large afferent nerve fibers, which then activates descending inhibitory fibers with the CNS to ultimately block the effects of small nociceptive c and A-delta fibers [108]. It is placed at the site where pain is located at or trigger points.

Temperature therapy involving cold and heat stimuli are typically not used in PPN because simultaneous decrease sensation is common and can lead to unfavorable skin injuries [62]. However, this treatment can provide some partial benefit in desensitization of hypersensitive neuropathic pain such as allodynia. For instance, patients with CRPS often have allodynia and/or erythromelalgia, and contrast baths can often be used to treat that. It is performed by using one bucket of moderately warm water and one bucket of cold water. Of note, each bucket should be extremely warm or extremely cold. The affected extremity with pain should be placed in one bucket for 2 min and/or until it adjusts, then switched immediately to the other bucket for the same length of time. This is repeated three times per day. Despite this benefit, there is still very limited research on the efficacy of this treatment [62]. Thus, more research is needed to establish the exact mechanisms and benefits in the treatment of PPNs.

Virtual reality is a growing and innovative field that has limited side effects and has recently been utilized in many pain pathologies. It is utilized as part of a larger effort to use visual feedback to regulate painful symptoms and processes. Treatments that have been leading up to this involve mirror visual feedback, which is a treatment that allows a clinician to create an illusion. When patients anticipate movements to be painful, mirrors help deceive their brains into thinking that there is no pain via dynamic feedback to their brains [109]. There are several working theories that are still being researched to determine how exactly this works.

Visual feedback is increasingly being used in treatment for PPN pathologies such as phantom limb pain, CRPS, and certain causes of SCI. For example, one case report showed extensive pain relief for a patient with chronic phantom limb pain when other conventional treatments such as pharmacotherapy, physical therapy, nerve blocks and nerve transformations did not work [110]. Another study found that the use of VR for patients with CRPS showed a 50% reduction in pain intensity scores [111]. Virtual reality has shown some advantages such as the ability to treat bilaterally, artificial and enhanced environments, and the option to customize [111]. However, this technology is extremely expensive. Some recent research has shown partial benefits for SCI patients experiencing PPN. However, this pain was short-lived, and more data is needed. Visual feedback treatments are a rapidly growing and innovative field of treatment modalities and can provide many benefits with minimal side effects and adverse events. Like all new treatments, however, more research is needed to determine the benefits.

Interventional

Various interventional procedures are used in the treatment of PPN. Neuromodulation and sympathetic ganglion blockade treatments are two examples that have been used to help manage the symptoms of PPN.

Neuromodulation

The use of neuromodulation with electrical stimulation can be traced back to the Romans, who used electric eels, a sea organism that can deliver electricity to stun prey, for the treatment of various pain conditions [112]. Now in modern times, Wall and Melzack's publication on the gate control theory of pain conceptualized neuromodulation for chronic pain [113]. Since then, it has been extensively studied in PPNs and CRPS. As already mentioned in the treatments for CP, spinal cord stimulation (or dorsal column stimulation) involves placing several electrical implanted devices with metal leads and a pulse generator into the spine or near the region that supplies the nerves to the pain area. Various waveforms have been utilized to deliver electrical impulses into the dorsal columns or dorsal root ganglions (DRGs) , but optimal waveforms are still yet to be determined. Many of these studies have shown that DRG stimulation is effective and frequently used as an interventional treatment [114–116]. In 2016, the FDA approved its use as a treatment option. It essentially functions similar as the dorsal column stimulation treatment, but instead places it over the spinal nerves instead of the spinal cord. It has been shown to provide significant efficacy in patients with CRPS in several studies [117, 118].

Sympathetic Ganglion Injections

Treating PPN through blocking sympathetic ganglia can be traced back to World War I. It has been shown to be effective in many pain conditions such as CRPS, cancer pain of different origins, and coccygodynia. Several mechanisms are proposed to be effective: the loss of regular inhibitory regulation on pain and adrenergic hypersensitivity. The therapeutic effects of the sympathetic injections typically outlast the original therapeutic duration of the agents that are applied [119]. This may suggest that the blocks disrupt the positive feedback mechanism and decrease the central hyperexcitability [119]. Some of the most common Sympathetic blocks include stellate (or cervicothoracic) ganglion block, lumbar sympathetic block, celiac block, superior hypogastric block and ganglion Impar block.

The stellate ganglion is part of the cervical sympathetic chain and is formed by the fusion of the first thoracic sympathetic ganglion and inferior cervical ganglion. Some structures that are close by involve the esophagus, scalene muscles, longus colli muscle, trachea, recurrent laryngeal nerve, and subclavian artery. The stellate ganglion provides sympathetic innervation to the ipsilateral head, face, chest, and upper extremity. Before, SGB was applied without any imaging guidance by palpating the C6 anterior transverse process and injecting slightly medial [119]. However now, it has now been done with imaging guidance such as computed tomography (CT) and ultrasound (US) [119]. The lumbar sympathetic ganglion is typically located anterolateral to the lumbar vertebral bodies [119]. They are typically blocked at the L2–L4 vertebrae with fluoroscopic guidance. It can also be blocked through utilizing neurolytic agents or radiofrequency ablation. It has been utilized for many clinical pathologies such as CRPS, herpes zoster, and amputation stump pain [119].

Peripheral Nerve Blocks and Hydrodissection

With the increase in advances in minimally invasive procedures and various surgical techniques, analgesic techniques must keep up with these advancements. These include peripheral nerve blocks which have been shown to be effective and well-tolerated to provide regional anesthesia that is superior to other methods such as general anesthesia and oral pain medications [120]. Generally, these are indicated once conservative treatments have been exhausted and failed or to avoid side effects of general anesthesia and oral medications [120]. For example, patients who are at high risk of respiratory depression related to general anesthesia, patients who want to avoid systematic medications, or patients who are intolerant to oral medications are all reasons that peripheral nerve blocks can be indicated. The mechanism of action remains unclear [120]. One theory is that repeated depolarization by a local anesthetic was proposed, but they have not been confirmed [120]. Another theory that emerged more recently is that fascial compression of nerves happens in various locations and a benefit of these blocks may be through partial improvement of fascial compression [120]. Some of the more common blocks include interscalene, supraclavicular, infraclavicular , axillary, intercostobrachial, radial nerve, median nerve, ulnar nerve, lumbar plexus, femoral nerve, fascia iliaca, obturator nerve, sciatic nerve, popliteal nerve, and saphenous nerve blocks.

Nerve Hydrodissection is a treatment method that involves the use of fluid injection under pressure to specifically target the separation of nerves from the surrounding tissue [121]. Oftentimes, ultrasound is also used to guide the fluid (hydro) and needles to separate and release (dissect) the nerves from the surrounding fascia. The pathophysiology of this method is also unclear but includes involvement of the reduction of TRPV1 receptors, hyperpolarizing normoglycemic C fibers and lowering their firing rates, and correction of local neural hypoglycemia [121].

Appendix

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