Research Signpost
37/661 (2), Fort P.O., Trivandrum-695 023, Kerala, India

Mechanisms of Pain in Peripheral Neuropathy, 2009: 295-375 ISBN: 978-81-308-0358-6
Editor: Maxim Dobretsov and Jun-Ming Zhang

12 Pharmacological and interventional treatments for neuropathic pain

Bryan S. Williams[1] and Paul J. Christo[1,2]
[1]Department of Anesthesiology and Critical Care Medicine
[2]Division of Pain Medicine, The Johns Hopkins University School of Medicine, 550 N. Broadway, Suite 301, Baltimore, Maryland 21205, USA

Abstract

Neuropathic pain originates from a lesion within the central or peripheral nervous system. The signs of neuropathic pain include heat hyperalgesia, mechano-hyperalgesia, and mechano- and cold allodynia. Traditionally, neuropathic pain responds poorly to conventional analgesics. This chapter will provide recommendations for medical and interventional management of neuropathic pain conditions based on the best scientific evidence in the literature. Anticonvulsants (e.g., gabapentin and pregabalin), antidepressants (e.g., amitritpyline and duloxetine), and topical lidocaine have been the most consistent

Correspondence/Reprint request: Dr. Paul J. Christo, Department of Anesthesiology and Critical Care Medicine, The Johns Hopkins University School of Medicine, 550 N. Broadway, Suite 301, Baltimore Maryland 21205, USA. E-mail: pchristo@jhmi.edu

in demonstrating effectiveness through randomized control trials. Certain circumstances may require the use of opioids as a first-line treatment for specific neuropathic pain states. Interventional strategies such as neural blockade, implantable drug delivery systems, and spinal cord stimulation can be beneficial for alleviating painful neuropathic conditions that respond less favorably to medical therapies, or as a method of augmenting current medical therapies. A rational approach for the treatment of specific neuropathic conditions is presented in the form of tables that consider first line, second line, and other therapies.

1. Introduction

Neuropathic pain (NP) is not a disease *per se*; rather, it is a manifestation of multiple and varied disorders that display both peripheral and central sensitization mechanisms[1] which affect the somatosensory components of the nervous system[2]. Animal and human models of neuropathic pain have shown that a number of pathophysiological and biochemical changes take place in the nervous system as a result of an insult. The change, known as neuroplasticity causes morphological & functional adaptation to external stimuli or insults and plays a crucial role in the onset and maintenance of pain symptoms[3]. Injured peripheral nerve fibers give rise to an intense and prolonged input to the central nervous system of ectopic activity and in some may induce secondary changes to the excitability of dorsal horn neurons. At the cellular level, formation of new channels, up and down regulation of certain receptors, and altered local or descending inhibition represent some of the biological mechanisms that can lead to a hyperexcitable state, known as chronic pain[4].

Randomized placebo-controlled trials investigating the treatment of neuropathic pain have increased recently, but the synthesis of information gained from these trials still lags clinical application, with less than half of patients achieving significant benefit with any pharmacological drug [5-7]. By definition, neuropathic pain originates from a lesion within the nervous system. In fact, there are many pathologic conditions that can produce a lesion in the nervous system from which neuropathic pain may originate. Examples include autoimmune disease (e.g., multiple sclerosis), metabolic diseases (e.g., diabetic neuropathy), infection (e.g., shingles and the sequelae, postherpetic neuralgia), vascular disease (e.g., stroke), trauma, and cancer[1] (Table 1).

Recently, therapeutic strategies aimed at selecting treatments by targeting the putative mechanisms of pain (mechanism-based strategies) have been proposed[7-9]. The signs of neuropathic pain (heat hyperalgesia, mechano-hyperalgesia, mechano- and cold allodynia) may have different pathophysiologic

Table 1. Types of Neuropathic Pain.

Peripheral Neuropathic Pain
Painful Polyneuropathy/Diabetic Peripheral Neuropathy
Radiculopathy
Trigeminal Neuropathy
Post-Herpetic Neuralgia
Post-Surgical/Phantom Limb
Chemotherapy-induced polyneuropathy
HIV sensory neuropathy
Iatrogenic neuralgias (e.g., postmastectomy pain or post-thoracotomy pain)
Complex Regional Pain Syndrome
Central Neuropathic Pain
Post-stroke Pain
Multiple Sclerosis-related pain
Compressive myelopathy from spinal stenosis
HIV myelopathy

mechanisms. Evidence from animal models indicate that distinct signs of neuropathic pain respond differently to various drugs[10-14]. For instance, in a rat model of mononeuropathy produced by a chronic constrictive injury to the sciatic nerve, the animals exhibit abnormal pain sensitivities to non-noxious cold and heat stimuli (e.g., allodynia) and to noxious thermal stimuli (e.g, hyperalgesia). These animals were treated with morphine and other selective opioid agonists at doses known to produce potent antinociceptive effects on mechano-allodynia. The opioids reversed heat hyperalgesia but failed to alleviate thermal allodynia[11, 13]. Another study demonstrated that dextromethorphan, an N-methyl-D-aspartic acid (NMDA) antagonist produced the opposite effect in the experimental trauma model; that is, dextromethorphan blocked heat hyperalgesia and had no effect on mechano-allodynia[10, 11]. Treatment with the synthetic ω-conotoxin (e.g., cone snail polypeptide) ziconotide was able to alleviate heat hyperalgesia but not mechano-hyperalgesia in rat models of neuropathic pain[11, 14]. Additionally, NMDA-receptor blockers such as dextromethorphan are usually effective in models of post-traumatic painful peripheral neuropathy, but fail to relieve the mechanical and cold hypersensitivity evoked in rats by the chemotherapeutic agent paclitaxel[11, 12].

Since patients report symptoms and not mechanisms and clinicians uncover signs and not mechanisms, researchers could focus on how symptoms and signs of neuropathic pain reflect mechanisms[4]. Practitioners treat signs and symptoms in the attempt to control the mechanism propagating the symptoms. Difficulty arises when critically assessing the source of neuropathic pain since at least four fairly broad etiologic groups

should be considered when a treatment decision is made: peripheral neuropathic pain (PNP), complex regional pain syndrome (CRPS), trigeminal neuralgia (TN), and central neuropathic pain (CNP)[15]. Neuropathic pain seems to respond poorly to conventional analgesics which adds to the challenge of treating patients due to the heterogeneity of etiologies, symptoms, and underlying mechanisms[15]. Finally, clinicians are confronted with an array of medications for the treatment of neuropathic pain that are commonly classified by their original therapeutic category and not by their effectiveness in treating a particular pain condition[15]. For instance, tricyclic antidepressants and antiepileptics are generally approved for depression and epilepsy respectively, rather than for the alleviation of neuropathic pain.

In addition to controlling pain, it is important to recognize and treat comorbidities, such as anxiety and depression. It is also important to recognize secondary treatment goals, such as improving sleep, advancing function, and enhancing overall quality of life. Treatment goals must be realistic and clinicians should validate a patient's pain in order to gain trust. Common treatment goals for the patient and clinician alike center on mitigating symptoms, reducing pain duration, decreasing pain severity, improving quality of life, and reducing psychological distress[16]. Setting reasonable expectations is equally important. For example, a patient should view pain attenuation as the primary goal and clinicians should realize that a 30% reduction in pain intensity can be considered a clinically relevant response[17] given that complete pain cessation is rarely possible.

When selecting among treatments for patients with neuropathic pain, clinicians should consider the efficacy data of various options. Most randomized controlled trials (RCT) examining the treatment options for neuropathic pain have included patients with postherpetic neuralgia (PHN), as well as painful polyneuropathies (PPN) & peripheral neuropathies (PN) that are a result of diabetes[7]. The extent to which the results of RCTs for one type of NP can apply to other types of NP is unknown. However, clinicians often extrapolate the data on effectiveness from one particular NP condition to another based on a broad spectrum of analgesic activity of a specific intervention. The ability to use medications for the treatment of neuropathic pain conditions requires an understanding of the pathophysiological manifestations of the pain state rather than the etiology. Ideally, treatment interventions should target pain mechanisms and efficacy data should be extrapolated from more comprehensively studied pain states to less investigated pain conditions. Until clinicians use mechanism-based treatments for the control of neuropathic pain, symptom manifestation will continue to direct analgesic interventions.

To date, no medication has shown long-term efficacy and tolerability for all neuropathic pain conditions. Therefore, this chapter will focus on

medications and interventions that consistently show efficacy in neuropathic pain states with mention of alternative medications. Although a number of drugs are commonly used to treat neuropathic pain, the only drugs presently approved by the Food and Drug Administration (FDA) include carbamazepine for the treatment of trigeminal and glossopharyngeal neuralgias, gabapentin for the treatment of postherpetic neuralgia, duloxetine for the treatment of painful diabetic neuropathy, topical lidocaine for control of post-herpetic neuralgia (PHN) and pregabalin for control of postherpetic neuralgia and painful diabetic peripheral neuropathy[18] (Table 2.). Moreover, certain interventional and pharmacological treatments that show promise in treating NP will be discussed.

Any listing of medications for treating neuropathic pain should serve as a guide based on the available data. No medication has been shown efficacious in treating all neuropathic pain states. A useful method of assessing the efficacy of medications, the "number needed to treat" (NNT) evaluates the efficacy of active treatment compared to placebo. Clinically, the NNT measures how many patients need to receive a certain treatment in order for one patient to derive a clear benefit. In pain studies, this translates into the number of patients needed to treat with a certain drug in order for one patient to achieve at least a 50% decrease in pain intensity. This value is calculated by 1/([goal achieved active group/total active]-[goal achieved placebo group/total placebo]), and the 95% confidence interval (CI) of NNT can be obtained by taking the reciprocal value of the 95% CI for the absolute risk reduction. The NNT can only be calculated from placebo-controlled trials, since a correction for "placebo responders" is included in the formula for NNT"[19]. The NNT is used in formulating treatment recommendations. That is, either the study provides the NNT or it can be calculated from available data. Therapeutic options for each pain condition are derived from evidence-based research, improvement in quality of life, the risk of adverse effects and clinical experience. Table 8 lists recommended medications for the treatment of neuropathic pain.

Table 2. FDA Approved Medications for Neuropathic Pain.

Medication	**Indication**
Carbamazepine	TN
Pregabalin	DPN, PHN
Gabapentin	PHN
Duloxetine	DPN
Topical lidocaine	PHN

FDA – Food and Drug Administration; **DPN** – Diabetic Peripheral Neuropathy; **PHN** – Post-Herpetic Neuralgia

2. Peripheral neuropathic pain

Peripheral neuropathy pain (PNP) or painful polyneuropathy are terms used to describe pain due to peripheral nerve injury and includes diabetic peripheral neuropathy (DPN), non-diabetic peripheral neuropathy, human-immunodeficiency virus (HIV) neuropathy, and chemotherapy-induced peripheral neuropathy (e.g., cisplatin, vincristine, paclitaxel). Diabetic and non-diabetic peripheral neuropathy are similar in symptomatology and treatment response although HIV- and chemotherapy-induced neuropathies may differ in both symptom presentation and treatments[7].

Painful polyneuropathy & diabetic peripheral neuropathy

Painful diabetic peripheral neuropathy (DPN) reflects long-standing peripheral neuropathic disease that occurs in one of six diabetic patients[20, 21]. An acutely detected abnormality in DPN is a disturbance of nerve electrophysiology[22]. Clinically, patients may present with loss of light touch and pressure sensation, a decrease in vibration detection threshold (VDT), decreased motor strength, and areflexia; however, pain is the most distressing symptom of DPN and the primary reason for patients to seek medical advice[23, 24]. Chronic diabetic peripheral neuropathy can cause symptoms that last for years and severely impair quality of life[21, 25]. Despite its many etiologies, neuropathic pain is usually spontaneous, continuous, burning, paroxysmal, and evoked by various mechanical or thermal stimuli[21, 23]. Treatment of DPN rests on a two-pronged approach: modification of the underlying disease and control of pain symptoms[26]. Currently, the only treatment that addresses the cause of painful diabetic neuropathy requires improved control of blood glucose levels. A combination of pharmacologic or nonpharmacologic therapy should be employed to control the symptoms of painful diabetic peripheral neuropathy[27]. Prevention of peripheral neuropathy centers on improved glycemic control, which may reduce the risk of developing diabetic neuropathy in patients with insulin-dependent diabetes by as much as 62%[28]. Symptomatology and treatment options for diabetic and non-diabetic peripheral neuropathy are similar. HIV- and chemotherapy-induced neuropathy do display different symptoms and respond differently to treatment[7]. Therefore, treatment choices for painful polyneuropathy and diabetic peripheral neuropathy will be discussed together, and separate options for HIV and chemotherapy-induced neuropathy will follow.

A. Antidepressants

1. Tricyclic antidepressants (TCA)

Tricyclic antidepressants (TCA) have an analgesic effect that is demonstrated to be independent of their antidepressant effect[5]. The

pharmacological actions of tricyclic antidepressants can be linked to their effect as a calcium channel antagonist, sodium channel antagonist, presynaptic reuptake inhibition of the monamines such as serotonin and norepinephrine, and NMDA receptor antagonist effect[29, 30]. More specifically, the analgesic effect is believed to occur primarily through reuptake inhibition of norepinephrine rather than serotonin at spinal dorsal horn synapses, with secondary activity at the sodium channels[31, 32]. The tricyclic antidepressants have no effect on dopamine reuptake, but may have some indirect dopaminergic action by means of their adrenergic effect and desensitization of dopamine D_2 receptors[29]. Within the class of tricyclic antidepressants, variation exists between the inhibition of norepinephrine and serotonin. The tertiary amine agents (e.g., amitriptyline & imipramine) demonstrate a balance in their ability to inhibit norepinephrine and serotonin, while the secondary amines (e.g., nortriptyline & desipramine) favor the inhibition of norepinephrine. The secondary amines appear to be as effective as the tertiary agents in treating neuropathic pain and produce markedly fewer side effects[33, 34].

Currently no TCA carries a US Food and Drug Administration (FDA) indication for DPN, despite many studies showing efficacy in treating painful polyneuropathy. Sindrup & Jensen reviewed RCTs of antidepressants for the treatment of neuropathic pain and found that the number needed to treat for DPN was 2.4[35]. Max et al., in a randomized, double-blind, crossover study in patients with painful diabetic neuropathy compared amitriptyline to desipramine, a relatively selective blocker of norepinephrine reuptake. They concluded that desipramine (e.g., secondary amine) was as effective as amitriptyline (e.g., tertiary amine) in relieving pain caused by diabetic neuropathy[36]. The NNT for TCAs and peripheral neuropathic pain, excluding HIV neuropathy is 2.3 (2.1–2.7) with no major difference across the different disease entities. For tricyclic antidepressants with balanced reuptake inhibition of norepinephrine and serotonin (e.g., amitriptyline & imipramine), the NNT is 2.2 (1.9–2.6) and for the relatively noradrenergic tricyclic antidepressants (e.g., nortriptyline & desipramine) the NNT is 2.5 (2.1–3.3)[29]. In a report published by the Cochrane Collaborative meta-analysis of studies examining antidepressants for the treatment of DPN, the NNT was 1.29. The Cochrane Collaborative NNT was consistent over several other studies and lends support for the effectiveness of TCA's in the treatment of diabetic peripheral neuropathy[37].

2. Serotonin-norepinephrine reuptake inhibitors (SNRI)

Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine & venlafaxine) inhibit the reuptake of both serotonin and norepinephrine and

are often referred to as a *dual* inhibitors[38] or "selective" serotonin-norepinephrine reuptake inhibitors. For example, duloxetine is a potent, balanced inhibitor of serotonin and norepinephrine reuptake[39]. Venlafaxine inhibits serotonin reuptake at lower dosages and inhibits both serotonin and norepinephrine reuptake at higher dosages[29, 40]. Venlafaxine produces no postsynaptic effects. It does however block sodium channels in a different manner from that of tricyclic antidepressants[41]. Moreover, venlafaxine is structurally related to the centrally acting and synthetic analgesic, tramadol which has a mechanism of action analogous to that of the TCAs[42]. Venlafaxine's lack of anticholinergic side effects results in a distinct advantage over traditional TCAs[43-45].

a. Duloxetine

Duloxetine is approved by the US Food and Drug Administration for painful diabetic neuropathy[46, 47]. Goldstein et al. examined the efficacy and safety of duloxetine, a balanced and potent dual reuptake inhibitor of serotonin and norepinephrine for the management of diabetic peripheral neuropathic pain. They found that duloxetine 60 mg and 120 mg per day compared to placebo significantly reduced pain severity beginning at week 1 and continued throughout the study. A 50% reduction in the 24 hour average pain score was achieved by 26% in the placebo group, 41% in the duloxetine 20 mg per day group, 49% in the 60 mg per day group, and 52% in the 120 mg per day group. The number of patients achieving a 50% reduction in the 24 hour average pain score was significantly greater for all three active treatment groups when compared to placebo ($p < 0.05$)[46]. No significant difference was found between the 60 mg per day group and the 120 mg per day group. Similar results were replicated by Raskin et al. who demonstrated that the efficacy of duloxetine for DPN was significantly better than placebo in reducing Brief Pain Inventory (BPI) pain severity scores. Further, duloxetine treatment groups were superior to placebo on Clinical Global Impressions (CGI) Severity and Patient's Global Impression Improvement scores. Patients also demonstrated an improvement in the sensory component of the Short-Form McGill Pain Questionnaire [48]. Although these two studies show efficacy in treating DPN, the NNT for duloxetine is greater than that for other pain pharmacotherapies. That is, the NNT is 2.7 for anticonvulsants, 3.4 for antidepressants, 2.6 for tricyclic antidepressants, and 5 for duloxetine. However, duloxetine's more favorable side effect profile may confer an advantage in treating certain diabetic patients with pre-existing comorbidities[49] such as cardiac conduction abnormalities, a relative contraindication to prescribing TCAs.

b. Venlafaxine

Venlafaxine exhibits serotonin and weak norepinephrine reuptake inhibition, but with increasing doses norepinephrine reuptake inhibition increases[29]. Currently, venlafaxine does not have an FDA indication for the treatment of diabetic peripheral neuropathy; rather, it is approved for major depressive disorder. However, venlafaxine has been investigated for the treatment of diabetic peripheral neuropathy. In a multicenter, double-blind, randomized, placebo-controlled study including 244 patients, venlafaxine was evaluated for its efficacy in treating diabetic peripheral neuropathy. In this study, venlafaxine was shown to be significantly more effective than placebo ($p < 0.001$) with an NNT of 4.5 (venlafaxine ER 150–225 mg per day)[50] according to the primary measures of efficacy; namely the Visual Analog Pain Intensity (VAS-PI) and Visual Analog Pain Relief (VAS-PR) scales. In a comparison study of drug efficacy for the treatment of polyneuropathy, Sindrup et al. reported that venlafaxine relieved pain equally as well as imipramine. Pain summation was used as the primary efficacy measure and showed no statistical difference between venlafaxine and imipramine. The calculated NNT for venlafaxine was 5.2 (95% CI 2.7 to 5.9) compared to 2.7 (95% CI 1.8 to 5.5) for imipramine[43]. In a review of antidepressants for the treatment of neuropathic pain, Sindrup et al. report an NNT for venlafaxine in painful polyneuropathy of 5.5 (3.4–13.5)[29]. These results support the use of venlafaxine for the treatment of peripheral neuropathy and in particular, diabetic peripheral neuropathy.

3. Selective serotonin reuptake inhibitors (SSRI)

Selective serotonin reuptake inhibitors differ from the tricyclic antidepressants in that SNRI's selectively inhibit serotonin rather than norepinephrine. The SSRI medication class (e.g., citalopram, escitalopram oxalate, fluoxetine, paroxetine, sertaline) have shown efficacy in the treatment of neuropathic pain in small studies. For instance, paroxetine was shown to have a NNT of 2.9 compared to placebo in a small crossover study investigating the treatment of diabetic neuropathy symptoms[51]. In other studies of patients with DPN, paroxetine and citalopram were associated with statistically significant greater pain relief than placebo, whereas fluoxetine was found to be no more effective than placebo[5]. Conversely, a small trial investigating pain treatment in diabetic neuropathy revealed that SSRIs may not offer greater effectiveness than placebo given that fluoxetine's NNT was 15.3[36]. Moreover, pooled data from three trials (e.g., 162 patient episodes) studying citalopram, fluoxetine, and paroxetine only demonstrated a relative benefit of 1.3 (1.0–1.8), indicating no significant difference in pain relief compared with placebo[52].

The reduced effectiveness of SSRIs compared to TCAs appears to be directly related to the specific mechanism by which they exert their effects.

Unlike TCAs, SSRIs selectively block the reuptake of 5-HT alone[45]. The higher NNT is comparable to other studies that examine the efficacy of SSRI's and provides little support for their use as a first or second-line medication in the treatment DPN (Table 4)[7, 40, 43, 50, 53].

B. Antiepileptic medications

1. Gabapentin

The gabapentinoid group of drugs, gabapentin and pregabalin appear to offer the most evidence-based data for the treatment of DPN[54]. The analgesic mechanism of action for gabapentin remains unknown, although possible mechanisms include the modulation of voltage-gated calcium channels. Initially developed to mimic the neurotransmitter γ-aminobutyric acid (GABA), but is not believed to act at the GABA receptor. Gabapentin blocks the tonic phase of nociception induced by formalin and carrageenan, and it exerts a potent inhibitory effect in several animal modes of neuropathic pain such as mechanical hyperalgesia, mechanical allodynia, thermal hyperalgesia, and thermo-allodynia[3, 55]. Gabapentin is FDA approved for the treatment of postherpetic neuralgia, and has shown efficacy for the treatment of other neuropathic pain conditions[56, 57]. For instance, a randomized, double-blind, placebo-controlled trial demonstrated the effectiveness of gabapentin in treating diabetic peripheral neuropathy based on a significant reduction in daily pain severity measured on an 11-point Likert scale[56]. The initial mean pain score was reduced from 6.4 to 3.9 at the conclusion of the study with a NNT of 3.7. To investigate the effects of gabapentin and venlafaxine on painful diabetic neuropathy, Simpson performed a randomized double-blind serial comparison study in three arms: [1]gabapentin versus placebo, [2]gabapentin and venlafaxine versus gabapentin, and an [3]uncontrolled arm for patients who did not improve on gabapentin monotherapy and who subsequently received venlafaxine in addition to gabapentin. The primary efficacy parameter was pain severity rating based on an 11-point Likert scale. The gabapentin-treated patients showed statistically significant improvement in pain reduction based on initial mean pain scores that decreased to 4.0 from an initial rating of 6.4 ($p < 0.01$). Among the placebo group, there was a decrement in pain scores from a 6.5 to 6.0, which was not statistically significant [58]. A systematic review of gabapentin for neuropathic pain further demonstrates the efficacy of gabapentin for the treatment of peripheral neuropathy and other neuropathic pain states[59].

2. Pregabalin

Similar to gabapentin, pregabalin is a GABA analog without proven agonistic effect on GABA receptors. Pregabalin also modifies voltage-gated calcium channels in a similar manner to gabapentin. Potent binding at this

site reduces calcium influx at nerve terminals and therefore, reduces the release of several neurotransmitters including glutamate, norepinephrine, and substance P [60, 61]. Pregabalin is FDA approved for the treatment diabetic peripheral neuropathy and has shown efficacy in several trials[61-63]. For example, Lesser et al. evaluated dose response to pregabalin and painful diabetic neuropathy in a multicenter double-blind, placebo-controlled trial. The primary efficacy measure of pain relief focused on patient recordings of daily pain in a daily diary, and pain rating was based on an 11-point Likert scale. The study determined that endpoint mean pain scores were significantly improved with pregabalin 300 mg per day and 600 mg per day compared to placebo when using ≥ 50% reduction in pain as a marker for response. The 300 mg per day (37/81, 46%) and 600 mg per day pregabalin groups (39/81 patients, 48%) both showed a significant response compared to placebo (17/97, 18%). The NNT for a ≥ 50% reduction in pain was calculated to be 3.52 for the 300 mg per day group and 3.26 for the 600 mg per day group. If a smaller 30% reduction in pain response rates was considered, similar NNT results were reported for the 300 mg per day (50/81, 62%) and 600 mg per day (53/81, 65%) groups. For instance, there was an NNT of 3.48 for the 300 mg per day group, and 3.08 for the 600-mg per day group[62]. Other studies provide comparable results of efficacy for pregabalin in relieving diabetic neuropathic pain[61, 63].

In another multicenter double-blind, placebo-controlled trial, pregabalin provided a statistically significant decrease in mean pain score at endpoint at a dose of 300 mg per day (baseline, 6.5; endpoint, 4.0) compared with placebo (baseline, 6.1; endpoint, 5.3; (p = 0.0001)[61]. Furthermore, pregabalin-treated patients attained significant improvements in secondary variables such as mean sleep interference scores, and the total SF-MPQ score compared with the placebo-treated group[61]. Treatment with pregabalin was not associated with serious adverse effects such as orthostatic hypotension, falls, cognitive changes, tachycardia, urinary hesitation and other risks more commonly seen in older patients, TCA associated cardiac arrhythmias, or nonsteroidal anti-inflammatory drug induced gastropathy[62, 64]. Pregabalin was generally well tolerated in clinical trials, and most treatment-related adverse effects were dose dependent. Adverse effects typically related to the central nervous system. Clinical trials reveal that the rate of adverse effects vary by pregabalin dosage and dosing regimen and generally include dizziness, somnolence, weight gain, peripheral edema and diplopia [65].

In a review of randomized controlled trials of antidepressants and anticonvulsants for the treatment of pain associated with diabetic and post-herpetic neuropathies, one third of patients achieved at least 50% pain relief with either category of drug[66].

3. Carbamazepine (Tegretol)

Carbamazepine is an iminostilbene derivative that is chemically related to the tricyclic antidepressants. The effect of carbamazepine on pain suppression is probably mediated via central and peripheral mechanisms. Carbamazepine, the first anticonvulsant studied in clinical trials for TN may alleviate pain by decreasing conductance of Na^+ channels and inhibiting ectopic neural discharges[3]. There are multiple studies investigating the efficacy of carbamazepine for the treatment of trigeminal neuralgia, but few quality studies have examined the usefulness of carbamazepine for the treatment of DPN. Yet, carbamazepine was one of the first antiepileptic drugs used for the treatment of painful diabetic neuropathy[67]. For example, a 1969 double-blind, placebo-controlled crossover study demonstrated pain relief in 28 of 30 participants with peripheral diabetic neuropathy[68]. Another 2-week, crossover study of 40 patients with painful diabetic neuropathy showed a significantly greater reduction in pain with carbamazepine than with placebo on days 10 and 14[67, 69]. Despite the smaller sample size of these trials and a weaker evidence base for the use of carbamazepine in DPN, the NNT is strongly suggestive of efficacy (e.g., for every 2.5 patients with neuropathic pain treated with carbamazepine, at least one will achieve moderate pain relief or greater)[70]. Safety concerns (e.g., skin rash, hyponatremia, decreased bone density, and hematopoetic issues) may limit the use of carbamazepine in the older population[7, 71]. Table 4 profiles medications used for the treatment of NP. There is supportive evidence for the use of carbamazepine in the treatment of DPN, but due to a weaker evidence base and significant adverse effect profile, it ranks as a second-line medication[5, 7, 70].

4. Oxcarbazepine (Trileptal)

Oxcarbazepine is keto-analogue of carbamazepine. The therapeutic window for the treatment of pain conditions with this drug has yet to be established[67, 72]. In a multicenter, placebo-controlled trial, the efficacy of oxcarbazepine in patients with diabetic peripheral neuropathy was evaluated using VAS scores as a primary efficacy variable[73]. In this study, Dogra et al. concluded that a significantly greater proportion of oxcarbazepine-treated patients experienced a >50% reduction from baseline VAS pain scores at study conclusion compared with placebo (35.2% vs. 18.4%, respectively; $p = 0.0156$), with a calculated NNT of 6.0. When utilizing global assessment of therapeutic effect (GATE) as a secondary efficacy variable, the NNT was 3.9[73]. In another oxcarbazepine study by Grosskopf, there were no significant differences in primary or secondary efficacy outcomes between patients treated with oxcarbazepine (1200 mg per day) and those taking

placebo[74]. In effect, the Dogra study shows a significant difference in pain relief comparing oxcarbazepine at 1800 mg per day to placebo, while the Grosskopf study showed no significant difference in pain relief. In yet another study examining dose ranging of oxcarbazepine for the treatment of DPN, no significant difference between the oxcarbazepine-treated groups and placebo groups was established[75]. The results of this study show a NNT of 7.9 at 1200 mg per day and 8.3 at 1800 mg per day when comparing global assessment of therapeutic effect. The lack of consistent efficacy data and a higher NNT supports the use of oxcarbazepine as a second tier medication for DPN[7, 40].

5. Phenytoin (Dilantin)

Phenytoin was one of the first non-sedating, sodium channel antagonists developed for treating epilepsy. Other mechanisms of action include the blockade of L-type mediated Ca^{2+} currents, inhibition of NMDA receptors, depression of basal intra-neuronal levels of cyclic guanosine monophosphate and an increase in concentration of neuronal GABA[54]. Two studies conducted on phenytoin and DPN yield opposite results[76, 77]. The difference may be due to the variation in study design including sample size, length of follow-up, and most importantly lack of statistical power to detect differences between the placebo and phenytoin[3, 76, 77]. For instance, Saudek et al. investigated the treatment of diabetic symmetrical polyneuropathy and concluded that phenytoin has no role in the treatment of this symptom entity given no significant symptomatic improvement among those patients in the phenytoin arm of the study[77]. However, Chadda et al. explored the effects of diphenlhydantoin sodium in diabetic neuropathy and reported improvements in pain[76]. Furthermore, evidence of phentyoin's efficacy for the treatment of diabetic sensorimotor neuropathy would need to be considerable in order to justify the clear risk of adverse effects (e.g., Stevens-Johnson syndrome, hyperglygemia, gingival hyperplasia, liver toxicity, nerphrotoxicty) and drug interactions (e.g., impairs coumadin efficacy) associated with this medication[78, 79].

6. Sodium valproate (Valproic acid)

Sodium valproate potentiates the inhibitory transmitter γ-aminobutyric acid (GABA), and thereby increases GABA levels. Moreover, sodium valproate blocks T-calcium channels, increases neuronal potassium conductance, and prevents the degradation and uptake of GABA[54]. Kochar et al. examined the utility of sodium valproate for the treatment of DPN. They found a statistically significant reduction in pain scores utilizing the

short-form McGill pain questionnaire (SF-MPQ), visual analogue scale (VAS), and present pain intensity (PPI) among patients treated with sodium valproate compared to placebo[80]. In an earlier study by Kochar et al., sodium valproate was investigated for its efficacy in treating DPN and was proved beneficial compared to placebo ($p < 0.05$) at study conclusion [81]. However, a randomized, double-blind, placebo-controlled cross-over trial found no significant difference between valproic acid and placebo in the assessment of total pain among DPN patients[82]. Other studies confirm valproic acid's poor efficacy compared to placebo for the reduction in overall pain or improvement in quality of life[83].

7. Lamotrigine (Lamictal)

Lamotrigine acts predominantly by voltage and frequency-dependent blockade of sodium channels. Other important actions include the blockade of Ca^{2+} currents, altering presynaptic release of glutamate and aspartate, as well as an increase in brain GABA concentrations[54]. A randomized placebo-controlled study of lamotrigine for the treatment of DPN found that lamotrigine attenuated painful diabetic neuropathy at a daily dosage of 200 to 400 mg, and had a significantly superior analgesic effect compared with placebo[84]. Vinik et al. investigated the efficacy of lamotrigine at 200 mg, 300 mg and 400 mg doses in two replicate randomized, double-blind, placebo-controlled studies. In one of the studies, lamotrigine was found to be efficacious in treating diabetic neuropathy, but the result was not replicated in the parallel study. Further, no difference between lamotrigine and placebo was found when measured by the McGill Pain Questionnaire, Pain Disability Index, and Beck Depression Inventory. Another study by Silver et al. reported no significant difference in primary outcome measures when examining the efficacy of lamotrigine compared with placebo[85]. The outcome variability between these studies demonstrates marginal improvement in pain scores which do not support the initial primary use of lamotrigine for the treatment of DPN[86]. Lamotrigine requires careful titration to avoid the potentially devastating adverse effect of a cutaneous hypersensitivity reaction (e.g., Steven's Johnson Syndrome), which may limit its use as a primary agent for DPN treatment.

8. Topiramate (Topomax)

Topiramate blocks activity-dependent voltage-gated sodium channels, enhances the action of GABA, inhibits L-type voltage-gated calcium channels, acts presynaptically to reduce the release of glutamate, and post-synaptically blocks kainite/α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) excitatory amino acid receptors[54]. Raskin et al. investigated

topiramate's efficacy in treating DPN in a multicenter, randomized, double-blind trial. The study included 323 subjects with DPN and utilized pain visual analog scoring (VAS) as the primary measure of efficacy. Using a 100 mm scale, the authors found mean score decreases from 68.0 mm at baseline to 46.2 mm among the topiramate group and decreases from 69.1 to 54.0 mm in the placebo group ($p = 0.038$) [87]. In contrast, a multicenter, randomized, double-blind trial examining pain reduction as the primary efficacy variable included 1269 subjects with DPN. The investigators reported no statistically significant difference in pain reduction between topiramate and placebo. There were three arms to the study: 100 mg per day, 200 mg per day, and 400 mg per day. Examining VAS scores as the primary measure of efficacy, mean pain scores decreased from 60.1 mm at baseline to 36.1 mm ($p < 0.043$) in the topiramate group 1 at 100 mg per day, and decreased from 60.4 mm to 44.7 mm in group 3 (i.e., no group 2). At 200 mg per day, mean pain decreased from 55.8 mm to 38.3 mm, 58 mm to 37.8 mm, and 59.3 mm to 44.7 mm in the three treatment groups (1, 2, and 3), respectively. In the 400 mg per day arm, mean VAS pain scores decreased from 56.3 mm at baseline to 39.7 mm at conclusion, and from 57.8 mm to 39.3 mm for groups 1 and 2 (no group 3). The placebo mean VAS scores in the three groups decreased from 57.7 mm at baseline to 43.1 mm, 57.5 mm to 41.6 mm, and 55.3 mm to 37.8 mm at study conclusion. Only topiramate at 100 mg per day reached statistical significance ($p = 0.05$) compared to placebo for the treatment of diabetic polyneuropathy[88]. Given mixed outcome data, the use of topiramate may be considered a second line agent for treatment of DPN.

C. Other medications

1. Lidocaine 5% patch (Lignocaine)

Lidocaine 5% patch produces a local effect by antagonizing sodium channels, and causing a reduction in spontaneous ectopic nerve discharge[89]. Topically administered pain medications provide a number of advantages over first-line agents for neuropathic pain, such as tricyclic antidepressants, anticonvulsants, and opioids[90, 91]. The most important of these advantages includes the avoidance of clinically significant systemic drug concentrations, which may reduce the risk of systemic adverse effects and the potential for drug–drug interactions[92]. This may be particularly important in older patients since nausea, constipation, urinary difficulties, sedation and dizziness are possible adverse effects in patients using TCA's, antiepileptic drugs (AED) and opioids and may lead to medication discontinuation[93]. Argoff et al. studied the effectiveness of the lidocaine patch 5% on pain qualities associated with postherpetic neuralgia (PHN), painful diabetic neuropathy

(DPN/PDN), and low-back pain (LBP)[94]. This open-label, non-randomized, prospective trial utilized the neuropathic pain scale (NPS) as the primary efficacy measure and showed significant improvement in several NPS measures ($p < 0.001$) among patients with DPN. Further, Barbano et al. evaluated the effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in painful diabetic polyneuropathy. Patients with and without allodynia were included and significant improvement was demonstrated in mean daily pain diary ratings from baseline SF-MPQ sensory, affective, and visual analog scores, as well as Brief Pain Inventory (BPI) pain relief scores[95].

2. Mexiletine

Mexiletine is an oral, local anesthetic-type antiarrhythmic agent which is similar to lidocaine. Mexiletine is a class Ib antiarrhythmic[38]. Blockade of sodium channels by mexiletine is frequency-dependent, having a greater effect on rapidly firing channels. The mechanism of action of mexiletine in painful diabetic neuropathy at the site or sites of action is unknown[96]. Mexiletine has shown promise in decreasing VAS pain scores in several small, high quality studies. Further, mexiletine has shown promise in reducing VAS pain scores, dysesthesia and paraesthesia[96, 97] and in select patients with stabbing or burning pain, heat sensations, or formication[98]. Adverse effects of mexiletine have been associated with agranulocytosis, hepatotoxicity, and toxic epidermal necrosis. It is absolutely contraindicated in patients with second- and third-degree atrioventricular block unless an artificial pacemaker is placed. Patients on mexiletine therapy should be monitored with complete blood count and platelet measurement, electrocardiogram, and liver enzyme tests[99]. These adverse effects may limit its use in selective patients who have failed first-line treatments for diabetic neuropathy.

3. Capsaicin

Capsaicin, the active component of hot chili pepper selectively stimulates unmyelinated C fiber afferent neurons and causes the release of substance P and subsequently depletes and prevents the reaccumulation of substance P. Moreover, capsaicin produces complete or nearly complete denervation of the epidermis[100]. Repeated application of capsaicin reversibly depletes stores of substance P, and possibly other neurotransmitters from sensory nerve endings[101]. In a 12-week double-blind, placebo-controlled randomized study, Low et al. investigated the efficacy of the capsaicin cream (0.075%) vs. inactive placebo cream for the treatment of chronic distal painful polyneuropathy. The group found no statistical difference in pain reduction measured by VAS, allodynia or activities of daily living [102]. In an 8-week

multicenter, double-blind, vehicle-controlled trial, 0.075% topical capsaicin was investigated for is efficacy in treating peripheral neuropathy associated with diabetes[103]. The investigators showed a statistically significant improvement compared placebo in physician's global evaluation scale (69.5% vs. 53.4%), pain intensity (38.1% vs. 27.4%) and pain relief (58.4% vs. 45.3%) among diabetic patients[103]. Biesbroeck et al. conducted an 8-week double-blind, multicenter, parallel study to compare the efficacy of topical capsaicin and oral amitriptyline in patients with painful diabetic neuropathy. They concluded that topical capsaicin and oral amitriptyline produced equal and statistically significant improvement in VAS pain and physician's global evaluation scale[104]. Other RCTs have been inconsistent with respect to capsaicin's effectiveness for the treatment of peripheral neuropathy[105]. Capsaicin can be difficult for patients to apply, must be applied multiple times a day to the entire painful area, and often causes painful cutaneous sensations during the initial weeks of application that may reduce patient compliance. However, capsaicin may be a reasonable alternative for patients with contraindications or intolerances to oral agents.

4. Tramadol

Tramadol acts as a μ-opioid receptor agonist and affects descending inhibitory pathways that modulate nociception, possibly by inhibiting presynaptic monoamine uptake and stimulating serotonin release. Theoretically, these properties may confer an advantage compared to opioids for the treatment of neuropathic pain[54]. For example, Sindrup et al. studied tramadol in a randomized, double-blind, placebo-controlled cross-over study and found better pain relief and allodynia reduction[106]. Patients rated their pain (median 4 vs. 6, $p < 0.001$), paraesthesias (median 4 vs. 6, $p < 0.001$), and touch-evoked pain (median 3 vs. 5, $p < 0.001$) as lower with tramadol than with placebo on a 0-10 point numeric scale. Their ratings of allodynia were decreased as well (0 vs. 4, $p < 0.012$). The NNT to obtain one patient with ≥ 50% pain relief was 4.3 (95%, CI 2.4-20), indicating statistically significant pain reduction in this study. Similar evidence for tramadol's effectiveness derives from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study[107]. Tramadol versus placebo was investigated using patient ratings on pain intensity as the primary efficacy measure (e.g., 5-point Likert scale). The group found that tramadol produced significantly ($p < 0.001$) greater pain relief compared to placebo with a NNT of 3.1. Finally, in a meta-analysis analyzing the effectiveness of tramadol in providing ≥ 50% pain relief, tramadol was found effective at relieving peripheral neuropathic pain, with a NNT of 3.8 (95% confidence interval 2.8

to 6.3)[108]. Hence, evidence suggests that tramadol may provide effective pain relief in peripheral neuropathic pain.

D. Opioids

Opioid agonists such as codeine, morphine, oxycodone, and fentanyl mimic the activity of enkephalins and endorphins at the central descending pathways of the pain-processing loop[45]. Endorphins and enkephalins are endogenous opioids that are released from the periaqueductal gray matter and nucleus raphe magnus, respectively and travel within the central nervous system (CNS) descending pain-control systems[109]. The use and efficacy of opioids for the treatment of chronic pain is controversial; however, a growing body of clinical evidence supports their use in treating neuropathic pain. Opioid-induced adverse effects such as constipation, nausea, sedation, and the potential for addiction continue to limit their use among health care practitioners. Furthermore there is evolving data that suggest immunologic and endocrine effects of long-term opioid therapy as well as the hypothesized production of opioid-induced hyperalgesia with prolonged use [110].

A meta-analysis of 22 articles (e.g., 14 investigating short-term [< 24 hrs] opioid use and 8 studying intermediate [8-56 days] opioid use) revealed contradictory results when analyzing opioids for the treatment of neuropathic pain[111]. In the intermediate analysis, all eight trials reported that opioids were efficacious in reducing spontaneous neuropathic pain by demonstrating either superiority over placebo or a dose-dependent analgesic response. Short-term studies provided only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Those studies suitable for pooled analysis did show overall mean pain intensity 14 points lower in the opioid-treated patients than in those treated with placebo (95% CI, −18 to −10; $p < 0.001$)[111]. Though substantial clinical evidence is lacking for the specific use of opioids for the treatment of DPN, a multicenter, randomized, double-blind, placebo-controlled trial by Gimbel et al. examined the efficacy and safety of controlled-release (CR) oxycodone in 159 patients[112]. They found that oxycodone provided statistically significant reductions in average daily pain intensity at study end (e.g., 42 days); that is, the oxycodone group demonstrated an average daily pain intensity of 4.1 ± 0.3 compared to 5.3 ± 0.3 ($p = 0.002$) for the placebo groups. Another confirmatory study by Watson et al. examined oxycodone in a randomized, double-blind, crossover comparison study of the efficacy, safety and clinical effectiveness of controlled-release (CR) oxycodone compared to benztropine, an active placebo. They included pain intensity scores on a 100 mm visual analogue scale and pain relief scores as primary efficacy measures. Secondary efficacy measures incorporated the Pain Disability Index (PDI),

health-related status outcome measure, SF-36, and pain and sleep questionnaire. At study completion, pain intensity outcomes showed significantly better pain intensity VAS scores (26.3 ± 24.7 vs. 46.7 ± 26.9, $p = 0.0001$) and significantly better pain relief scores (1.8 ± 1.4 vs. 2.7 ± 1.2, $p = 0.0006$) than placebo. When examining secondary measures, health-related quality of life domains were significantly better during the controlled-release oxycodone treatment period than placebo treatment for the Physical Functioning ($p = 0.0029$), Pain Index ($p = 0.0001$), Vitality ($p = 0.0005$), Social Functioning ($p = 0.0369$) and Mental Health Index ($p = 0.0317$) domains of the SF-36. Both the Standardized Physical Component ($p = 0.0002$) and the Standardized Mental Component ($p = 0.0338$) were significantly better during the CR oxycodone treatment period than the placebo treatment period. The calculated NNT was 2.6 based on the number of patients with at least moderate pain relief [113].

A Cochrane Collaborative meta-analysis on opioid use for neuropathic pain concluded that opioids reduce neuropathic pain, but are treatment-duration dependent[114]. The analysis of short-term trials showed varying statistically significant results. Although all short-term studies showed positive results in attenuating neuropathic pain, 4 trials reported means and standard deviations for pain intensity, which permitted meta-analysis for pain intensity after active drug or placebo. The Cochrane group concluded that short-term opioid trials yielded mixed analgesic efficacy, but emphasize that the analysis was based on only four studies. In contrast, the intermediate-term analysis found that opioids were efficacious in reducing the pain associated with neuropathy[114]. Rowbotham et al. studied high-strength and low-strength opioids for patients with refractory, chronic peripheral and central neuropathic pain[115]. Primary outcome variables include daily VAS scores. They found significantly greater pain reduction at eight weeks in the high-strength group (65.4 ± 18.2 mm to 42.1 ± 26.5 mm) than in the low-strength group (69.3 ± 17.0 mm to 53.4 ± 24.7 mm, $p = 0.02$)[115]. The investigators concluded that high dose opioids reduce neuropathic pain, but this decrement is accompanied by increasing side effects at higher doses. Finally, compelling but lower quality evidence from an open label trial of transdermal fentanyl for neuropathic pain conditions demonstrated a significant reduction in pain (-2.94 ± 0.27), meaningful percent pain relief (33.7 ± 14%), and a 37.4% increase in daytime activity[116]. The authors concluded that transdermal fentanyl provides significant reduction in neuropathic pain.

Although opioids have shown efficacy for the treatment of several pain conditions including cancer pain, peripheral neuropathy, and post-herpetic neuralgia, they should be considered second-line medications when treating neuropathic pain. Table 3 provides a useful model for considering opioid use in neuropathic pain based on pain quality and adverse effects[40].

Table 3. Second and First Line Considerations for Opioids and Tramadol in Neuropathic Pain.

Second Line Consideration
Side effect profile compared to other therapies
Lack of long-term opioid therapy studies
Risk of opioid induced hyperalgesia
Risk of addiction
First Line Consideration
Titration of a first-line medication to an efficacious dosage for prompt pain relief
Episodic exacerbations of severe pain
Acute Neuropathic pain
Neuropathic cancer pain

Eisenberg et al. acknowledge the value of opioids in their review of the efficacy and safety of opioids for the treatment of neuropathic pain[111]. They further describe opioid-induced adverse effects in their analysis. For instance, the most common adverse effects included nausea (NNH, 3.6; 95% CI, 2.9-4.8), constipation (NNH, 4.6; 95% CI, 3.4-7.1), drowsiness (NNH, 5.3; 95% CI, 3.7-8.3), vomiting (NNH, 6.2; 95% CI, 4.6-11.1), and dizziness (NNH, 6.7; 95% CI, 4.8-10.0). In a systematic review of opioid use for chronic non-malignant pain, Moore & McQuay reported that approximately 50% of patients may experience at least one adverse event (e.g., nausea, vomiting, constipation, and drowsiness) and 20% of patients will discontinue opioid therapy due to adverse events[117]. Morever, Højsted & Sjøgren's review of opioids for the management of non-malignant neuropathic pain expresses concern over long-term adverse effects of opioids, including physical dependence, tolerance, addiction, immune suppression and opioid-induced hyperalgesia[118]. A significant evidence base exists for the effectiveness of short-term opioid use; however, the benefits and risks of long-term use remain inconclusive. As investigators perform additional RCTs and longitudinal studies of increasing duration, a more complete understanding of the value of opioids will be uncovered.

E. Dextromethorphan & levorphanol

Dextromethorphan (DM) is a dextrorotatory analogue of levorphanol, a noncompetitive antagonist of the NMDA-sensitive inotropic glutamate receptor[119-121]. It is also an agonist of the σ-1 receptor which suppresses the release of excitatory neurotransmitters, and may act on the N-type calcium channel[119-121]. Improvement in the function of NMDA receptor antagonists may improve the treatment of neuropathic pain. Investigators who research NMDA antagonists and other channel blockers theorize that relatively high doses of low-affinity, noncompetitive, channel blocking NMDA receptor

antagonists such as dextromethorphan may offer a better therapeutic ratio than dissociative, anesthetic-like blockers such as ketamine[122-124]. Randomized controlled clinical trials have demonstrated that acute, single-dose administration of intraspinal and systemic NMDA glutamate receptor antagonists in patients with chronic neuropathic pain reduces spontaneous pain and hyperalgesia[121]. Furthermore, Sang et al. examined patients with painful diabetic neuropathy (DN) and postherpetic neuralgia (PHN) in two crossover trials[120]. The first trial examined the efficacy of dextromethorphan vs. memantine vs. active placebo (e.g., lorazepam) and the second was a dose–response trial. In the first study, dextromethorphan reduced pain intensity by a mean of 33.4% from baseline in patients with DPN and improved the efficacy variable of emotional dimension (e.g., QOL variable) related to the disease and to pain. Responders from the first trial were enrolled in the dose-response trial which showed that full-dose treatment with dextromethorphan reduced pain significantly more than lorazepam (34.8%, $p = 0.027$). A study by Thisted et al. examined the efficacy and tolerability of concomitiant administration of dextromethorphan and quinidine (DM/Q) for the treatment of DPN in an open-label, dose-escalation study conducted at 5 clinical sites. They found that mean (SD) changes from baseline in pain intensity rating scale (PIRS) scores were -1.8 (1.0) in the DM120/Q120 mg per day group. Including all escalation intervals, the PIRS change from baseline was -1.6 (0.9) ($p < 0.001$)[121]. The addition of quinidine was hypothesized to contribute to the significant reduction in pain by increasing the plasma concentration of dextromethorphan. Doses of quinidine however were considerably lower than those used to treat arrhythmias (e.g., 200-400 mg three times daily or four times daily is used to suppress arrhythmias). The authors caution that these findings should be considered merely suggestive of quinidine's benefit given that the study was neither blinded nor placebo controlled.

F. Nonsteroidal anti-inflammatory drugs (NSAIDS)

Nonsteroidal anti-inflammatory drugs (NSAID) are used to treat inflammation, pain, and fever. The analgesic effect of NSAIDs result from their ability to block prostaglandin synthesis by inhibiting the precursor enzyme, cyclooxygenase (COX)[45, 125, 126]. Generally, NSAIDs are effective in treating acute musculoskeletal pain and various other conditions such as arthritis, dysmenorrhea, and headaches[45, 126]. The efficacy of treating NP is questionable since multiple studies have yielded contradictory results. For example, ibuprofen and sulindac offered some pain relief for the treatment of diabetic neuropathy [127, 128]. Cohen et al. examined the efficacy of ibuprofen

and sulindac for the treatment of DPN and found that compared to baseline, both drugs significantly reduced pain; however, long term use of NSAIDS may produce gastrointestinal and renal effects which limit their use[127].

Advancements in medicine have led to an increasing number of modalities for the treatment of pain, though prevention remains the best method for controlling diabetic pain. Strict blood glucose control with insulin can delay the onset of neuropathy in type 1 diabetes mellitus. For example, the diabetes control and complications trial demonstrated that strict insulin therapy decreased the incidence of neuropathy by 57-69%[129]. Although intensive therapy did not preclude the development of neuropathy, insulin therapy remained the best strategy for prevention and amelioration of diabetic peripheral neuropathy.

Table 4 lists medications based on level of efficacy and provides an algorithm for the treatment of peripheral neuropathy. First line medications offer the highest quality evidence, along with a more favorable side effect profile. For instance, the algorithm begins with first line medications. Clinicians may add or "cycle" through first-line medications, progress to second-line medications, and then other medications for the treatment of peripheral neuropathy. Monotherapy is recommended initially, though combinations of first line, second line, or other medication categories may be required to achieve meaningful analgesia.

Table 4. Algorithm for Treatment of Peripheral Polyneuropathy/Diabetic Peripheral Neuropathy.

First Line:	TCA ↔ Duloxetine ↔ Gabapentin ↔ Pregabalin
Second Line:	Venlafaxine ↔ Lidocaine 5% Patch ↔ Lamotrigine ↔ Tramadol ↔ Carbamazepine ↔ Capsaicin
Others:	SSRI ↔ Phenytoin ↔ Topiramate ↔ Opioids ↔ Mexiletine ↔ Oxcarbazepine ↔ Dextromethorphan

3. Human immunodeficiency virus (HIV) neuropathy

The etiology of human immunodeficiency virus (HIV) neuropathy or distal symmetrical polyneuropathy is unknown, but symptoms of polyneuropathy have been estimated to occur in > 35% of HIV+ patients[130-133]. As with diabetic neuropathy, optimizing pain therapies is essential for reducing pain. Tricyclic antidepressants and anticonvulsants have been investigated for their potential efficacy in treating HIV related neuropathy. For instance, amitriptyline and mexiletine were investigated in a randomized, double-blind

trial of 145 patients with painful sensory neuropathy[133]. The primary efficacy measure in the study was a change in mean pain intensity from baseline. At study completion, the difference in mean pain intensities between amitriptyline and placebo was only 0.035 units which did not reach statistical significance. This finding was previously supported by an earlier study by Shlay et al.[134]. A randomized, double-blind placebo-controlled study by Hahn et al. examined the efficacy of gabapentin for the treatment of HIV neuropathy[135]. Median pain scores were compared in the treatment and placebo groups which showed that gabapentin reduced pain scores by 44.1% ($p < 0.05$). The authors concluded that gabapentin was efficacious in treating neuropathic pain related to HIV. In evaluating lamotrigine, Simpson et al. found lamotrigine to be more effective than placebo for treating HIV related neuropathy when comparing mean VAS scores in a randomized, double-blind placebo controlled trial[136].

4. Chemotherapy-induced neuropathy

The mechanism by which chemotaxic agents cause neuropathy is unknown. The most neurotoxic agents include the vinca alkaloids (e.g., cisplatin and its derivatives) as well as the taxanes[137]. These induced neuropathies are often time sensitive and reversible and are drug, cumulative dose, and duration dependent[138]. There are very few clinical trials assessing effective drug treatment for chemotherapy-induced neuropathy. Hammack et al. evaluated nortriptyline for the treatment of cis-diamminedichloroplatinum (cisplatin)-induced neuropathy in a randomized, double-blind, placebo-controlled trial. The group investigated the efficacy of nortriptyline and utilized pain/paresthesias and change in the effect of pain on daily activities as the primary efficacy measures. Results from the study indicated that nortriptyline provided “modest improvement” in chemotherapy-related neuropathy[139]. However, amitriptyline was recently examined for its efficacy in the treatment of chemotherapy-induced neuropathy in a randomized double-blind placebo control study[137]. The investigators used severity/intensity of neuropathic pain, global improvement/quality of life, and sleep and change in physical activity as efficacy measures. It was determined that amitriptyline did not enhance global improvement/quality of life, nor did it demonstrate statistical significance in improving sensory neuropathic symptoms.

5. Postherpetic neuralgia

Postherpetic neuralgia (PHN) is a term that is used to describe prolonged pain associated with herpes zoster or shingles. Among all of the neuralgic diseases, herpes zoster (HZ) has the highest incidence and occurs annually in

approximately 500,000 people in the United States alone. Most of these individuals are 60 years of age and older and represent as much as 20 to 30% of the population. In fact, HZ occurs in as many as 50% of those people living until 85 years of age[140-146]. Herpes zoster typically erupts along one or two adjacent dermatomes. Thoracic, cervical, and ophthalmic involvement are the most common. Lesions progress from discrete patches of erythema to grouped vesicles which pustulate and crust in 7 to 10 days and may require a month to heal. The healed lesions often result in anesthetic scars, changes in pigmentation, and pain. Complete scab resolution usually occurs within 4 weeks. Thoracic dermatomes are affected in approximately 50% to 70% of all cases and cranial (e.g., especially the ophthalmic division of the trigeminal nerve), cervical, and lumbar dermatomes each account for 10% to 20% of cases. Affected sacral dermatomes represent only 2% to 8% of cases[142, 147-153]. Herpes zoster is caused by viral replication. The virus spreads from a single sensory ganglion antidromically to the corresponding dermatome and eventually to the dorsal columns of the spinal cord[141, 147, 154]. The pain of acute zoster can be distinguished from postherpetic neuralgia (PHN), although the nature and timing of the symptoms may overlap. The most common definition of postherpetic neuralgia is the presence of pain for more than a month following the onset of the vesicular rash[141, 151, 152]. An algorithm for the treatment of PHN is suggested in Table 5.

Multiple studies suggest that older age is a strong risk factor for the development of PHN. For instance, few children develop postherpetic neuralgia whereas 27, 47, and 73 percent of untreated adults over 55, 60, and 70 years of age respectively develop postherpetic neuralgia[142, 151, 152, 155-157]. Furthermore, greater severity of acute pain and greater rash severity represent risk factors for prolonged herpes zoster pain[153, 158-160]. Both the vaccine against varicella zoster virus (Varivax ®) and the newly released vaccine against herpes zoster (Zostavax ®) may lead to substantial reductions in morbidity from herpes zoster and PHN, respectively though long term epidemiological studies are needed to confirm the benefit of both vaccines.

Table 5. Algorithm for Treatment of Postherpetic Neuralgia.

First Line:	TCA ↔ Lidocaine 5% Patch ↔ Gabapentin ↔ Pregabalin ↔ SSRI
Second Line:	Venlafaxine ↔ Opioids ↔ Duloxetine ↔ Tramadol ↔ Carbamazepine
Others:	Phenytoin ↔ Topiramate ↔ Lamotrigine ↔ Mexiletine ↔ Capsaicin Corticosteroids ↔ Antiviral Therapy ↔ VZV Vaccine (Preventive)

a. Antidepressants

Tricyclic antidepressants (TCA's)

The tricyclic antidepressants (amitriptyline, imipramine, nortriptyline, and desipramine) have been successfully used for the treatment of PHN. For instance, multiple studies have established the TCAs as effective medications for PHN with a NNT ranging from 1.6-4.1[161-164]. Kishore-Kumar et al. in a randomized double-blind study examined the efficacy of desipramine in patients diagnosed with PHN and reported that the treatment group demonstrated statistically significant pain relief compared to placebo [162]. Raja et al. studied the effects of TCA's and opioids on pain relief, pain intensity, and cognitive function associated with PHN using a randomized, double-blind, placebo-controlled crossover study[163]. The investigators discovered that TCAs and opioids provided greater mean pain decreases than placebo ($p < 0.001$) with no statistical difference between opioids and TCA ($p = 0.06$)[163]. An early placebo-controlled study by Watson et al. highlighted the effectiveness of amitriptyline in treating PHN[161]. Watson et al. also showed no difference in the relief of continuous or brief pain, nor a difference in allodynia between amitriptyline compared to nortriptyline using a VAS pain scale [165]. This randomized, double-blind, crossover trial of amitriptyline versus nortriptyline was performed in 33 patients and further demonstrated equal drug effect on mood, disability, and satisfaction. However, a greater number of intolerable side effects were associated with amitriptyline compared to nortriptyline ($p = 0.05$). Most notably, patients more commonly reported xerostomia, constipation, and drowsiness. The beneficial effects of TCAs for the treatment of PHN have been replicated in several studies which support the use of these agents in PHN[164, 166].

Consistent with many pharmaceutical agents, TCAs may be contraindicated in patients with certain medical conditions and cause adverse effects that may require discontinuation. For example, clinicians should be mindful of using TCAs in older patients with cardiac rhythm disturbances[167-169]. One study indicated that 20% of patients treated with nortriptyline after a myocardial infarction developed adverse cardiac events[167, 170]. The overdose potential for TCAs is significant. That is, accidental or intentional overdose of TCAs can be lethal. In fact, the likelihood of successful suicide is 8-to 16-fold higher with TCAs compared to the non-tricyclic, serotonin-selective reuptake inhibitors (SSRI) such as trazodone and fluoxetine[171]. Accordingly, clinicians should use TCAs with the utmost caution in patients at risk for suicide or at risk of accidental death from overdose [40]. Although tricyclic antidepressants may be used for treating depression in patients with chronic pain, the risk of intentional overdose among depressed individuals must be

acknowledged given a substantially greater risk of suicide associated with TCA use compared to other antidepressants[5].

Other antidepressants

SSRIs may reduce pain in PHN. For example, Rowbotham et al. examined TCAs and SSRIs for the treatment of PHN. No significant differences (ANOVA $p = 0.120$) among desipramine, amitriptyline, and fluoxetine were discovered in their randomized, double-blind, parallel design study of 38 subjects[167]. More specifically, desipramine produced the greatest reduction in pain intensity (47%), followed by amitriptyline (38%), and then fluoxetine (35%) [167]. At time of publication, there were no published studies examining the efficacy of serotonin-norepinephrine reuptake inhibitors (SNRI) for the treatment of PHN.

b. Antiepileptic medications

The efficacy of gabapentin and pregabalin in relieving pain associated with PHN has been demonstrated in several randomized, placebo-controlled trials[172, 173]. In fact, gabapentin has produced greater pain reduction than placebo in RCTs of PHN[172-174]. In a multicenter, randomized, double-blind, placebo-controlled trial of 184 patients comparing gabapentin to placebo, gabapentin demonstrated greater effectiveness at treating PHN-associated pain than placebo[174]. The investigators used a change in average daily pain score based on an 11-point Likert scale as the primary efficacy variable. Patients receiving gabapentin showed a significant reduction in average daily pain score from 6.3 to 4.2 points compared to a reduction from 6.5 to 6.0 in the placebo group ($p < 0.001$)[174]. Dworkin et al. evaluated the efficacy of pregabalin for the treatment of PHN in a multicenter, parallel-group, double-blind, placebo-controlled trial [175]. His group used the mean of the last seven daily pain ratings as the primary efficacy variable. Dworkin et al. concluded that pregabalin was more efficacious in reducing mean pain ratings from the last 7 days compared to placebo. That is, the pregabalin-treated patients reported greater decreases in pain than the placebo group (endpoint mean scores 3.60 vs. 5.29, $p = 0.0001$). Further support for pregabalin's efficacy derives from another multicenter, double-blind, placebo-controlled trial of 238 patients[176]. Mean pain score was used as the primary efficacy variable while pregabalin was compared to placebo for response. Responders were defined as having a $\geq 50\%$ reduction in pain. At study endpoint, there were statistically significantly greater proportions of responders in the pregabalin groups taking 150 mg per day (21/81, 26%, $p = 0.006$) and 300 mg per day (21/76, 28%, $p = 0.003$) than in the placebo group (8/81, 10%). Moreover, equally significant results were seen

in assessing VAS scores. The 150 mg per day pregabalin group (VAS: 52.03, p = 0.006) and the 300 mg per day group (VAS: 48.41, p = 0.0003) demonstrated statistically significantly better mean VAS scores than in the placebo group (62.05). In examining a reduction in sleep disturbance, the investigators discovered a significant improvement in mean sleep interference with the 150 mg per day group (3.13, p = 0.0003) and the 300 mg per day (2.81, p = 0.0001) pregabalin group. Both groups were significantly superior to placebo (4.24) in reducing pain-associated sleep interference[176].

c. Lidocaine 5% patch (Lignocaine)

The lidocaine patch received US FDA approval for the treatment of postherpetic neuralgia in 1999. Several trials have supported the efficacy of topical lidocaine. For instance, Rowbotham et al. demonstrated the efficacy of topically applied 5% lidocaine compared with both gel vehicle and observation (e.g., no treatment) for the treatment of PHN in a randomized, double-blind, vehicle-controlled study[177]. When compared to observation only, the five percent lidocaine patch was superior at all time points from 30 minutes to 12 h (individual time points p = 0.0001 to p = 0.021). In contrast to vehicle patch, the lidocaine patch (5%) provided superior relief at 4 h, 6 h, 9 h, and 12 h (individual time points $p < 0.001$ to p = 0.038). The vehicle patch, however was superior to observation only at 2 h and 6 h (individual time points p = 0.016 and p = 0.041)[177]. These findings have been replicated in subsequent studies[94] including a multicenter randomized, placebo-controlled, two-way, cross-over study utilizing VAS as the primary efficacy measure[178]. This study by Meier et al. found that the reported decrease in ongoing pain intensity and allodynia was highly significant in the lidocaine 5% patch group ($p < 0.001$) and even significant in the placebo group ($p < 0.05$) compared with the pre-treatment (basal) values at all time points of the assessment (2h, 4h, day 4, day 5, & day 7)[178]. A Cochrane Collaborative meta-analysis examining the efficacy of lidocaine 5% patches for the treatment of PHN concluded that topical lidocaine was better than placebo for pain relief (p = 0.003). However, the Collaborative did not recommend topical lidocaine as a first line treatment for postherpetic neuralgia[179]. Although the Cochrane Collaborative and select consensus statements and guidelines do not recommend topical lidocaine as an agent of first choice due to a of lack of comparison studies[7, 180], compelling arguments for its efficacy and value have been advanced by other publications[40, 181]. Topical lidocaine offers a good safety profile; therefore, it can provide excellent adjunctive therapy in older patients who may be more susceptible to the adverse effects of systemic medications.

d. Mexiletine

Mexiletine is an oral analog of lidocaine. There is a paucity of data to support the use of mexiletine for the treatment of PHN. In fact, Finnerup et al. concluded in an evidenced-based proposal for neuropathic pain treatment that mexiletine seems to lack a pain relieving effect in HIV neuropathy, spinal cord injury, and neuropathic pain conditions with prominent allodynia. He further adds that mexiletine's proarrhythmic potential limits dose escalation and consequently efficacy[6]. Dworkin et al. conclude that mexiletine shows only modest or no benefit compared to placebo in treating NP[40]. Finally, a Cochrane Collaborative meta-analysis of systemic lidocaine states that intravenous lidocaine and mexiletine are more effective than placebo in decreasing neuropathic pain; yet, the subgroup analysis reveals that lidocaine and mexiletine are more effective for pain resulting from diabetes, trauma, and cerebrovascular disease than from other causes[182]. In short, clinicians should use mexiletine very cautiously in the older population given its significant risk of adverse effects and poor evidence base for effectiveness.

e. Topical capsaicin

Capsaicin is a hot chili pepper extract that is available in the US as a cream or lotion in strengths of 0.025% and 0.075%. The mechanisms of action may include the release of substance P and other neuropeptides from nociceptive fibers (e.g., unmyelinated C fibers). Continued release of substance P depletes neuronal stores of neurotransmitters which ultimately inactivates local nociceptive function and therefore produces analgesia[183-185]. The topical application of capsaicin has been shown to relieve pain in postherpetic neuralgia, nerve injury pain, and mixed neuropathic pain conditions. For instance, a double-blind, vehicle-controlled study of 143 patients with chronic postherpetic changes in pain severity as reported on the categorical scale, visual analogue scale for pain severity, visual analogue scale for pain relief, and functional capacity scale showed significant improvement with capsaicin 0.075% cream[186]. The authors concluded from their study that capsaicin is safe and effective for controlling the pain of postherpetic neuralgia. In contrast, a review of six double-blind placebo controlled trials (656 patients) analyzing the efficacy of capsaicin for the treatment of neuropathic pain conditions found that capsaicin offered moderate to poor efficacy[187]. The relative benefit of topical capsaicin at 0.075% compared to placebo was 1.4 (95% confidence interval 1.2 to 1.7) and the NNT was 5.7 (4.0 to 10.0)[187]. Hence, capsaicin may be useful as adjunctive therapy or even monotherapy for a small number of patients who fail to respond to or become intolerant to other treatments. The application of capsaicin may cause discomfort and a burning sensation associated with initial nociceptor activation. However, it

is not associated with systemic adverse effects and may serve as a beneficial therapy in older patients who are more intolerant to systemic medications.

f. Dextromethorphan

Dextromethorphan acts as an NMDA receptor antagonist as well as a weak analgesic. It can be combined with opioids to reduce the development of tolerance. Data indicate that dextromethorphan provides little relief of PHN pain or neuropathic pain. For example, dextromethorphan reduced pain intensity by a mean of only 6.5% and did not show a significant reduction in baseline pain intensity (mean difference, - 0.9; 95% confidence interval, - 2.3 to 0.5) when studied a multicenter randomized, placebo-controlled, double-blinded trial for PHN and DPN[120]. These results are consistent with other studies that indicate the extent to which dextromethorphan is an ineffective treatment for PHN[6, 7, 40, 122].

6. Trigeminal neuralgia

Trigeminal neuralgia (TN) occurs in one or more branches of the fifth cranial nerve and is described as an excruciating, stabbing, transient (< 2 minutes) and usually unilateral facial pain that may erupt spontaneously or can be triggered by gentle, innocuous stimuli and is separated by pain-free intervals of varying duration[188]. TN represents a well-known cause of recurrent facial pain and ranks as the most common cause of facial neuralgia. The incidence of TN is 4 to 5 per 100,000 people[189-191] and occurs in approximately 1% of patients with multiple sclerosis[190-192]. Approximately 2% to 8% of patients with TN suffer from multiple sclerosis[190-192]. TN is more common in females, ranging from 1:2 to 2:3 (male to female) and most commonly presents in the sixth decade of life[189-198]. Development of TN in a patient younger than 40 years of age (< 10%) suggests the possibility of multiple sclerosis as well as secondary (e.g., symptomatic) TN in which an underlying disease can be identified such as an intracranial tumor[191,192,194,199]. Idiopathic TN if often difficult to treat because the etiology remains unknown. Despite the availability of several successful treatment options, no universally accepted medical or surgical treatment protocol exists. It is important to differentiate TN from trigeminal neuropathy. For instance, trigeminal neuropathy presents with prominent sensory loss and only mild pain. This distinction can be detected with a careful history and physical examination. The pain of TN also differs from the pain following reactivation of the varicella zoster virus, which typically presents in older adults [195]. Table 6 provides a suggested algorithm for the treatment of TN.

In many chronic neurogenic pain disorders, therapeutic options are limited and therapeutic responses may only be partial. TN is unique because the majority of patients respond to treatment and many have complete elimination of painful attacks for months or even years[200]. Anticonvulsants are one of the most effective classes of drugs for controlling the paroxysmal pain associated with trigeminal neuralgia. Consequently, they have become the mainstay of treatment despite the evidence from just a few RCTs. Although antidepressants can be quite effective agents for neuropathic pain, there is only one trial of their use in trigeminal neuralgia which demonstrated some improvement in pain[201].

Current evidence suggests the use of carbamazepine as a first line agent, and oxcarbazepine if patients experience inadequate analgesia or intolerable adverse effects. Limited evidence supports the use of lamotrigine and baclofen as alternative agents as well as antidepressants, pregabalin, gabapentin, opioids, and transdermal products[201].

Table 6. Algorithm for Treatment of Trigeminal Neuralgia.

First Line:	Carbamazepine ↔ TCA ↔ Gabapentin ↔ Pregabalin ↔ Duloxetine
Second Line:	Oxcarbazepine ↔ Venlafaxine ↔ Opioids ↔ Tramadol ↔ Lidocaine Patch (5%)
Others:	SSRI ↔ Phenytoin ↔ Capsaicin ↔ Topiramate ↔ Lamotrigine ↔ Mexiletine ↔ Corticosteroids ↔ Antiviral Therapy ↔ VZV Vaccine

a. Carbamazepine

Carbamazepine is FDA approved for the treatment of trigeminal neuralgia (TN) and remains the treatment of choice for this painful condition. Multiple studies have proven the efficacy of carbamazepine for the treatment of TN[202-205]. However, the drug has limited usage due to adverse effects such as drowsiness, dizziness, constipation, rash, leukopenia, abnormal liver function tests, ataxia and drug-drug interactions particularly with warfarin (NNH 3, 95% CI 2 – 4)[201]. Finnerup et al. calculated a NNT of 1.7 (1.3–2.2) for the treatment of trigeminal neuralgia[6]. In a Cochrane Collaborative meta analysis, carbamazepine was shown to be effective for treating pain caused by nerve damage, including TN and calculated a NNT of 2.5 (95% confidence interval 2.0 - 3.4)[70]. Notwithstanding carbamazepine's poor tolerability (e.g., thrombocytopenia, leukopenia, hyponatremia) and the introduction of newer agents to the market, carbamazepine probably remains the most effective drug for controlling TN[6, 201].

b. Oxcarbazepine

The use of carbamazepine is complicated by pharmacokinetic factors and sometimes severe adverse events, particularly in elderly patients. Oxcarbazepine, a keto analog of carbamazepine is shown to be of comparable efficacy and is significantly better tolerated than carbamazepine for the treatment of newly diagnosed epilepsy[18, 206]. Multi center, randomized trials have reported comparable efficacy between carbamazepine and oxcarbazepine for the treatment of TN[207]. It is considered a second line therapy for trigeminal neuralgia. The drug's more favorable adverse effect profile and reduced drug-drug interactions make it especially useful for patients that typically require multiple medications for the control of other systemic conditions [201]. Clinicians must carefully titrate higher doses while monitoring for hyponatremia.

7. Central/post-stroke pain

Central pain (CP) can be defined as pain initiated or caused by a primary lesion or dysfunction in the CNS [208]. CP can occur after lesions of the spinal cord caused by various mechanisms (e.g., injury, syringomyelia, infarction, tumor, myelitis) or cerebral lesions of nonvascular origin (e.g., multiple sclerosis, tumor)[209, 210]. The injury to the central nervous system is insufficient to cause hypoalgesia; rather, the insult disrupts spinothalamic pathways that may contribute to neuronal hyperexcitability, loss of descending inhibitory control mechanisms, and alterations in the processing of incoming noxious and non-noxious stimuli. This pathologic process results in abnormal pain perception[211-213]. Regardless of the etiology, CP poses many challenges to treatment. Similar to other neuropathic pain states, pain control rather than complete pain relief should be the focus of therapy.

a. Tricyclic antidepressants

Tricyclic antidepressants (TCA) have been used for the treatment of neuropathic pain for several years and may confer additional benefit through their anxiolytic actions and sedative properties (antihistaminergic)[214]. In a double-blind, 3-phase, placebo controlled crossover trial, Leijon & Boivie studied the pain-relieving effect of amitriptyline and carbamazepine in 15 patients with central post-stroke pain[215]. Efficacy was measured by daily ratings of pain intensity, post-treatment global ratings of pain relief, and estimation of depression scores at the 28 day study end. The authors concluded that amitriptyline produced a statistically significant reduction in pain when compared to placebo (NNT = 1.7; CI 1.2–3.1) and compared to carbamazepine (800 mg)[7, 215]. In a meta-analysis by Finnerup et al., the

calculated NNT for the treatment of central pain by TCAs was 4.0 (95% confidence interval 2.6–8.5)[6]. In general, RCT's for pain therapy that achieve a NNT of 5.5 or lower demonstrate statistically significant pain reduction for active treatment compared to placebo. Therefore, a NNT of 4.0 for TCAs in central pain suggests an effective agent for this condition. However, there is limited drug efficacy data across different etiologies of central pain, and there are flaws in treatment recommendations based on extrapolating data from peripheral neuropathic pain conditions rather than studies on specific central pain states such as post-stroke pain or spinal cord injury pain. Further, TCAs may not be well tolerated in older patients with stroke; therefore clinicians should consider gabapentin or pregabalin in these circumstances[6, 7].

b. Antiepileptic medications

Some anticonvulsants show benefit in treating central pain caused by stoke or spinal cord injury. For instance, carbamazepine and amitriptyline were studied for the treatment of CP and carbamazepine's effect showed no statistical significance in the treatment of central post-stroke pain compared to placebo[215]. Lamotrigine, however does appear to have benefit. For example, Vestergaard et al. showed that lamotrigine-treated patients with central post stroke pain achieved significantly lower pain scores with a reduction in the mean pain score of 2 points[216]. A reduction of 2 points was deemed clinically significant due to the generally poor response to treatment in CP states. Furthermore, Finnerup et al. reported that lamotrigine significantly reduced pain at or below the level of spinal cord injury in patients with incomplete damage to the spinal cord[217].

Both gabapentin and pregabalin have been investigated for the treatment of central pain. Levendoglu et al. studied gabapentin's effect on neuropathic pain associated with spinal cord injury in a randomized, double-blind, placebo-controlled, crossover trial[218]. VAS scores were significantly different between the gabapentin-treated group and placebo group at study end ($p < 0.001$), but the results failed to reach statistical significance for treating itchy, dull, sensitive, and cold type NP related to spinal cord injury. Pregabalin does demonstrate effectiveness in central pain. For example, Siddall et al. compared pregabalin to placebo in patients with spinal cord injury using the endpoint of mean pain score as the primary efficacy measure[219]. Pregabalin was superior to placebo using the primary efficacy variable. Efficacy comparison yielded a $\geq$ 30% reduction (42% vs. 16%; $p < 0.001$) and a $\geq$ 50% reduction (22% vs. 8%; $p < 0.05$) in pain scores from baseline at study endpoint for the pregabalin treated group versus the placebo group. Moreover, the 30% responder group yielded a

NNT of 3.9 and the 50% responder group an NNT of 7.1[219]. Another study by Vranken et al. evaluated pregabalin in patients with central pain induced by brain or spinal cord injuries[213] and used pain intensity scores recorded on the visual analog scale (VAS) as the primary efficacy measure. A statistically significant decrease was shown in mean pain score at study endpoint for pregabalin treatment (7.6 ± 0.8 to 5.1 ± 2.9) compared with placebo (7.4 ± 1.0 to 7.3 ± 2.0). In fact, the visual analog scale-score difference between pregabalin and placebo was 2.18 (95% CI: 0.57–3.80, $p = 0.01$).

8. Postsurgical/traumatic and phantom limb pain

The incidence of persistent postsurgical pain (e.g., > 3–6 months) may be alarmingly high. However, incidence of persistent postoperative pain remains controversial, but has been reported following numerous surgical procedures including limb amputation, thoracotomy, mastectomy, cholecystectomy, and inguinal hernia repair[220]. Phantom limb phenomena have been described as abnormal sensations, with or without pain that is referred to the surgically or traumatically amputated limb[221]. The incidence of phantom pain ranges broadly from 0% to 100%[221, 222]. Distinctions should be noted between phantom limb pain (e.g., painful sensations referred to the absent limb), phantom limb sensation (e.g., any sensation except pain that is experienced in the absent limb), and stump pain (e.g., pain localized to the stump), although each of these may coexist in an individual patient at different times[220, 223]. In the immediate postoperative period, the incidence of phantom pain and phantom sensation is reported to be 72% and 84% respectively whereas 6 months after amputation, the incidence of each is 67% and 90% respectively[221, 224, 225]. Similar to the incidence of phantom pain, an estimation of the long-term prevalence of phantom pain varies considerably from 60% to 80%[221, 223]. Several risk factors have been identified for the development of phantom limb pain including the degree of preoperative pain, the magnitude of intraoperative noxious input, the intensity of postoperative pain, and psychological factors[220, 226, 227].

Post-thoracotomy pain syndrome is defined as pain that recurs or persists along a thoracotomy incision for at least 2 months after the surgical procedure[220, 228]. The true incidence of post-thoracotomy pain syndrome is difficult to determine and ranges from 5% to 80%[220, 229]. It has been estimated that 50% of all patients will suffer from persistent chest wall pain 1 to 2 years after thoracotomy. Indeed as many as 30% of patients may still experience pain 4 to 5 years after surgery [220, 230].

Postmastectomy pain syndrome consists of persistent pain in the anterior chest and axilla, as well as medial and posterior parts of the arm following

breast surgery[220]. The reported incidence of postmastectomy pain after surgery for breast cancer varies between 4% to 100%[220, 231, 232]. This pain can be sufficiently severe to interfere with sleep and performance of daily activities[220, 233, 234]. Furthermore, inadequately treated postmastectomy pain may result in an immobilized arm, severe lymphedema, frozen shoulder syndrome, and even complex regional pain syndrome (CRPS)[220, 235].

Both TCAs and anticonvulsants have been studied in phantom limb phenomena and gabapentin seems to offer some benefit. For example, Robinson et al. investigated the efficacy of amitriptyline for the treatment of phantom limb pain and residual limb pain in a double-blind, randomized, active placebo-controlled study[236]. The authors concluded from the study that there was no significant statistical difference between amitriptyline and placebo for the treatment of phantom limb pain. In a study examining the effects of gabapentin on post-amputation pain, gabapentin was compared to placebo in patients undergoing limb amputation for peripheral vascular disease[237]. Primary outcome measures included rates of phantom pain and intensity of stump and phantom pain at the conclusion of the 30-day treatment period and then six months later. Secondary outcome measures were frequency, duration, intensity of phantom pain attacks, descriptions of pain (e.g., using the MPQ) and consumption of opioids. Treatment with gabapentin in the early postoperative period produced no short-term (e.g., 30 days) or long-term (e.g., 6 months) effect on post-amputation pain. These results are consistent with a study conducted by Smith et al. who found no reduction in phantom limb pain among post-amputee patients treated with gabapentin[238]. In contrast, gabapentin was found to be effective for phantom limb pain based on a study by Bone et al.[239]. This was a randomized, double-blind, placebo-controlled, cross-over study. Primary outcome measures included VAS pain intensity differences compared with baseline. At the end of the six-week treatment period, weekly VAS scores were 2.9 ± 2.2 in the gabapentin arm (baseline 6.1 ± 1.8) and 5.1 ± 2.2 for the placebo arm (baseline 6.7 ± 1.9), $p = 0.025$. The authors concluded that gabapentin was efficacious in reducing spontaneous phantom limb pain.

Various other pharmacologic and interventional strategies have been proposed to reduce acute and chronic post-thoracotomy pain. Such therapies include NSAIDS, parenteral opioids, epidural and paravertebral infusions of local anesthetics, intercostal and phrenic nerve blockade, and cryotherapy[240, 241]. Each therapy, however has produced variable results and no single strategy demonstrates effectiveness in all patients[241]. Tricyclic antidepressants show mixed effectiveness for the treatment of chronic thoracic pain[242] and for other neuropathic pain conditions. Clinicians may initiate TCAs for chronic post-thoracotomy pain, but be

mindful of their risks associated with patients having a history of myocardial infarction, heart block, and congestive heart failure. These cardiac conditions may indeed be more prevalent in the post-thoracotomy population. Gabapentin may offer a safer and more effective alternative to TCAs for post-thoracotomy pain. For instance, Sihoe et al. studied sixty consecutive patients complaining of refractory pain following thoracic surgery or trauma and in whom gabapentin was prescribed for a mean duration of 21.9 weeks[240]. At study termination, 73.3% of patients reported a reduction in their pain scores on a 10-point analog scale compared to their scores prior to gabapentin treatment. There were 19 patients (e.g., 42.2%) who reported a reduction in their pain scores of ≥ 50%. Furthermore, 75% of patients affected with chest wall paresthesia reported statistically significant relief. Solak et al. examined the efficacy of gabapentin and naproxen in a similar patient population of those suffering from post-thoracotomy pain[241]. The primary outcome measures included a reduction in VAS pain score to <5, and a Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score of <12 as evidence of pain reduction. At study conclusion, 17 (e.g., 85%) gabapentin-treated patients and 3 (e.g., 15%) naproxen-treated patients reported VAS scores <5 ($p = 0.001$), and 17 (85%) patients in the gabapentin group and 0 (e.g., 0%) patients in the naproxen group reported LANSS scores of <12 ($p = 0.001$). The authors concluded that gabapentin is safe and effective for the treatment of post-thoracotomy pain with minimal side effects and high patient compliance. The calculated NNT of the study was 1.4, indicating a clinically meaningful measure of effect and low risk liability related to gabapentin.

Antidepressants have been used for the treatment of neuropathic pain following surgery for breast cancer. Kalso et al. studied amitriptyline in a randomized, double-blind placebo-controlled crossover trial, and used the VAS and verbal rating scale as outcome measures[243]. In this study, 8/15 patients experienced a ≥ 50% decrease in pain intensity, while only 2/15 in the placebo group responded favorably (e.g., NNT was 2.5). The serotonin-norepinephrine reuptake inhibitors (SNRI's) have also been studied in the treatment of neuropathic pain following surgery for breast cancer. For example, Tasmuth et al. examined venlafaxine in a randomized, double-blind placebo-controlled crossover trial using VAS and verbal rating scale (VRS) as outcome measures[244]. The authors concluded that average daily pain intensity was not significantly reduced by venlafaxine compared to placebo, but a statistically significant difference was observed in average pain relief and maximum pain intensity with venlafaxine compared with placebo.

9. Cancer pain

Fifteen to 40% of all persons with cancer are estimated to experience neuropathic pain[245-252]. Cancer patients may present with more than one source of their pain and describe features of both nociceptive and neuropathic pain. Neuropathic pain may be directly related to the malignant disease such as tumor infiltration of peripheral nerves, plexi, roots, or spinal cord. It may arise from efforts to treat the disease such as surgery, chemotherapy, or other drug induced neuropathy or neuritis, and even from radiation induced injury to peripheral nerves and the spinal cord. This type of pain is invariably associated with sensory changes caused by injury to the central or peripheral nervous system and may be incompletely responsive to opioid therapy. Patients typically describe this pain as burning, shooting, pins/needles, electrical or numb, and it tends to radiate over dermatomal distributions. In contrast, nociceptive pain is associated with tissue injury from surgery, trauma, inflammation, or tumor. The pain is caused by stimulation of pain receptors in cutaneous and deeper musculoskeletal structures. It is often proportional to the degree of nociceptor activation. Both somatic and visceral pain conditions may be characterized as nociceptive. Patients frequently describe features of both neuropathic and nociceptive pain. For instance, a patient with a solid-tumor may report painful symptoms of both a nociceptive and neuropathic nature.

Cancer pain may result from direct invasion of tumor into nerves, bones, soft tissue, ligaments and fascia, and may induce visceral pain through distension and obstruction. While over two-thirds of cancer pain usually results from the tumor burden, a quarter of pain experienced by cancer patients can be attributed to the cancer-related treatments[253]. For instance, surgery, radiation, and chemotherapeutics may all elicit acute pain that diminishes in time while other therapies may cause chronic pain conditions[254]. Radiation treatment frequently causes acute muscle stiffness and aching, but carries the risk of chronic pain secondary to nerve injury, chronic inflammation, osteoradionecrosis, or myofascial injury. Surgery-associated pain may result from direct nerve injury, inflammation, post-amputation phantom pain conditions, and even the development of Complex Regional Pain Syndrome (CRPS). Many chemotherapeutic agents are known to cause pain. Several classes, such as the alkaloids, platinum-based compounds, and the antimitotics are known to contribute to peripheral neuropathies. The World Health Organization (WHO) has published three-step guidelines for the treatment of cancer pain which promote the use of systemic opioid therapy in concert with non-opioids and adjuvant medications (Figure 1)[255-257]. Some authors have found that application of these guidelines provides adequate

analgesia in 75% to 95% of all patients with cancer pain[255-257]; however, others report that as many as 50% of cancer patients with pain may remain undertreated[258]. Clinical experience and literature-based reports suggest that neuropathic cancer pain may poorly respond to opioids, thus requiring other strategies to effectively treat a neuropathic component of cancer pain[259, 260]. For example, Arner and Meyerson's paper examining the effectiveness of opioids in treating neuropathic pain described that opioids failed to provide moderate or complete relief among this group of patients[261]. Kupers et al. found a similar result in their randomized double-blind placebo controlled trial examining opioids and their responsiveness to idiopathic pain and neuropathic pain states[262]. The group concluded that opioids more effectively reduce idiopathic pain compared to neuropathic pain. Yet, studies in non-cancer pain conditions do reveal the value of using opioids to control neuropathic pain. For instance, Agarwal et al. investigated the use of transdermal fentanyl in neuropathic pain of non-cancer origin and found that transdermal fentanyl significantly reduced pain intensity and increased levels of activity[116]. Moreover, Raja et al. found that opioids effectively treat neuropathic pain (e.g., postherpetic neuralgia) without impairing cognition[163].

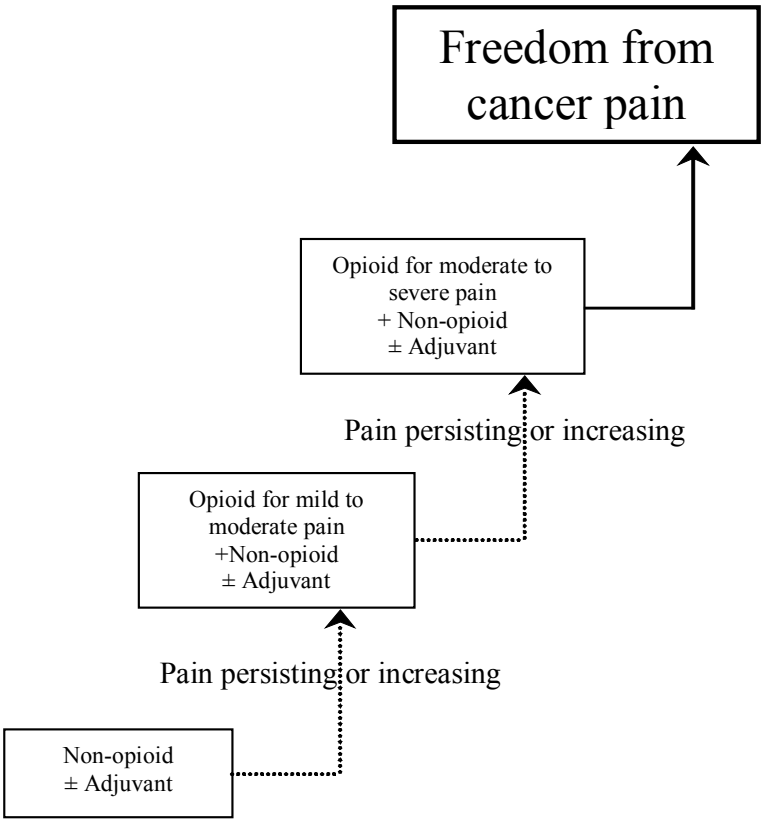

Figure 1. WHO Analgesic Ladder for Cancer Pain.

Adjuvants include non-opioids that confer analgesic effects in certain medical conditions, but primarily treat conditions that do not involve pain. Clinicians typically prescribe adjuvants for the treatment of neuropathic pain like postherpetic neuralgia (PHN) or painful diabetic neuropathy. The evidence for their effectiveness derives more from studies in the nonmalignant pain population rather than the cancer pain population. However, the pathologic processes of neuropathic pain are assumed to be similar in both groups of patients; therefore, these agents can be successfully used in treating neuropathic pain in cancer patients. Medications such as corticosteroids, topical local anesthetics, antidepressants, anticonvulsants, bisphosphonates, and radiopharmaceuticals are included among the group of agents viewed as adjuvants. For example, Stute et al. investigated the neuropathic pain presentation (e.g., nerve compression pain, nerve injury pain, and sympathetically-maintained pain) among 213 cancer patients and found that 79% exhibited nerve compression pain, 16% nerve injury pain, and 5% sympathetically-maintained pain[263]. Patients with nerve injury or sympathetically mediated pain were more likely to require adjuvant therapy including anticonvulsants or antidepressants in order to adequately control their pain. Along with anticonvulsants and antidepressants, clinicians may use corticosteroids while treating advanced malignancies which can improve pain, combat anorexia, ease nausea, and reduce malaise [259].

Adjuvants have been shown to improve pain ratings in several pain conditions and can confer meaningful relief to patients suffering from neurogenic cancer pain. The antidepressants can treat neuropathic pain and offer analgesic effects independent of their antidepressant effects[34, 35]. The strongest level of evidence for analgesic efficacy exists for the tricyclic antidepressants (TCA) and specifically the tertiary amines (e.g., doxepin, amitriptyline)[34]. The secondary amines (e.g., nortriptyline, desipramine) also produce analgesia and offer a more favorable side effect profile, especially if clinicians are concerned about sedation, anticholinergic effects, and dysrhythmias. Clinicians tend to use TCAs in cancer pain linked to surgery, chemotherapy, radiation therapy, or malignant neural infiltration. TCAs may also be useful as anxiolytics and sedatives, often promoting sleep. The selective serotonin reuptake inhibitors (SSRI) provide little analgesia based on clinical experience, and the literature demonstrates mixed results in RCTs. Some clinicians may use the SSRIs in managing neuropathic pain for patients who fail TCAs because SSRIs yield a lowered risk of adverse events[44].

Anticonvulsants may be effective for various types of neuropathic malignant pain. These medications typically attenuate shooting, stabbing, burning, and electric-like sensations associated with a dysfunctional nervous

system. Gabapentin, for instance could be considered a first line agent for treating neuropathic pain. High quality evidence (e.g., RCTs) supports its analgesic effect, safety, good tolerability, and absence of drug-drug interactions[56, 264, 265]. In the malignant pain population, Ross et al. examined the effectiveness of gabapentin for the treatment of cancer-related neuropathic pain [266]. Patients either presented with treatment-related (n = 25) or tumor-related (n = 37) neuropathic pain. At a median gabapentin dose of 1200 (range of 300–1800) mg per day, there was a statistically significant reduction in the worst ($p < 0.0001$), average ($p < 0.0001$), and current ($p = 0.0018$) pain scores. Twenty-eight of sixty-two (28/62 [45.2%]) patients achieved at least a one-third reduction in their pain score (95% CI 32.5–58.3). This corresponds to a NNT of 2.2 (95% CI 1.7–3.1). The authors concluded that gabapentin is an effective treatment for cancer-related neuropathic pain[266]. Adding gabapentin to opioids substantially improves pain control among cancer patients. For instance, Bennett conducted a multicenter RCT of 121 cancer patients with neuropathic pain and found that gabapentin provided better pain relief when combined with systemic opioids[267]. Clinicians may consider pregabalin for use in neuropathic cancer pain given strong evidence for its analgesic effect, rapid titration schedule, and tolerability[5, 268]. Although there is no evidence base for the use of pregabalin in cancer-related neuropathic pain, clinicians may extrapolate its potential benefit in cancer pain from studies in non-malignant neuropathic pain conditions[175, 268].

10. Complex regional pain syndrome (CRPS)

The term Complex Regional Pain Syndrome (CRPS) is broad, non-specific, and incorporates an array of signs and symptoms that this syndrome exhibits. Two subtypes exist: complex regional pain syndrome, Type I (RSD) and complex regional pain syndrome Type II (Causalgia)[269]. CRPS, Type I refers to a posttraumatic syndrome causing spontaneous pain not limited to the distribution of a single nerve and disproportionate to the inciting event. CRPS Type II represents a pain syndrome occurring after evidence of a specific nerve injury and not necessarily limited to the territory of the injured nerve. The syndrome is characterized by intense, excruciating (aching, burning, shooting, stabbing) pain usually in one extremity or part of an extremity. Manifestations of CRPS reflect pathologic changes in the autonomic, sensory, and motor systems. Patients typically report pain caused from stimuli that ordinarily do not provoke pain (allodynia) and/or describe exaggerated responses to stimuli that are normally painful (hyperalgesia). Other common CRPS symptoms include vasomotor disturbances such as temperature asymmetry and/or skin color changes as well as sudomotor

changes in the form of asymmetry of hyperhidrosis (sweating), dryness, edema, or shiny skin in the affected region. Motor dysfunction may manifest as spasm, tremor, dystonia, weakness, atrophy, or contracture in the affected extremity and trophic disturbances may present as changes in skin, nails, or hair pattern. The name commonly used for this syndrome, reflex sympathetic dystrophy (RSD) is actually a misnomer in that it implies a reflex mechanism associated with a hyperactive sympathetic nervous system. However, animal models suggest that altered neuromodulation, nerve hyperexcitability, and central sensitization may all contribute to this complicated disease process known as CRPS. Generally, pain can be elicited by movements and pressure at the joints, even if these are not directly affected by the inciting lesion[270]. Weakness of all muscles of the affected extremity are often present[270, 271]. Furthermore, sequalae of persistent motor and trophic abnormalities may cause passive movement restrictions of the joints and tendons[270].

The tenets of proper CRPS treatment include pain control and functional restoration. Medications such as the TCAs, gabapentin, and opioids have shown broad enough analgesic activity in other neuropathic pain conditions (e.g., DPN and PHN) that they can be applied to the treatment of CRPS. Clinical goals focus on reducing stimulus-evoked pain, lessening pain associated with extremity movement, and increasing the functional state of the extremity through physical therapy. The initiation of early functional restorative therapy is critical and correlates with improved outcomes[272-274].

CRPS is complex and poorly understood. A lack of long-term evidence for conventional neuropathic medications such as the tricyclic antidepressants may not necessarily reflect a lack of efficacy. Researchers have avoided inclusion of patients with CRPS in the efficacy trials of neuropathic pain medications due to the lack of precise "diagnostic" criteria for this disease[275]. Consequently, multiple medications are currently used to ease the pain of CRPS with incomplete results including corticosteroids, nonsteroidal anti-inflammatory drugs, calcitonin, dimethylsulfoxide (DMSO), *N*-acetylcysteine, antidepressants, antiepileptics, clonidine, and opioids. An algorithm for the treatment of CRPS is outlined in table 7.

Table 7. Algorithm for Treatment of Complex Regional Pain Syndrome.

First Line:	TCA ↔ Gabapentin ↔ Pregabalin ↔ Bisphosphonate/Calcitonin
Second Line:	SNRI ↔ Lidocaine 5% Patch ↔ Corticosteroids ↔ Lamotrigine ↔ Tramadol ↔ Opioids ↔ Pregabalin
Others:	SSRI ↔ Phenytoin ↔ Capsaicin ↔ Topiramate ↔ Mexiletine ↔ Oxcarbazepine ↔ Carbamazepine ↔ Dextromethorphan

a. NSAIDS and corticosteroids

There are few RCTs of oral medications that have been performed in CRPS patients; however, some controlled trials of oral therapies for neuropathic pain have included CRPS patients. Features that may characterize the acute phase of the disease, such as edema, warmth, and erythema illustrate an inflammatory component[275, 276]. Consequently, nonsteroidal anti-inflammatory drugs[275, 277] and corticosteroids have shown some efficacy in relieving pain associated with early signs of CRPS[270,275, 278]. Numerous studies have examined the efficacy of nonsteroidal anti-inflammatory drugs for the treatment of neuropathic pain and none have proved effective for sustained use in CRPS. In contrast, corticosteroids have shown efficacy for the treatment of CRPS and not only in the acute phase. For example, Braus et al. evaluated the efficacy of systemic corticosteroids combined with physical therapy for the prevention of CRPS following stroke and discovered that systemic corticosteroids effectively treated 31/34 patients (e.g., 91%)[279]. A previous study by Christensen et al. had also reported the benefit of steroids[278]. This investigation studied 23 CRPS patients and randomized them to a prednisone-treated group or placebo group. More than 75% clinical improvement was noted within the twelve-week study period for the prednisone-treated group. In addition, a study by Grundberg reported favorable results with the use of corticosteroids in CRPS[280].

b. Opioids

Intravenous morphine or morphine equivalents have shown efficacy in providing analgesia compared with placebo in neuropathic pain[111]. Opioids should be considered in CRPS if pain limits the patient's participation in physical restorative therapies that aim to establish, maintain, or enhance function of the affected extremity. Although opioids may control chronic neuropathic pain conditions less effectively than nociceptive pain conditions[281, 282] the data for opioid use do support improvements in quality of life for patients with neuropathic pain[113, 282]. Clinicians may titrate opioids to effect without a ceiling, though unwanted adverse effects (e.g., sedation, constipation, nausea and vomiting, hyperalgesia, pruritis, hypogonadism) may limit their use in patients with CRPS. Furthermore, tolerance, physical dependence, and addiction may all occur with chronic opioid use. The use of opioids in CRPS was recently studied by Agarwal et al. in a prospective, open-label trial[116]. Three groups of patients with neuropathic pain (e.g., small fiber or diabetic peripheral neuropathy), CRPS, and postamputation pain were investigated to determine the effect of transdermal fentanyl on pain and function. Primary outcome variables included change in pain intensity

and daily activity and secondary outcomes included pain relief, cognition, physical function, and mood. All three groups reported significant decreases in pain at study conclusion. The CRPS group reported a reduction of 2.4 ± 0.40 ($p < 0.001$) from baseline on a 0-10 numerical rating scale. Moreover, the CRPS group experienced a 37.5% increase in daily activities compared to baseline[116].

Tramadol, a weak μ agonist with serotonin and norepinephrine reuptake inhibition demonstrates effective pain control in neuropathic pain conditions [108]. Its effectiveness may derive from serotonin/norepinephrine reuptake inhibition at the level of the spinal cord. No RCTs have been published supporting its efficacy in CRPS, however.

c. Antidepressants

Antidepressants (e.g., TCAs and SNRIs) are effective in treating a mix of neuropathic pain conditions[29, 163]. The literature does not yet support their use in CRPS, though their success in treating PHN and DPN leads many to believe that these agents will reduce CRPS-associated pain. TCA's may be tailored to the individual patient. For instance, an overweight, lethargic patient may benefit from an agent with more noradrenergic selectivity (e.g., desipramine) that may be activating and lead to appetite suppression. For those with poor sleep hygiene, the sedating properties of amitriptyline may be quite beneficial[36, 282]. Duloxetine, an FDA approved medication for diabetic peripheral neuropathy may anecdotally help to relieve pain in CRPS[46, 47].

d. Antiepileptics

Antiepileptics for CRPS have shown mixed results. Gabapentin, in a double-blind, randomized, placebo-controlled study of mixed neuropathic pain states ($n = 305$) was investigated for its efficacy in treating CRPS ($n = 85$)[283]. The primary outcome variable was a change in average daily pain score from baseline to the final week, and the secondary outcome variable included the SF-36 Health Survey. Using an 11-point Likert scale, the treatment group showed a mean decrease in average daily pain score of 1.5 (e.g., 21%) (7.1 to 5.6) compared to 1.0 (14%) (7.3 to 6.3) for the placebo group ($p = 0.048$). Secondary outcome measures demonstrated that gabapentin-treated patients scored significantly better for the bodily pain improvement, social functioning, and role-emotional domains ($p < 0.05$) compared to those receiving placebo[283]. This study included 85 (28%) patients with CRPS, and concluded that gabapentin was effective in treating neuropathic pain in general; however, no specific outcome data were reported for CRPS patients. Furthermore, a randomized double-blind placebo controlled crossover study of 58 patients with CRPS I showed no

Table 8. Medications for the Treatment of Peripheral Neuropathy.

Medication	Starting Dose and Titration	Dose Range	Drug Interactions	Side Effects
Antidepressants				
Tricyclic				
Nortriptyline	10-25 mg qhs; increase by 10-25 mg/wk	75-150 mg/day	Monoamine oxidase inhibitor contraindicated with all TCAS	Common to all tricyclic agents: dry mouth, drowsiness, dizziness, constipation, urinary retention, blurred vision, confusion, disorientation, increased appetite, tachycardia
Desipramine	10-25 mg qhs; increase by 10-25 mg/wk	75-200 mg/day	Monoamine oxidase inhibitor contraindicated with all TCAS	Common to all tricyclic agents: dry mouth, drowsiness, dizziness, constipation, urinary retention, blurred vision, confusion, disorientation, increased appetite, tachycardia
Amitriptyline	10-25 mg qhs; increase by 10-25 mg/wk	75-150 mg/day	Monoamine oxidase inhibitor contraindicated with all TCAS	Common to all tricyclic agents: dry mouth, drowsiness, dizziness, constipation, urinary retention, blurred vision, confusion, disorientation, increased appetite, tachycardia
SNRI				
Duloxetine	30 mg qd; increase by 30 mg/wk	30-60 mg/day	SSRI, potent inhibitors of CYP1A2, CYP2D6; potentiates central nervous system depression with tramadol and tricyclic agents	Most common adverse: nausea, dry mouth, somnolence, constipation, decreased appetite, hyperhidrosis, delayed ejaculation
Venlafaxine	37.5 mg/day; increase by 37.5 mg/wk	150–375 mg/day		
SSRI				
Paroxetine	10 mg/day; increase by 10 mg/wk	20–60 mg/day	Monoamine oxidase inhibitors contraindicated; antagonizes codeine and hydroxycodone; potentiates effects of bupropion, phenytoin, tricyclic agents; increases risk of serotonin syndrome with other SSRIs, tramadol, venlafaxine	Sweating, nausea, anorexia, diarrhea, dizziness, dry mouth, nervousness, delayed ejaculation, impotence, decreased libido, constipation, tremor, headache, somnolence, insomnia, tremor, blurred vision, flushing, hyponatremia, serotonin syndrome, extrapyramidal symptoms
Anticonvulsants				
Gabapentin	100-300 mg po tid; increase by 100-300 mg every 5 days	1800-3600 mg/day in divided doses (tid)	Antacids may decrease absorption (separate by 2 hr); potentiates effects of other central nervous system depressants	Somnolence, dizziness, ataxia, fatigue, nystagmus, diplopia, blurred vision, tremor, dyspepsia, dry mouth, nausea, vomiting, constipation, leucopenia

Table 8. Continued.

Medication	Starting Dose and Titration	Dose Range	Drug Interactions	Side Effects
Pregabalin	75 mg qhs; increase by 75 mg/3-5days	75-300 mg/day in divided dose	Antacids may decrease absorption (separate by 2 hr); potentiates effects of other central nervous system depressants	Dizziness, somnolence, dry mouth and edema; dose adjustment with renal impairment
Carbamazepine	200 mg/day; increase by 200 mg/wk	1000-1600 mg/wk	Monoamine oxidase inhibitors contraindicated; antagonized by phenytoin; antagonizes lamotrigine, methadone, phenytoin, and tramadol; potentiates risk of central nervous system depression with tricyclic agents	Dizziness, drowsiness, ataxia, nausea, vomiting, blurred vision, confusion, weakness, fatigue, nystagmus, aplastic anemia, hyponatremia (SIADH)
Oxcarbazepine	300 mg/day; increase by 300 mg/wk	1200–2400 mg/day	Antagonized by carbamazepine, phenytoin, lamotrigine; potentiates effects of phenytoin and risk of central nervous system depression with tricyclic agents	Dizziness, somnolence, fatigue, nausea, vomiting, ataxia, abdominal pain, tremor, dyspepsia, nystagmus, hyponatremia, confusion, leukopenia, thrombocytopenia, erythema multiforme.
Lamotrigine	50 mg/day; increase by 100 mg biweekly	200–600 mg/day	Antagonized by carbamazepine, oxcarbazepine, phenytoin	Dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, fatigue, confusion, impaired memory, nystagmus, aplastic anemia, agranulocytosis, hemolytic anemia, red cell aplasia, disseminated intravascular coagulation, neutropenia and pancytopenia, Stevens-Johnson syndrome or toxic epidermal necrolysis.
Topiramate	25 mg/day; increase by 25 mg/wk	400–800 mg/day	Antagonized by phenytoin, carbamazepine; potentiates effects of phenytoin	Somnolence, dizziness, ataxia, memory loss, weight loss, psychomotor slowing, language disturbance, confusion, nystagmus, fatigue, paresthesias, tremor, abdominal pain, anxiety
Phenytoin	100 mg/day; increase by 100 mg/wk	300–500 mg/day	Antagonized by bupropion, carbamazepine, fentanyl, lamotrigine, tramadol; antagonizes tricyclic agents; effects potentiated by oxcarbazepine, paroxetine, and SSRIs	Nausea, vomiting, nystagmus, ataxia, dizziness, confusion, blurred vision, somnolence, constipation, headache, insomnia, gum hypertrophy, osteomalacia, lymphadenopathy, hepatotoxicity, systemic lupus erythematosus, blood dyscrasias, hypertrichosis

Table 8. Continued.

Medication	Starting Dose and Titration	Dose Range	Drug Interactions	Side Effects
Non-Opioid Analgesics				
Tramadol	150 mg/day; increase by 50 mg/wk	200–400 mg/day	Increased risk of serotonin syndrome with monoamine oxidase inhibitors, SSRIs, tricyclic agents, venlafaxine; antagonized by carbamazepine, phenytoin; effects potentiated by paroxetine, tricyclic agents	Nausea, constipation, somnolence, headache, dry mouth, seizures, confusion, tremor, anorexia, urinary retention
Opioids				
Morphine IR	15–30 mg every 8 hr	90–360 mg/day	Increased risk of central nervous system depression with tramadol, tricyclic agents, clonazepam	Sedation, dizziness, nausea, constipation, urinary retention, respiratory depression, hypogonadism
Oxycodone SR	20 mg every 12 hr; increase by 10 mg/wk	40–160 mg/day	Increased risk of central nervous system depression with tramadol, tricyclic agents, clonazepam	Somnolence, dizziness, constipation, nausea, vomiting, headache, dry mouth, sweating, respiratory depression, hypogonadism
Methadone	5mg q8h; increase by 10mg/wk	5-20mgq8h	Anti-retroviral, potent inducers and inhibitors of CYP3A4; high doses, hypokalemia prolong QT interval; ctyochrome p450 inhibitors can increase levels.	Sedation, dizziness, constipation, urinary retention, respiratory depression; Caution when initiating treatment as medication accumulation may occur; hypogonadism
Fentanyl (transdermal)	12-25 mcg/hr; increase by 25 mcg/hr/14 days	150-200 mcg/hr	MAOI, increased risk of central nervous system depression with potent inhibitor of CYP3A4	Somnolence, dizziness, constipation, nausea, vomiting, headache, dry mouth, sweating, respiratory depression, local skin reaction, hypogonadism
Topical Analgesics				
Lidocaine 5% patch	1-3 patches to affected area	Three patches, only once for up to 12 hours within a 24-hour period	Class I antiarrhythmic drugs	Local skin irritation, bradycardia, hypotension, dizziness, headache

CYP3A4, CYP1A2, CYP2D6 - cytochrome P-450 isozymes; **MAOI** - monamine oxidase inhibitors; **IR** - immediate release; **SR** - sustained release

improvement with gabapentin when measuring pain via the VAS[284]. Pregabalin, a new GABA analog similar to gabapentin has yet to be studied in CRPS, but may show similar results to gabapentin.

e. Calcitonin and bisphosphonates

Calcitonin is a hormone secreted by the parafollicular cells of the thyroid gland. It acts on bone and kidneys to inhibit osteoclastic bone resorption and thereby reduces serum calcium and phosphate[275]. Gobelet et al. examined the efficacy of intranasal calcitonin in 63 patients with CRPS in a double-blind randomized study[285]. Treatment efficacy was assessed by pain at rest and during active movement, range of motion (ROM), degree of edema, and ability to work. At study conclusion, the treatment group showed significant reduction in pain at rest ($p < 0.007$), pain at motion ($p < 0.04$) and an increase in mobility ($p < 0.04$). Moreover, patients with CRPS of the wrist reported significant improvement ($p < 0.03$) in their ability to return to work, while those with CRPS of the ankle failed to show significant improvement and were not able to return to work[285]. A meta-analysis of RCTs on pharmacologic treatments for CRPS by Perez et al. concluded that calcitonin may provide effective pain relief in this group of patients[286].

Bisphosphonates, pyrophosphate analogues have recently been promoted as effective agents for the treatment of CRPS. For instance, clodronate, pamidronate, and alendronate have been tested in recent RCTs[275]. Patients with CRPS do manifest some degree of regional osteoporosis in the involved extremity, and some researchers hypothesize that the antinociceptive effect of bisphosphonates relate to their capacity to inactivate osteoclasts and antagonize osteoclastogenesis[275]. Verenna et al. demonstrated that intravenous clodronate produced significant improvements in VAS pain ($p = 0.002$ and clinical global assessment ($p = 0.001$) in a small ($n = 32$) randomized, double-blind, placebo controlled trial[287]. Other studies support the benefit of bisphosphonates for the treatment of CRPS[288-290].

11. Failed back surgery syndrome (FBSS)

Failed back surgery syndrome (FBSS) or post-laminectomy pain syndrome describes a clinical syndrome in which patients report persistent back and/or leg pain subsequent to one or more surgical procedures performed to correct their lumbosacral spine disease [291]. Furthermore, FBSS may reflect a failure of outcome agreement between patient and surgeon prior to the procedure, resulting from an incorrect initial diagnosis, poor patient selection, incomplete decompression, or decompression at the incorrect level. The syndrome may result in recurrent disk herniation,

segmental spinal instability, facet joint disease, permanent nerve root damage, epidural fibrosis, or arachnoiditis[292-295]. Many of these pathologic processes can produce neuropathic pain. FBSS patients who have experienced neuropathic pain and/or radicular symptoms prior to surgery may continue to suffer from the same symptoms after the procedure which typically persist and lead to debilitating pain as well as a reduced quality of life[296]. Medical management of FBSS depends on the primary symptoms that the patient exhibits. That is, patients may present with radicular symptoms, low back pain, or both. Pharmacologic intervention should follow the treatment for either low back pain or primary peripheral neuropathic pain to include NSAIDS[297-300]. Clinical studies support the use of antiepileptic medications[3,6,298], antidepressants[299, 301, 302], and opioids[275, 299, 303] for the treatment of low back pain or neuropathic pain, and can be applied to the treatment of FBSS patients. Interventionally, stimulation represents a procedure that clinicians may incorporate into FBSS treatment. For instance, Kumar et al. compared conventional medical management to spinal cord stimulation for the treatment of FBSS and found in favor of spinal cord stimulation[296]. More advanced strategies for FBSS will be discussed in the following section entitled, "*I*nterventional Techniques for Neuropathic Pain."

12. Interventional techniques for neuropathic pain

Interventional strategies can be employed in managing neuropathic pain when conventional medical management fails to achieve treatment goals (Figure 2). These strategies include multiple neuromodulatory techniques (e.g., epidural injections, nerve blocks, spinal cord stimulation, and intrathecal drug delivery systems). Practitioners may even incorporate interventional techniques and pharmacologic strategies concurrently. Either way, the goal remains to achieve adequate pain relief, functional improvement, and a satisfactiory quality of life. We present the following neuropathic pain conditions with proposed interventional strategies that may be useful in management.

A. Failed back surgery syndrome (FBSS)

1. Epidural steroid injections

Neuropathic pain associated with FBSS results in part from proinflammatory substances that extrude from the nucleus pulposus into the spinal canal after surgery. These foreign proteins initiate an inflammatory and immunologic response that causes nerve root irritation. Inflammation renders the nociceptors or nociceptive axons more sensitive to mechanical stimuli such as pressure or movement. Fibrous tissue may entrap the nerve root creating pain on movement[304, 305]. The clinical hallmark of FBSS is chronic

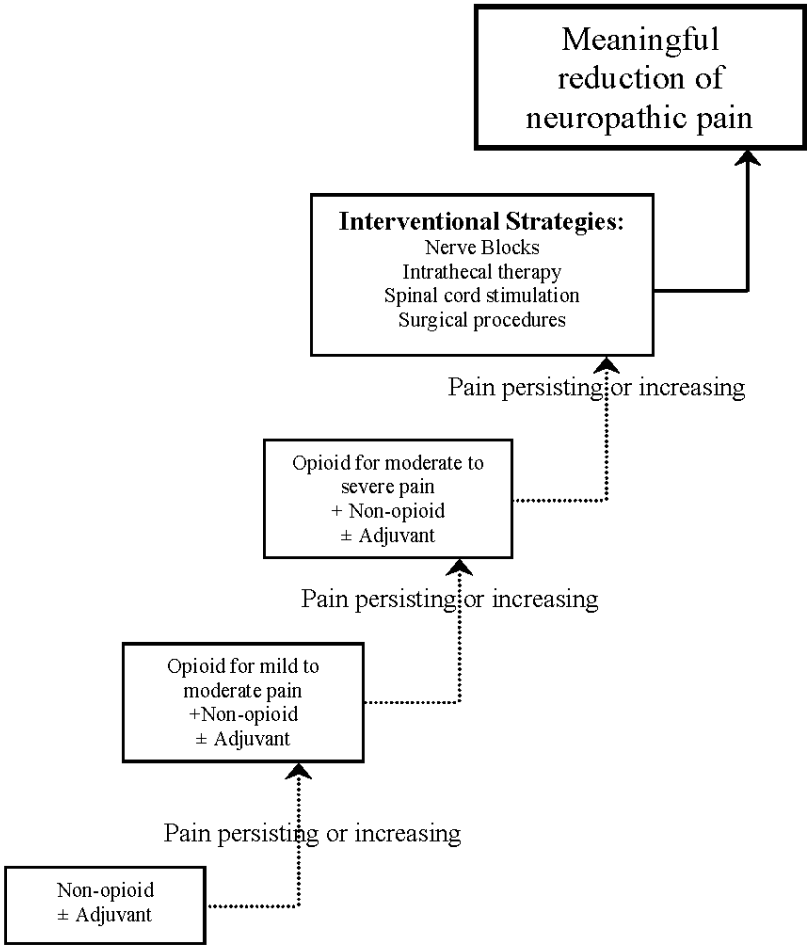

Figure 2. Analgesic Ladder for Neuropathic Pain.

postoperative pain. Two types of pain may be present: *mechanical* which is exacerbated by weight-bearing activities such as standing and bending; and *neuropathic* which is a more constant, insidious pain typically located in a radicular distribution[306]. The back and lower extremities represent the most common location of chronic neuropathic pain[5, 296] and 10–40% of patients undergoing lumbosacral spine surgery to alleviate neuropathic radicular pain experience persistent or recurrent pain instead of pain relief[296, 307]. Interlaminar and transforaminal epidural steroid injections can provide diagnostic information on the etiology of continued pain after surgery,[308] or may identify a specific spinal nerve as a pain generator because there may be poor concordance between radicular symptoms and standard dermatomal maps in as many as 20% of patients[309-311]. Imaging modalities alone may fail to identify a specific etiology in FBSS[312]. Some suggest that revision surgery may be necessary to confirm or refute the diagnosis of FBSS. Neither surgery nor imaging modalities provide an opportunity for the patient to provide feedback

in terms of pain relief[308]. Studies of lumbar interlaminar and transforaminal injections for lower back pain and leg pain have produced equivocal outcomes[313-315]; therefore, additional studies are needed better examine the effectiveness of epidural steroid injections for patients with FBSS.

B. Postherpetic neuralgia (PHN)

1. Neuraxial steroids

Trials have investigated the utility of steroids administered to the epidural space. Such injections theoretically reduce inflammation at the dorsal root ganglion, a process which may be a causative factor for the development of postherpetic neuralgia[316-318]. Kotani et al. injected intrathecal methylprednisolone acetate as a treatment intervention for intractable pain associated with postherpetic neuralgia[319]. The primary outcome measures included severity of burning and lancinating pain, and dynamic allodynia on a 10-cm visual-analogue scale. At study conclusion, the burning, lancinating and allodynic component were significantly less in the steroid-treated groups compared to placebo ($p < 0.001$). Furthermore, global pain relief was significantly improved ($p < 0.001$) and diclofenac use was decreased as well ($p < 0.001$)[319]. Pasqualucci et al. reported significant pain reduction in patients treated with epidural local anesthetic and methylprednisolone along with a substantial reduction in the number of patients who progressed to PHN from acute herpes zoster [320]. In contrast, van Wijck et al. investigated the efficacy of epidural steroid injection in an open label, randomized multicenter trial (n = 598) for the prevention of postherpetic neuralgia in older patients with herpes zoster[317]. Primary endpoint included the presence of zoster-associated pain one month after inclusion. At one month after inclusion, 48% of patients in the epidural group reported zoster-associated pain compared with (58%) in the control group (RR 0.83, 95% CI 0.71–0.97, $p = 0.02$). The NNT at one month was 10. At three months and at six months, the modest difference between the treatment and control groups diminished to 21% vs. 24% (RR 0.89, 95% CI 0.65-1.21, $p = 0.47$ and 15% vs. 17% (RR 0.85, CI 0.57–1.13, $p = 0.43$), respectively. The authors indicate that there was no difference in progression to PHN between the epidural and control groups[317].

2. Sympathetic blockade

Traditionally, clinicians have performed sympathetic blocks for patients with herpes zoster and PHN. The therapeutic goals have been threefold: pain relief during acute herpes zoster, pain relief during PHN, and PHN prevention by treating acute zoster[321]. However, clinicians may limit the use of sympathetic

blocks for persistent PHN given the lack of sufficient evidence for their efficacy, and instead consider sympathetic blockade for occasions when short-term relief is an important treatment goal[321-323]. Winnie et al. reported that sympathetic blocks (e.g., stellate ganglion/epidural/paravertebral/intercostal) may assist in treating the pain of herpes zoster or intractable PHN[316]. Although such therapies may help reduce pain, they have been associated with disappointing results. For instance, as many as 50% of patients fail to experience acceptable pain relief following sympathetic blockade. Hence, it is likely that the most effective future treatment for this disease may focus less on procedural interventions and more on prevention of both varicella zoster infection and herpes zoster infection with their respective vaccines[324].

C. Trigeminal neuralgia

1. Nerve blocks

Medical management remains the treatment of choice for trigeminal neuralgia (TN). In the event that medical management fails to relieve the symptoms or unacceptable side effects occur from pharmacotherapies, interventional options are available. For example, both percutaneous procedures and surgical procedures exist. Such strategies include radiofrequency ablation of the trigeminal nerve, fogarty balloon compression, neurolytic block (e.g., glycerol and alcohol), microvascular decompression and teflon padding, and gamma knife radiosurgery. The percutaneous procedures may produce procedure-related sensory deficits by creating lesions at the trigeminal nerve or trigeminal ganglion[325]. Non-ablative techniques include the use of local anesthetics, either at the trigeminal ganglion or post ganglion. For instance, Han et al. in a case-series (n = 35) examined the efficacy of high concentration lidocaine for the treatment of trigeminal neuralgia[326]. Ten percent lidocaine was injected after appropriate test dose at either the gasserian ganglion or appropriate pain-generating branch. The outcome measure included pain at 24 hrs following the block, and patients were followed for a mean of 43 months. The authors reported success (e.g., favorable results) as complete pain relief or mild pain without medication 1 day following treatment. Success was achieved in 12/35 patients (34.3%). The duration of pain relief in responders was reported to be between 3 weeks and 172 weeks (mean 79 weeks)[326]. In a case series of three patients receiving peripheral nerve blocks for TN, all patients reported pain relief beyond 3 months with a mixture of tetracaine and bupivacaine[327]. More rigorous RCTs of high concentration local anesthetic to the trigeminal ganglion must be conducted before application of this procedure is routinely adopted.

D. Peripheral neuropathy (PN)/diabetic peripheral neuropathy (DPN)

Multiple interventional techniques can be applied to relieve pain associated with peripheral neuropathies. For instance, paravertebral sympathetic blocks may be beneficial in relieving the pain associated with DPN. One published case report highlights the value of lumbar sympathetic blockade for the treatment of DPN and describes the patient's ability to return to daily activities with near complete resolution of lower extremity pain [328]. Typically, patients with DPN may require several lumbar sympathetic blocks for continued relief and although lumbar sympathetic blocks may provide short-term benefit, they may not be practical in many clinical settings. Moreover, the procedure is not without possible complications (e.g., infection, bleeding, orthostatic hypotension, perforation of abdominal viscera) therefore, it may be reserved for intractable cases.

Advanced strategies for the treatment of neuropathic pain

A. Spinal cord stimulation (SCS)

Despite advances in pharmacotherapy for neuropathic pain, less than half of patients achieve significant benefit with any pharmacological agent [5-7]. When sufficient pain relief is not achieved by pharmacological therapies, spinal cord stimulation serves as an alternative or supplement to medical management for treating patients with chronic intractable neuropathic pain[296, 329-335]. The proposed mechanism of SCS began with the "gate theory" advanced by Melzack and Wall in 1965[336]. Specifically, the "gate" represents the termination of painful peripheral stimuli carried by C fibers (e.g., burning sensation) and thinly myelinated A-δ fibers (e.g., sharp, intense, tingling sensation) in the dorsal horn of the spinal cord. Large, myelinated A-β fibers (e.g., light touch, pressure, vibration or hair movement) also terminate in the dorsal horn. Melzack and Wall hypothesized that sensory input could be manipulated in order to close the "gate" to the transmission of painful stimuli. The mechanisms by which dorsal column stimulation modulate pain perception have yet to be fully elucidated; however, current understanding attributes pain reduction to the activation of large-diameter afferent fibers (e.g., A-β fibers) by electrical stimulation. In addition, neurochemical modulation may play a role in the mechanism of action of dorsal column stimulation[337]. For instance, Stiller et al. examined extracellular [gamma]-aminobutyric acid (GABA) levels in the lumbar dorsal horn of allodynic rats. Utilizing a constrictive sciatic nerve injury model,

concentrations of GABA were analyzed with spinal cord electrode leads[338]. The investigators found that extracellular GABA levels were significantly lower ($p < 0.001$) in rats with sciatic nerve lesions and allodynia (2.3 ± 0.5 nmol/L) than in control rats with intact sciatic nerves (8.1 ± 1.0 nmol/L. In non-allodynic rats, only a slight decrease in GABA levels was observed (5.7 ± 1.1 nmol/L). Among allodynic rats that responded to SCS by normalization of the tactile withdrawal threshold, GABA levels were significantly increased (6.7 ± 2.3 nmol/L; $p < 0.001$) after SCS[338]. Other neurochemical mechanisms of pain modulation associated with SCS include increased levels of substance P, serotonin, and glycine[337]. Also, adenosine delivered intraveneously or intrathecally has been shown to abolish neuropathic pain acutely[339] and spinal cord stimulation induces adenosine production[337].

The salutary effects of SCS are not equivalent for both acute and chronic pain,[337] nor does it affect nociceptive pain, neuropathic pain, or sympathetically mediated pain equally[329]. If cancer pain is believed to be predominantly nociceptive, it would respond poorly to stimulation of the dorsal columns[329]. In contrast, cancer-induced neuropathic pain may respond to SCS.

In general, SCS can most effectively relieve symptoms such as burning pain and allodynia, and relief may persist beyond active stimulation[337]. Some evidence suggests that several neuropathic pain conditions may respond to SCS therapy including CRPS, FBSS, DPN, and PHN.

1. Diabetic peripheral neuropathy

Spinal cord stimulation has established efficacy for the treatment of peripheral neuropathic pain and peripheral ischemic pain [340]. At least two published studies report favorable results with SCS in the treatment of DPN[341, 342]. Prevention, however remains the principle therapeutic tool against DPN. Because diabetic neuropathy tends to progress, patients may lose initial paresthesia coverage provided by the spinal cord stimulator, thus rendering the treatment less effective in time.

2. Failed back surgery syndrome (FBSS)

Ten to 40% of patients who have undergone lumbosacral spine surgery in the United States experience persistent or recurrent pain[307, 343-347]. Multiple studies have been conducted examining SCS and FBSS. Success rates in long-term studies for FBBS and SCS range between 40% to 60%[294, 348, 349], though most are case series. Few RCTs exist and most studies rank at level IV or level V in quality of evidence. Higher quality studies do exist, however.

For instance, North et al. conducted a randomized prospective crossover study and examined spinal cord stimulation versus reoperation utilizing frequency of crossover to the alternative procedure as the outcome measure[350]. Study patients complained of persistent radicular pain after spine surgery. Some patients suffered from concomitant low back pain and others did not. At 6 months, the authors reported a statistically significant crossover rate from reoperation to spinal cord stimulation ($p = 0.018$)[350]. A prospective multicenter trial by Burchiel et al. investigated the efficacy of spinal cord stimulation for chronic back and extremity pain[330]. Outcome measures included patient self-report and multiple other assessment tools: visual analogue scale, McGill Pain Questionnaire, Oswestry Disability Questionnaire, and Beck Depression Inventory. Fifty-six percent of study subjects reported at least 50% pain relief at the 1-year follow-up, and VAS pain scores decreased by 14% ($p < 0.0005$) compared to pre-implantation levels. Patient ratings of pain relief from SCS included: good or excellent – 35%, fair – 43%, poor – 20%, and no pain relief – 2%. Work status and opioid use did not significant change from pre-implantion values. The authors concluded that SCS is associated with improvements in multiple dimensions of the pain experience including quality-of-life measures such as sleep, depression and mobility. Further support for SCS derives from another RCT by North et al. in which they evaluated the effectiveness of SCS versus reoperation in 50 patients with previous lumbosacral spine surgery[344]. Fourteen out of 26 (54%) reoperation patients crossed over to SCS, and only 5/24 (21%) patients that were randomized to SCS crossed over to reoperation ($p < 0.02$). Nine of nineteen patients randomized to SCS (47%), and 3/26 (12%) of patients randomized to reoperation achieved ≥ 50% pain relief and were satisfied with treatment ($p < 0.01$). Fifteen patients randomized to SCS received an implant and did not crossover. Nine of 15 (60%) were deemed long-term successes with respect to pain relief and patient satisfaction. Among the 12 patients randomized to reoperation who did not cross over, only 3 (25%) were considered long-term successes. The authors concluded that SCS is more effective than reoperation for persistent radicular pain following lumbosacral spine surgery.

More recently, a multicenter randomized controlled trial by Kumar et al. evaluated the effectiveness of SCS versus conventional medical management (CMM) in patients with failed back surgery syndrome[296]. Primary outcome measure included the proportion of patients achieving ≥ 50% relief of leg pain at 6 months. Secondary outcomes variables included improvement in back and leg pain, health-related quality of life, and functional capacity. In addition, the authors examined patient

satisfaction and incidence of adverse effects. One hundred patients were randomized to either SCS or CMM and 52 patients were included in the SCS group and 48 in the CMM group. Nine of the 52 patients randomized to the SCS group failed to achieve ≥ 50% leg pain relief or 80% paresthesia coverage during the screening trial (5 of these 9 patients still requested implantation). Crossover data indicate that at 6 months, 5/50 SCS patients and 32/44 of the CMM patients crossed over to the alternate arm. Twenty-eight of the 32 CMM patients that crossed over to SCS were implanted. Twenty-four of the 50 patients who were primary implants achieved ≥ 50% leg pain relief compared to 4/44 of the primary CCM group who achieved ≥ 50% leg pain relief ($p < 0.001$, CI 99%). At 12 months, 48% of patients implanted achieved ≥ 50% leg pain relief and 18% of CMM patients achieved ≥ 50% leg pain relief ($p = 0.03$)[296]. Moreover, secondary outcome measures (e.g., improvement in back and leg pain, health related quality of life, and functional capacity; change in the use of pain medication and non-drug pain therapy; patient satisfaction with treatment; and incidence of adverse effects) mirrored the results of the primary outcome measures. The authors concluded that spinal cord stimulation provides better pain relief, better health-related quality of life, and improved functional capacity compared to traditional strategies for medical management.

3. Complex regional pain syndrome (CRPS)

Conventional pain medications, physical therapy, sympathetic blockade, and transcutaneous electrical nerve stimulation all represent modalities applied to the reduction of the intense pain caused CRPS with less than favorable results[333, 351, 352]. Among CRPS patients, only one in five is capable of returning to a normal level of functioning[333, 353]. CRPS symptoms rank as the second most frequent indicator for SCS therapy in the USA (FBSS ranks as the first indication), and pain relief as high as 70% has been reported with neurostimulation (e.g., SCS or peripheral nerve stimulation) when patients are properly selected[354-356]. Expert opinion suggests that SCS should be considered in the treatment algorithm when conservative or traditional therapies fail[354].

The literature supports the use of SCS in CRPS. For example, Kemler et al. studied the effectiveness of spinal cord stimulation and physical therapy versus physical therapy alone in CRPS affected patients[333]. Thirty six patients with diagnosed CRPS of either one hand or foot that was present for ≥ 6 months were included. Outcome variables included pain intensity, global perceived effect, functional status, and health-related quality of life. At 6 months, the SCS + physiotherapy group reported a significantly greater reduction in pain (mean reduction of 2.4 cm) on the VAS compared to the

physiotherapy alone group (mean increase of 0.2 cm) ($p < 0.001$). Further, the SCS + physiotherapy group reported a greater percentage improvement on the global perceived effect (39 percent vs. 6 percent, $p = 0.01$) assessment. Another study by Harke et al. evaluated the long-term effect of SCS on improvement in functional status for patients with CRPS, Type I[357]. The authors hypothesized that patients with sympathetically-maintained pain diagnosed by successful sympathetic blockade would achieve a better outcome with SCS. Accordingly, a positive response to sympathetic blockade could be used as a prognostic indicator for successful SCS therapy. The study included 29 patients with sympathetically maintained CRPS, Type I. Outcome measures included pain intensity, allodynia, PDI, drug consumption, functional status of the limbs, back-to-work rate, and technical status of the device. Twelve month outcomes showed a reduction in mean deep pain as reported by VAS from 9.4 cm to 1.7 cm and mean allodynia from 7.2 cm to 0.03 cm. Furthermore, an "inactivation test" (e.g., cessation of SCS stimulation) caused deep pain as noted on VAS to escalate from a mean of 1.7 cm with SCS stimulation, to 7.1 cm with SCS inactivation. Also, an increase in allodynia from a mean VAS of 0.3 cm to 4.0 cm occurred with cessation of stimulation. Following SCS inactivation, the affected regions showed a mean skin temperature decline of 1.5 ^{o}C, compared to the contralateral (e.g., non-affected) areas. At study termination (mean 35.6 ± 21 months), SCS- treated patients reported sustained reduction in both deep pain (9.4 cm to 2.1 cm) and allodynia (7.2 cm to 0.0 cm) on the visual analogue scale (VAS) ($p < 0.01$) and a significant decrease in pain disability index (PDI) scores $p < 0.01$) compared to the period prior to SCS treatment. Importantly, 12/16 patients (75%) with impaired hand and finger function regained functional activity to near normal levels including increased grip strength to almost 50% of normal values ($p < 0.01$). Eight of ten patients (80%) with an affected lower extremity were able to resume ambulation without crutches and 70% were able to return to work. Finally, 17/29 (59%) of SCS-treated patients no longer required pain medication during stimulation periods, and a 70% back-to-work rate was observed. The authors concluded that in patients with CRPS Type I, long-term use of SCS combined with physiotherapy may improve functional status and quality of life[357].

Multiple cases series and a meta-analysis support the use of SCS for treatment of CRPS. For instance, Taylor conducted a meta-analysis of CRPS using the Harbour and Miller Scale for grading recommendations in evidence-based guidelines[358]. His analysis included 1 RCT, 25 case series, and one cost analysis. Spinal cord stimulation for CRPS, Type I was given grade A evidence (strong), and SCS for CRPS, Type II grade D evidence (weak)[334]. It seems reasonable to suggest that patients with CRPS, Type I

who fail previous pharmacological and interventional therapies should be considered for a trial of spinal cord stimulation.

4. Postherpetic neuralgia (PHN)

There is some evidence supporting the use of SCS for herpes zoster and post-herpetic neuralgia. For example, Meglio et al. retrospectively analyzed the results of 10 patients suffering from postherpetic neuralgia treated with spinal cord stimulation[359]. Six of ten patients underwent implantation and at mean follow-up of 15 months, all 6 patients were still reporting satisfactory pain relief with SCS. Harke et al. examined the effectiveness of SCS in 28 patients with intractable pain secondary to post-herpetic neuralgia and in 4 patients with herpes zoster[335]. Both VAS and Pain Disability Index (PDI) were investigated along with consumption of analgesics, antidepressants, and anticonvulsants. The efficacy of the SCS was assessed by an inactivation test. Prior to SCS, the investigators conducted sympathetic blocks and obtained favorable responses in all patients who were subsequently implanted. All PHN and HZ patients were implanted. At study end twenty-three of 28 PHN patients with SCS reported long-term pain relief and median VAS reduction from 9.0 cm to 1.0 cm (quartiles 1.0–2.75) for burning, lancinating, and allodynic pain even at a median stimulation period of 29 months. Furthermore, an inactivation test (e.g., cessation of SCS stimulation) caused a VAS increase from 1.0 cm to 7.0 cm. Responders showed significant improvement in PDI ($p < 0.001$) and only one prescription opioid was continued during the stimulation period ($p = 0.002$). Among the herpes zoster patients, all were implanted and responded favorably, reporting a decrement in median VAS values from 9.0 to 0.0 at study completion. The investigators concluded that SCS was an effective long-term treatment for medical non-responders with intractable pain secondary to post-herpetic neuralgia and herpes zoster[335].

B. Implantable drug delivery system (IDDS)

The first clinical use of an implantable intrathecal opioid delivery device occurred in 1981 for the treatment of chronic malignant pain [360, 361], though trials of opioids for intractable cancer pain were begun by Wang in 1979[362]. Intrathecal medications for pain control were studied in malignant pain conditions because progression of solid organ tumors required large dose escalations of systemic medications to provide analgesia. Opioid escalation raised concerns of adverse effects such as drowsiness, respiratory depression, physical dependence, tolerance, lack of efficacy, and addiction. Intrathecally delivered medications however, could significantly reduce the systemic side effects of medications by delivering small doses of medication to its site of action in the spinal cord called the substantia gelatinosa.

The burden of chronic pain is experienced by about one-third of all cancer patients, and 70-90% of those with advanced disease[363, 364]. For example, Ground et al. found that 64.1%, 5.4% and 30.5% of study participants experienced cancer related nociceptive, neuropathic, and mixed (e.g., neuropathic and nociceptive) pain, respectively[247]. Application of the WHO principles of systemic opioid therapy in combination with adjuvant drugs can provide adequate analgesia in 75% to 95% of all patients with cancer pain[257]. Yet, approximately 2% to 15% of cancer patients suffer unrelieved and refractory pain and require advanced techniques such as adjunctive medications, nerve/neurolytic blocks, or implantable drug delivery systems (IDDS)[257, 365-368]. Currently, clinicians use IDDSs to help control both malignant and non-malignant pain conditions. An important challenge for the intrathecal delivery of medications relates to correctly targeting and modulating specific receptor sites in the spinal cord for even better analgesia and fewer adverse effects. The only drugs approved by the FDA for use intrathecally include morphine and ziconitide, although hydromorphone, fentanyl, bupivacaine and the alpha-2 agonist, clonidine are routinely used in clinical practice. While evidence exists for long-term efficacy of intrathecal analgesics, proper patient selection remains critical and must be predicated on objective evidence of nonreversible pathology, coupled with a failure to achieve adequate analgesia from oral/systemic therapies and/or an inability to withstand the side-effects of conventional therapies.

In an RCT of 200 patients with advanced cancer and refractory pain, Smith et al. compared IDDS with medical management to medical management alone and demonstrated the effectiveness of intrathecal opioid therapy [366]. The primary outcome measure included at least a 20% reduction in the VAS pain scores from baseline. Also investigators compared quality of life in patients and caregivers by Brief Pain Inventory, SF-12 Health Survey, and Caregiver Quality of Life. Mortality was followed to identify any detrimental effects of therapy on survival, but was not a stated end point of the trial. The distribution of nociceptive, neuropathic pain, and mixed pain states for the medical management group was 14.3%, 25.5%, 60.2% respectively, and 12.9%, 25.7%, and 61.4% respectively for the IDDS plus medical management group. The results from the study indicated that 60/71 (84.5%) of the IDDS patients achieved clinical success (e.g., greater reduction in pain and toxicity) compared to 51/72 (70.8%) of the medical management group ($p < .05$). Further, IDDS patients reported a significant decrease in fatigue and an elevated level of consciousness ($p < .05$) compared with the CMM group. Most striking was the difference in the estimated cumulative survival. Nearly fifty-four percent (53.4) of the IDDS group were alive at 6 months compared to 37.2% in the CMM group ($p = .06$)[366].

Presumed reasons for the increased survival among the IDDS group focused on their ability to increase their activity level which lead to a decrease in the incidence of pulmonary emboli and improved nutrition. The authors noted that an enhanced quality of life may have lead to a greater "will to live" among the IDDS group. Positive results from retrospective studies, case series, and a meta-analysis also reflect the benefit of intrathecal therapies for refractory cancer pain[367, 369, 370].

There is broad understanding of oral and intravenous opioid administration for pain relief, but the systemic side effects of opioids often limit their use[371]. Properly dosed intrathecal opioids may circumvent the limitations of oral and intravenous agents including opioid-induced hyperalgesia[372]. Growing application but limited evidence for intrathecal opioid administration in non-malignant pain conditions exist. For example, Anderson et al. studied 40 patients with severe, chronic nonmalignant pain that was poorly managed by systemic medications, and evaluated the long-term efficacy of IT morphine[373]. Thirty patients were trialed and responded to intrathecal morphine and were subsequently implanted with permanent drug delivery systems. Among the 30 patients, 1/30 (3%) reported intractable nociceptive pain, 10/30 (33%) reported intractable neuropathic pain, 15/30 (50%) reported intractable mixed nociceptive/neuropathic pain, and 4/30 (13%) reported deafferentation pain. Included within the patient population were 14 patients diagnosed with FBSS. The primary outcome measures included VAS pain scores and the McGill Pain Questionnaire (MPQ). The initial mean VAS was 78.5 ± 15.9 (39-100) and pain was assessed at 3, 6, 12, and 18 months intervals. The decline in VAS was more significant at the 3, 6, 12, and 18 month intervals ($p < 0.0001$) than when the study ended at 24 months with a VAS of 58.5 ± 24.63 ($p = 0.002$). The initial MPQ score was 20.17 ± 8.78 and at study end, the initial significance had declined to 17.80 ± 9.22 ($p = 0.1$)[373]. The investigators concluded that continuous intrathecal morphine is efficacious and can result in long-term improvement in several areas of daily function for the management of severe, nonmalignant pain.

Another study of severe, chronic, nonmalignant pain trialed 25 patients with intrathecal morphine and 16 responded favorably and were subsequently implanted with infusion pumps[374]. Three of 16 patients (19%) reported intractable nociceptive pain, 4 (25%) reported intractable neuropathic pain, 8 (50%) reported intractable mixed nociceptive/neuropathic pain, and 1 (6%) reported deafferentation pain. Outcome measures included VAS, MPQ, activity level, and additional medication use along with IT opioid treatment. The initial mean VAS was 91.8 ± 2.8 and at study conclusion (mean 29.14 months ± 12.44 months), the mean VAS score had dropped to 34.3 ± 13.2 ($p = 0.0026$). At last follow up, the nociceptive pain group reported pain

relief of 57% the neuropathic group 37% relief, mixed group 61% relief, and the deafferentation group 75% relief. Furthermore, patients increased their daily activity compared to the period prior to IT therapy. The authors concluded that intrathecal opioids were important for the long-term management of intractable, non-malignant pain states.

A systematic review by Turner highlighted the effectiveness and possible complications associated with programmable IDDSs using opioids or ziconotide, and reported their effects on pain and functioning[375]. Six observational studies were identified and deemed suitable for inclusion in the review. Four of the studies included FBSS patients along with other pain diagnoses, and 2 studies included just FBSS patients. None of the ziconitide studies included in the review met inclusion criteria. All six of the studies showed improvements on a 0 to 100 mm VAS, with a mean (weighted) pre-IDDS rating of 82, and post-IDDS ratings of 45 at 6 months and 44 at 12 months follow up. Moreover, all 6 studies reported improvements in physical functioning compared to baseline[375]. Success rates, defined as the proportion of patients with greater than or equal to 50% relief ranged from 38%-56% at 6 months to 30%-44% at longer follow up intervals. The authors concluded that IDDSs provide improvement in non-malignant pain conditions, but acknowledged the uncertainty of long-term benefits on pain due to the lack of data that extends beyond one year.

13. Combination therapy

Due to the diversity of underlying pathologic processes, patient populations, and manifestations of painful conditions, it is impossible to predict with certainty which patients will benefit from specific therapies. Although there are many pharmacologic and interventional therapies available, it is estimated that only 50-70% of neuropathic pain is sufficiently relieved by current treatments[376, 377]. The 30-50% of patients who fail to achieve adequate relief or who sustain dose-related adverse effects may benefit from combination therapy. Clinicians should consider drugs from diverse medication classes to enhance efficacy in treating neuropathic pain. First line medications may fail to provide satisfactory pain relief and dose escalations may lead to side effects. Therefore, practitioners should consider adding additional first line medications and then second line medications if patients fail to report sufficient analgesia. Certain medications may need to be discontinued if adverse effects cannot be managed or if they fail to provide adequate pain relief. Refractory pain necessitates additional treatment strategies including medications listed in the “other” category and/or interventional techniques.

14. Conclusion

The varied etiologies and manifestations of neuropathic pain require the selection of treatment strategies that focus on functional restoration and meaningful pain relief. No singular medication or procedural intervention has shown promise in treating all neuropathic pain conditions. Many medications in the pain armamentarium are indicated for the treatment of other disease states, but a growing evidence base in the literature supports their application for neuropathic pain. We have developed certain algorithms for treatment that can serve as a framework for clinicians and patients in their quest to alleviate persistent and disabling neuropathic pain. Key points in the sequence of treating neuropathic pain are listed in Table 9.

In general, first line medications offer the best established efficacy in various neuropathic conditions, and a favorably side effect profile. These include gabapentin, pregabalin, and TCAs. Serotonin-Norepinephrine Reuptake Inhibitors show equal promise in the treatment of neuropathic pain and are recommend as a first line medication in most neuropathic pain states. Carbamazepine is the drug of choice for the treatment of TN. Lidocaine 5% patch carries an FDA indication for the treatment of PHN and is recommended as a first line agent, though it fails to show equal efficacy in other NP conditions. Second line and "other" medications may show promise in treating neuropathic pain and should be considered when first-line medications fail or in combination therapy.

Interventional strategies for treating neuropathic pain can offer pain amelioration and improvement of functional status. These strategies include spinal cord stimulation, implantable drug deliver systems, and neural blockade. Such modalities are often employed when medical management fails, but practitioners may consider joint therapy with both pharmacologic and interventional strategies as a means of earlier and more effective analgesia.

The control of neuropathic pain requires a multidisciplinary approach involving physiotherapy, pharmacotherapy, psychology and procedural interventions. Future management will focus on targeted therapies that modulate specific mechanisms involved in each neuropathic pain condition.

Table 9. Key Points in the Treatment of Neuropathic Pain.

• Expectation setting with realistic treatment goals
• Multimodal treatment plan (pharmacological management, physical therapy, emotional support (e.g., pain psychology), interventional strategies)
• Adequate trial of medications
• Mechanistically-based treatment strategies
• Cycling first line medications and combination therapy
• Prevention (e.g., VZV vaccine, glycemic control)

References

1. Campbell, J.N. and R.A. Meyer, *Mechanisms of neuropathic pain.* Neuron, 2006. **52**(1): p. 77-92.
2. Horowitz, S.H., *The diagnostic workup of patients with neuropathic pain.* Med Clin North Am, 2007. **91**(1): p. 21-30.
3. Tremont-Lukats, I.W., C. Megeff, and M.M. Backonja, *Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy.* Drugs, 2000. **60**(5): p. 1029-52.
4. Jensen, T.S. and R. Baron, *Translation of symptoms and signs into mechanisms in neuropathic pain.* Pain, 2003. **102**(1-2): p. 1-8.
5. Dworkin, R.H., et al., *Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations.* Arch Neurol, 2003. **60**(11): p. 1524-34.
6. Finnerup, N.B., et al., *Algorithm for neuropathic pain treatment: an evidence based proposal.* Pain, 2005. **118**(3): p. 289-305.
7. Attal, N., et al., *EFNS guidelines on pharmacological treatment of neuropathic pain.* Eur J Neurol, 2006. **13**(11): p. 1153-69.
8. Baron, R., *[Neuropathic pain. The long path from mechanisms to mechanism-based treatment].* Anaesthesist, 2000. **49**(5): p. 373-86.
9. Woolf, C.J. and M.B. Max, *Mechanism-based pain diagnosis: issues for analgesic drug development.* Anesthesiology, 2001. **95**(1): p. 241-9.
10. Tal, M. and G.J. Bennett, *Neuropathic pain sensations are differentially sensitive to dextrorphan.* Neuroreport, 1994. **5**(12): p. 1438-40.
11. Gallagher, R.M., *Management of neuropathic pain: translating mechanistic advances and evidence-based research into clinical practice.* Clin J Pain, 2006. **22**(1 Suppl): p. S2-8.
12. Flatters, S.J. and G.J. Bennett, *Ethosuximide reverses paclitaxel- and vincristine-induced painful peripheral neuropathy.* Pain, 2004. **109**(1-2): p. 150-61.
13. Lee, S.H., et al., *Differential action of morphine and various opioid agonists on thermal allodynia and hyperalgesia in mononeuropathic rats.* Pain, 1994. **57**(2): p. 233-40.
14. Xiao, W.H. and G.J. Bennett, *Synthetic omega-conopeptides applied to the site of nerve injury suppress neuropathic pains in rats.* J Pharmacol Exp Ther, 1995. **274**(2): p. 666-72.
15. Vadalouca, A., et al., *Therapeutic management of chronic neuropathic pain: an examination of pharmacologic treatment.* Ann N Y Acad Sci, 2006. **1088**: p. 164-86.
16. Forde, G., *Adjuvant analgesics for the treatment of neuropathic pain: evaluating efficacy and safety profiles.* J Fam Pract, 2007. **56**(2 Suppl Pain): p. 3-12.
17. Farrar, J.T., et al., *Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale.* Pain, 2001. **94**(2): p. 149-58.
18. Nasreddine, W. and A. Beydoun, *Oxcarbazepine in neuropathic pain.* Expert Opin Investig Drugs, 2007. **16**(10): p. 1615-25.
19. Sindrup, S.H. and T.S. Jensen, *Pharmacologic treatment of pain in polyneuropathy.* Neurology, 2000. **55**(7): p. 915-20.

20. Daousi, C., et al., *Chronic painful peripheral neuropathy in an urban community: a controlled comparison of people with and without diabetes.* Diabet Med, 2004. **21**(9): p. 976-82.
21. Davies, M., et al., *The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes.* Diabetes Care, 2006. **29**(7): p. 1518-22.
22. Tesfaye, S., et al., *Factors that impact symptomatic diabetic peripheral neuropathy in placebo-administered patients from two 1-year clinical trials.* Diabetes Care, 2007. **30**(10): p. 2626-32.
23. Quattrini, C. and S. Tesfaye, *Understanding the impact of painful diabetic neuropathy.* Diabetes Metab Res Rev, 2003. **19 Suppl 1**: p. S2-8.
24. Tesfaye, S., *Advances in the management of painful diabetic neuropathy.* Clin Med, 2007. **7**(2): p. 113-4.
25. Harris, M., R. Eastman, and C. Cowie, *Symptoms of sensory neuropathy in adults with NIDDM in the U.S. population.* Diabetes Care, 1993. **16**(11): p. 1446-52.
26. Low, P.A. and R.M. Dotson, *Symptomatic treatment of painful neuropathy.* Jama, 1998. **280**(21): p. 1863-4.
27. Smith, R.G., *Painful diabetic peripheral neuropathy.* J Am Podiatr Med Assoc, 2007. **97**(5): p. 394-401.
28. Research Group, D., *The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group.* Ann Intern Med, 1995. **122**(8): p. 561-8.
29. Sindrup, S.H., et al., *Antidepressants in the treatment of neuropathic pain.* Basic Clin Pharmacol Toxicol, 2005. **96**(6): p. 399-409.
30. Colombo, B., P.O. Annovazzi, and G. Comi, *Medications for neuropathic pain: current trends.* Neurol Sci, 2006. **27 Suppl 2**: p. S183-9.
31. Sawynok, J., M.J. Esser, and A.R. Reid, *Antidepressants as analgesics: an overview of central and peripheral mechanisms of action.* J Psychiatry Neurosci, 2001. **26**(1): p. 21-9.
32. Gordon, D.B. and G. Love, *Pharmacologic management of neuropathic pain.* Pain Manag Nurs, 2004. **5**(4 Suppl 1): p. 19-33.
33. Jackson, K.C., 2nd, *Pharmacotherapy for neuropathic pain.* Pain Pract, 2006. **6**(1): p. 27-33.
34. McQuay, H.J., et al., *A systematic review of antidepressants in neuropathic pain.* Pain, 1996. **68**(2-3): p. 217-27.
35. Sindrup, S.H. and T.S. Jensen, *Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action.* Pain, 1999. **83**(3): p. 389-400.
36. Max, M.B., et al., *Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy.* N Engl J Med, 1992. **326**(19): p. 1250-6.
37. Saarto, T. and P.J. Wiffen, *Antidepressants for neuropathic pain.* Cochrane Database Syst Rev, 2005(3): p. CD005454.
38. Goodman, L.S., et al., *Goodman & Gilman's the pharmacological basis of therapeutics*. 11th ed. 2006, New York: McGraw-Hill. xxiii, 2021 p.

39. Wong, D.T. and F.P. Bymaster, *Dual serotonin and noradrenaline uptake inhibitor class of antidepressants potential for greater efficacy or just hype?* Prog Drug Res, 2002. **58**: p. 169-222.
40. Dworkin, R.H., et al., *Pharmacologic management of neuropathic pain: evidence-based recommendations.* Pain, 2007. **132**(3): p. 237-51.
41. Khalifa, M., P. Daleau, and J. Turgeon, *Mechanism of sodium channel block by venlafaxine in guinea pig ventricular myocytes.* J Pharmacol Exp Ther, 1999. **291**(1): p. 280-4.
42. Verma, S. and R.M. Gallagher, *The psychopharmacologic treatment of depression and anxiety in the context of chronic pain.* Curr Pain Headache Rep, 2002. **6**(1): p. 30-9.
43. Sindrup, S.H., et al., *Venlafaxine versus imipramine in painful polyneuropathy: a randomized, controlled trial.* Neurology, 2003. **60**(8): p. 1284-9.
44. Mattia, C., et al., *New antidepressants in the treatment of neuropathic pain. A review.* Minerva Anestesiol, 2002. **68**(3): p. 105-14.
45. Namaka, M., et al., *A treatment algorithm for neuropathic pain.* Clin Ther, 2004. **26**(7): p. 951-79.
46. Goldstein, D.J., et al., *Duloxetine vs. placebo in patients with painful diabetic neuropathy.* Pain, 2005. **116**(1-2): p. 109-18.
47. Lilly, C.E. (2007) *Prescribing Information*. **Volume**,
48. Raskin, J., et al., *A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain.* Pain Med, 2005. **6**(5): p. 346-56.
49. Goodman, A., *Duloxetine Reported to be Effective Treatment for Diabetic Neuropathic Pain.* Neurology Today, 2005. **5**(5): p. 59-60.
50. Rowbotham, M.C., et al., *Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study.* Pain, 2004. **110**(3): p. 697-706.
51. Sindrup, S.H., et al., *The selective serotonin reuptake inhibitor paroxetine is effective in the treatment of diabetic neuropathy symptoms.* Pain, 1990. **42**(2): p. 135-44.
52. Collins, S.L., et al., *Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review.* J Pain Symptom Manage, 2000. **20**(6): p. 449-58.
53. Sindrup, S.H., et al., *The selective serotonin reuptake inhibitor citalopram relieves the symptoms of diabetic neuropathy.* Clin Pharmacol Ther, 1992. **52**(5): p. 547-52.
54. Chong, M.S. and J. Hester, *Diabetic painful neuropathy: current and future treatment options.* Drugs, 2007. **67**(4): p. 569-85.
55. Field, M.J., et al., *Gabapentin and pregabalin, but not morphine and amitriptyline, block both static and dynamic components of mechanical allodynia induced by streptozocin in the rat.* Pain, 1999. **80**(1-2): p. 391-8.
56. Backonja, M., et al., *Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial.* Jama, 1998. **280**(21): p. 1831-6.

57. Rosenberg, J.M., et al., *The effect of gabapentin on neuropathic pain.* Clin J Pain, 1997. **13**(3): p. 251-5.
58. Simpson, D., *Gabapentin and Venlafaxine for the Treatment of Painful Diabetic Neuropathy.* J Clin Neuromusc Dis 2001. **3**: p. 53-62.
59. Mellegers, M.A., A.D. Furlan, and A. Mailis, *Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature.* Clin J Pain, 2001. **17**(4): p. 284-95.
60. Fink, K., et al., *Inhibition of neuronal Ca(2+) influx by gabapentin and pregabalin in the human neocortex.* Neuropharmacology, 2002. **42**(2): p. 229-36.
61. Rosenstock, J., et al., *Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial.* Pain, 2004. **110**(3): p. 628-38.
62. Lesser, H., et al., *Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial.* Neurology, 2004. **63**(11): p. 2104-10.
63. Richter, R.W., et al., *Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial.* J Pain, 2005. **6**(4): p. 253-60.
64. Guay, D.R., *Adjunctive agents in the management of chronic pain.* Pharmacotherapy, 2001. **21**(9): p. 1070-81.
65. Blommel, M.L. and A.L. Blommel, *Pregabalin: an antiepileptic agent useful for neuropathic pain.* Am J Health Syst Pharm, 2007. **64**(14): p. 1475-82.
66. Leo, R.J., *Treatment considerations in neuropathic pain.* Curr Treat Options Neurol, 2006. **8**(5): p. 389-400.
67. Eisenberg, E., et al., *Antiepileptic drugs in the treatment of neuropathic pain.* Drugs, 2007. **67**(9): p. 1265-89.
68. Rull, J.A., et al., *Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial.* Diabetologia, 1969. **5**(4): p. 215-8.
69. Wilton, T.D., *Tegretol in the treatment of diabetic neuropathy.* S Afr Med J, 1974. **48**(20): p. 869-72.
70. Wiffen, P.J., H.J. McQuay, and R.A. Moore, *Carbamazepine for acute and chronic pain.* Cochrane Database Syst Rev, 2005(3): p. CD005451.
71. Mendell, J.R. and Z. Sahenk, *Clinical practice. Painful sensory neuropathy.* N Engl J Med, 2003. **348**(13): p. 1243-55.
72. Zakrzewska, J.M. and P.N. Patsalos, *Oxcarbazepine: a new drug in the management of intractable trigeminal neuralgia.* J Neurol Neurosurg Psychiatry, 1989. **52**(4): p. 472-6.
73. Dogra, S., et al., *Oxcarbazepine in painful diabetic neuropathy: a randomized, placebo-controlled study.* Eur J Pain, 2005. **9**(5): p. 543-54.
74. Grosskopf, J., et al., *A randomized, placebo-controlled study of oxcarbazepine in painful diabetic neuropathy.* Acta Neurol Scand, 2006. **114**(3): p. 177-80.
75. Beydoun, A., et al., *Oxcarbazepine in painful diabetic neuropathy: results of a dose-ranging study.* Acta Neurol Scand, 2006. **113**(6): p. 395-404.
76. Chadda, V.S. and M.S. Mathur, *Double blind study of the effects of diphenylhydantoin sodium on diabetic neuropathy.* J Assoc Physicians India, 1978. **26**(5): p. 403-6.

77. Saudek, C.D., S. Werns, and M.M. Reidenberg, *Phenytoin in the treatment of diabetic symmetrical polyneuropathy.* Clin Pharmacol Ther, 1977. **22**(2): p. 196-9.
78. Duby, J.J., et al., *Diabetic neuropathy: an intensive review.* Am J Health Syst Pharm, 2004. **61**(2): p. 160-73; quiz 175-6.
79. So, E.L. and J.K. Penry, *Adverse effects of phenytoin on peripheral nerves and neuromuscular junction: a review.* Epilepsia, 1981. **22**(4): p. 467-73.
80. Kochar, D.K., et al., *Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study.* Qjm, 2004. **97**(1): p. 33-8.
81. Kochar, D.K., et al., *Sodium valproate in the management of painful neuropathy in type 2 diabetes - a randomized placebo controlled study.* Acta Neurol Scand, 2002. **106**(5): p. 248-52.
82. Otto, M., et al., *Valproic acid has no effect on pain in polyneuropathy: a randomized, controlled trial.* Neurology, 2004. **62**(2): p. 285-8.
83. Otto, M., et al., *Health-related quality of life and its predictive role for analgesic effect in patients with painful polyneuropathy.* Eur J Pain, 2007. **11**(5): p. 572-8.
84. Eisenberg, E., et al., *Lamotrigine reduces painful diabetic neuropathy: a randomized, controlled study.* Neurology, 2001. **57**(3): p. 505-9.
85. Silver, M., et al., *Double-blind, placebo-controlled trial of lamotrigine in combination with other medications for neuropathic pain.* J Pain Symptom Manage, 2007. **34**(4): p. 446-54.
86. Vinik, A.I., et al., *Lamotrigine for treatment of pain associated with diabetic neuropathy: results of two randomized, double-blind, placebo-controlled studies.* Pain, 2007. **128**(1-2): p. 169-79.
87. Raskin, P., et al., *Topiramate vs placebo in painful diabetic neuropathy: analgesic and metabolic effects.* Neurology, 2004. **63**(5): p. 865-73.
88. Thienel, U., et al., *Topiramate in painful diabetic polyneuropathy: findings from three double-blind placebo-controlled trials.* Acta Neurol Scand, 2004. **110**(4): p. 221-31.
89. Chabal, C., L.C. Russell, and K.J. Burchiel, *The effect of intravenous lidocaine, tocainide, and mexiletine on spontaneously active fibers originating in rat sciatic neuromas.* Pain, 1989. **38**(3): p. 333-8.
90. Galer, B.S., et al., *Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study.* Pain, 1999. **80**(3): p. 533-8.
91. Rowbotham, M., Petersen KL, Davies PS, Friedman EK, Fields HL, *Proceedings of the 9th World Congress of Pain. Progress in pain research and management. Vol. 16*. Recent developments in the treatment of neuropathic pain. , ed. M. Devor, Rowbotham, Michael C., and Wiesenfeld-Hallin, Zsuzsanna, . Vol. 16. 2000: Intl Assn for the Study of Pain. 833-855.
92. Gammaitoni, A.R. and M.W. Davis, *Pharmacokinetics and tolerability of lidocaine patch 5% with extended dosing.* Ann Pharmacother, 2002. **36**(2): p. 236-40.
93. Priano, L., M.R. Gasco, and A. Mauro, *Transdermal treatment options for neurological disorders: impact on the elderly.* Drugs Aging, 2006. **23**(5): p. 357-75.

94. Argoff, C.E., et al., *Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the Neuropathic Pain Scale.* Curr Med Res Opin, 2004. **20 Suppl 2**: p. S21-8.
95. Barbano, R.L., et al., *Effectiveness, tolerability, and impact on quality of life of the 5% lidocaine patch in diabetic polyneuropathy.* Arch Neurol, 2004. **61**(6): p. 914-8.
96. Jarvis, B. and A.J. Coukell, *Mexiletine. A review of its therapeutic use in painful diabetic neuropathy.* Drugs, 1998. **56**(4): p. 691-707.
97. Dejgard, A., P. Petersen, and J. Kastrup, *Mexiletine for treatment of chronic painful diabetic neuropathy.* Lancet, 1988. **1**(8575-6): p. 9-11.
98. Stracke, H., et al., *Mexiletine in the treatment of diabetic neuropathy.* Diabetes Care, 1992. **15**(11): p. 1550-5.
99. Peltier, M.M.H.a.A., *Painful Diabetic Neuropathy: A Management-Centered Review.* Clinical Diabetes, 2007. **25**(1): p. 6-15.
100. Polydefkis, M., et al., *The time course of epidermal nerve fibre regeneration: studies in normal controls and in people with diabetes, with and without neuropathy.* Brain, 2004. **127**(Pt 7): p. 1606-15.
101. Argoff, C.E., et al., *Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain.* Mayo Clin Proc, 2006. **81**(4 Suppl): p. S12-25.
102. Low, P.A., et al., *Double-blind, placebo-controlled study of the application of capsaicin cream in chronic distal painful polyneuropathy.* Pain, 1995. **62**(2): p. 163-8.
103. *Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, double-blind, vehicle-controlled study. The Capsaicin Study Group.* Arch Intern Med, 1991. **151**(11): p. 2225-9.
104. Biesbroeck, R., et al., *A double-blind comparison of topical capsaicin and oral amitriptyline in painful diabetic neuropathy.* Adv Ther, 1995. **12**(2): p. 111-20.
105. Wong, M.C., J.W. Chung, and T.K. Wong, *Effects of treatments for symptoms of painful diabetic neuropathy: systematic review.* Bmj, 2007. **335**(7610): p. 87.
106. Sindrup, S.H., et al., *Tramadol relieves pain and allodynia in polyneuropathy: a randomised, double-blind, controlled trial.* Pain, 1999. **83**(1): p. 85-90.
107. Harati, Y., et al., *Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy.* Neurology, 1998. **50**(6): p. 1842-6.
108. Hollingshead, J., R.M. Duhmke, and D.R. Cornblath, *Tramadol for neuropathic pain.* Cochrane Database Syst Rev, 2006. **3**: p. CD003726.
109. Brookoff, D., *Chronic pain: 1. A new disease?* Hosp Pract (Minneap), 2000. **35**(7): p. 45-52, 59.
110. Mao, J., *Opioid-induced abnormal pain sensitivity: implications in clinical opioid therapy.* Pain, 2002. **100**(3): p. 213-7.
111. Eisenberg, E., E.D. McNicol, and D.B. Carr, *Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials.* Jama, 2005. **293**(24): p. 3043-52.

112. Gimbel, J.S., P. Richards, and R.K. Portenoy, *Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial.* Neurology, 2003. **60**(6): p. 927-34.
113. Watson, C.P., et al., *Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy.* Pain, 2003. **105**(1-2): p. 71-8.
114. Eisenberg, E., E. McNicol, and D.B. Carr, *Opioids for neuropathic pain.* Cochrane Database Syst Rev, 2006. **3**: p. CD006146.
115. Rowbotham, M.C., et al., *Oral opioid therapy for chronic peripheral and central neuropathic pain.* N Engl J Med, 2003. **348**(13): p. 1223-32.
116. Agarwal, S., et al., *Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states.* Pain Med, 2007. **8**(7): p. 554-62.
117. Moore, R.A. and H.J. McQuay, *Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids.* Arthritis Res Ther, 2005. **7**(5): p. R1046-51.
118. Hojsted, J. and P. Sjogren, *An update on the role of opioids in the management of chronic pain of nonmalignant origin.* Curr Opin Anaesthesiol, 2007. **20**(5): p. 451-5.
119. Carpenter, C.L., et al., *Dextromethorphan and dextrorphan as calcium channel antagonists.* Brain Res, 1988. **439**(1-2): p. 372-5.
120. Sang, C.N., et al., *Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials.* Anesthesiology, 2002. **96**(5): p. 1053-61.
121. Thisted, R.A., et al., *Dextromethorphan and quinidine in adult patients with uncontrolled painful diabetic peripheral neuropathy: a 29-day, multicenter, open-label, dose-escalation study.* Clin Ther, 2006. **28**(10): p. 1607-18.
122. Nelson, K.A., et al., *High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia.* Neurology, 1997. **48**(5): p. 1212-8.
123. Rogawski, M.A., *Therapeutic potential of excitatory amino acid antagonists: channel blockers and 2,3-benzodiazepines.* Trends Pharmacol Sci, 1993. **14**(9): p. 325-31.
124. Chen, H.S., et al., *Open-channel block of N-methyl-D-aspartate (NMDA) responses by memantine: therapeutic advantage against NMDA receptor-mediated neurotoxicity.* J Neurosci, 1992. **12**(11): p. 4427-36.
125. Garcia, J. and R.D. Altman, *Chronic pain states: pathophysiology and medical therapy.* Semin Arthritis Rheum, 1997. **27**(1): p. 1-16.
126. Remington, J., *Remington's Pharmaceutical Sciences*. 2000, Easton, Pa: Mack Publishing Company.
127. Cohen, K.L. and S. Harris, *Efficacy and safety of nonsteroidal anti-inflammatory drugs in the therapy of diabetic neuropathy.* Arch Intern Med, 1987. **147**(8): p. 1442-4.
128. Jensen, P.G. and J.R. Larson, *Management of painful diabetic neuropathy.* Drugs Aging, 2001. **18**(10): p. 737-49.

129. *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group.* N Engl J Med, 1993. **329**(14): p. 977-86.
130. Schifitto, G., et al., *Incidence of and risk factors for HIV-associated distal sensory polyneuropathy.* Neurology, 2002. **58**(12): p. 1764-8.
131. Schifitto, G., et al., *Markers of immune activation and viral load in HIV-associated sensory neuropathy.* Neurology, 2005. **64**(5): p. 842-8.
132. Gonzalez-Duarte, A., K. Cikurel, and D.M. Simpson, *Managing HIV peripheral neuropathy.* Curr HIV/AIDS Rep, 2007. **4**(3): p. 114-8.
133. Kieburtz, K., et al., *A randomized trial of amitriptyline and mexiletine for painful neuropathy in HIV infection. AIDS Clinical Trial Group 242 Protocol Team.* Neurology, 1998. **51**(6): p. 1682-8.
134. Shlay, J.C., et al., *Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS.* Jama, 1998. **280**(18): p. 1590-5.
135. Hahn, K., et al., *A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies.* J Neurol, 2004. **251**(10): p. 1260-6.
136. Simpson, D.M., et al., *Lamotrigine for HIV-associated painful sensory neuropathies: a placebo-controlled trial.* Neurology, 2003. **60**(9): p. 1508-14.
137. Kautio, A.L., et al., *Amitriptyline in the treatment of chemotherapy-induced neuropathic symptoms.* J Pain Symptom Manage, 2008. **35**(1): p. 31-9.
138. Quasthoff, S. and H.P. Hartung, *Chemotherapy-induced peripheral neuropathy.* J Neurol, 2002. **249**(1): p. 9-17.
139. Hammack, J.E., et al., *Phase III evaluation of nortriptyline for alleviation of symptoms of cis-platinum-induced peripheral neuropathy.* Pain, 2002. **98**(1-2): p. 195-203.
140. Jung, B.F., et al., *Risk factors for postherpetic neuralgia in patients with herpes zoster.* Neurology, 2004. **62**(9): p. 1545-51.
141. Hope-Simpson, R.E., *The Nature of Herpes Zoster: a Long-Term Study and a New Hypothesis.* Proc R Soc Med, 1965. **58**: p. 9-20.
142. Hope-Simpson, R.E., *Postherpetic neuralgia.* J R Coll Gen Pract, 1975. **25**(157): p. 571-5.
143. Kurtzke, J.F., *Neuroepidemiology.* Ann Neurol, 1984. **16**(3): p. 265-77.
144. Donahue, J.G., et al., *The incidence of herpes zoster.* Arch Intern Med, 1995. **155**(15): p. 1605-9.
145. Brisson, M., et al., *Epidemiology of varicella zoster virus infection in Canada and the United Kingdom.* Epidemiol Infect, 2001. **127**(2): p. 305-14.
146. Johnson, R.W., et al., *Postherpetic neuralgia: epidemiology, pathophysiology and management.* Expert Rev Neurother, 2007. **7**(11): p. 1581-95.
147. Nagasako, E.M., et al., *Rash severity in herpes zoster: correlates and relationship to postherpetic neuralgia.* J Am Acad Dermatol, 2002. **46**(6): p. 834-9.
148. Ragozzino, M.W., et al., *Population-based study of herpes zoster and its sequelae.* Medicine (Baltimore), 1982. **61**(5): p. 310-6.

149. Burgoon, C.F., Jr., J.S. Burgoon, and G.D. Baldridge, *The natural history of herpes zoster.* J Am Med Assoc, 1957. **164**(3): p. 265-9.
150. Glynn, C., et al., *Epidemiology of shingles.* J R Soc Med, 1990. **83**(10): p. 617-9.
151. Rogers, R.S., 3rd and J.P. Tindall, *Geriatric herpes zoster.* J Am Geriatr Soc, 1971. **19**(6): p. 495-504.
152. Kost, R.G. and S.E. Straus, *Postherpetic neuralgia--pathogenesis, treatment, and prevention.* N Engl J Med, 1996. **335**(1): p. 32-42.
153. Dworkin, R.S.K., *Herpes zoster and postherpetic neuralgia*. 2nd ed. The epidemiology and natural history of herpes zoster and postherpetic neuralgia ed. G.A. Watson CPN. 2001: Elsevier Sciences. 39-64.
154. McCrary, M.L., J. Severson, and S.K. Tyring, *Varicella zoster virus.* J Am Acad Dermatol, 1999. **41**(1): p. 1-14; quiz 15-6.
155. Guess, H.A., et al., *Epidemiology of herpes zoster in children and adolescents: a population-based study.* Pediatrics, 1985. **76**(4): p. 512-7.
156. De Moragas, J.M. and R.R. Kierland, *The outcome of patients with herpes zoster.* AMA Arch Derm, 1957. **75**(2): p. 193-6.
157. Clemmensen, O.J. and K.E. Andersen, *ACTH versus prednisone and placebo in herpes zoster treatment.* Clin Exp Dermatol, 1984. **9**(6): p. 557-63.
158. Dworkin, R.H., et al., *Postherpetic neuralgia: impact of famciclovir, age, rash severity, and acute pain in herpes zoster patients.* J Infect Dis, 1998. **178 Suppl 1**: p. S76-80.
159. Harrison, R.A., et al., *A mixed model for factors predictive of pain in AIDS patients with herpes zoster.* J Pain Symptom Manage, 1999. **17**(6): p. 410-7.
160. Whitley, R.J., et al., *Herpes zoster: risk categories for persistent pain.* J Infect Dis, 1999. **179**(1): p. 9-15.
161. Watson, C.P., et al., *Amitriptyline versus placebo in postherpetic neuralgia.* Neurology, 1982. **32**(6): p. 671-3.
162. Kishore-Kumar, R., et al., *Desipramine relieves postherpetic neuralgia.* Clin Pharmacol Ther, 1990. **47**(3): p. 305-12.
163. Raja, S.N., et al., *Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial.* Neurology, 2002. **59**(7): p. 1015-21.
164. Max, M.B., et al., *Amitriptyline, but not lorazepam, relieves postherpetic neuralgia.* Neurology, 1988. **38**(9): p. 1427-32.
165. Watson, C.P., et al., *Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial.* Neurology, 1998. **51**(4): p. 1166-71.
166. Graff-Radford, S.B., L.R. Shaw, and B.N. Naliboff, *Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia.* Clin J Pain, 2000. **16**(3): p. 188-92.
167. Rowbotham, M.C., et al., *Treatment response in antidepressant-naive postherpetic neuralgia patients: double-blind, randomized trial.* J Pain, 2005. **6**(11): p. 741-6.
168. Bryson, H.M. and M.I. Wilde, *Amitriptyline. A review of its pharmacological properties and therapeutic use in chronic pain states.* Drugs Aging, 1996. **8**(6): p. 459-76.

169. Janowsky, D.S. and B. Byerley, *Desipramine: an overview.* J Clin Psychiatry, 1984. **45**(10 Pt 2): p. 3-9.
170. Roose, S.P., et al., *Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease.* Jama, 1998. **279**(4): p. 287-91.
171. Kapur, S., T. Mieczkowski, and J.J. Mann, *Antidepressant medications and the relative risk of suicide attempt and suicide.* Jama, 1992. **268**(24): p. 3441-5.
172. Van Seventer, R., Bladin, C, Hoggart, B., Martin, S., *Pregabalin Dosed Twice a Day (BID) Efficacioulsy and Safely Treats Neuropatic Pain Asssociated with Postherpetic Neuralgia.* J of Pain, 2004. **5**(S1: 58): p. S58.
173. Van Seventer, R., Bladin, C, Hoggart, B., Martin, S., *Novel Therapeutic Agents: Pregabalin Dosed BID is Efficacious for Improving Sleep Interference in Patients Suffering from Postherpetic Neuralgia: Results of a Large, Randomized, Placebo-Controlled Trial.* J of Pain, 2004. **5**(S1): p. S60.
174. Rowbotham, M., et al., *Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial.* Jama, 1998. **280**(21): p. 1837-42.
175. Dworkin, R.H., et al., *Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial.* Neurology, 2003. **60**(8): p. 1274-83.
176. Sabatowski, R., et al., *Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial.* Pain, 2004. **109**(1-2): p. 26-35.
177. Rowbotham, M.C., et al., *Lidocaine patch: double-blind controlled study of a new treatment method for post-herpetic neuralgia.* Pain, 1996. **65**(1): p. 39-44.
178. Meier, T., et al., *Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study.* Pain, 2003. **106**(1-2): p. 151-8.
179. Khaliq, W., S. Alam, and N. Puri, *Topical lidocaine for the treatment of postherpetic neuralgia.* Cochrane Database Syst Rev, 2007(2): p. CD004846.
180. Moulin, D.E., et al., *Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society.* Pain Res Manag, 2007. **12**(1): p. 13-21.
181. Dubinsky, R.M., et al., *Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology.* Neurology, 2004. **63**(6): p. 959-65.
182. Challapalli, V., et al., *Systemic administration of local anesthetic agents to relieve neuropathic pain.* Cochrane Database Syst Rev, 2005(4): p. CD003345.
183. Fusco, B.M. and M. Giacovazzo, *Peppers and pain. The promise of capsaicin.* Drugs, 1997. **53**(6): p. 909-14.
184. Lincoff NS, R.P., Hirano M. The treatment of periocular and facial pain with topical capsaicin. J Neuroophthalmol 1998; 18 (1): 17-20.
185. Rumsfield JA, W.D.T.c.i.d.a.p.p.d.D.-.
186. Watson, C.P., et al., *A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia.* Clin Ther, 1993. **15**(3): p. 510-26.
187. Mason, L., et al., *Systematic review of topical capsaicin for the treatment of chronic pain.* Bmj, 2004. **328**(7446): p. 991.

188. Lewis, M.A., et al., *Management of neuropathic orofacial pain.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2007. **103 Suppl**: p. S32 e1-24.
189. Jackson, E.M., et al., *Trigeminal neuralgia: a diagnostic challenge.* Am J Emerg Med, 1999. **17**(6): p. 597-600.
190. Tenser, R.B., *Trigeminal neuralgia: mechanisms of treatment.* Neurology, 1998. **51**(1): p. 17-9.
191. Kapur, N., I.R. Kamel, and A. Herlich, *Oral and craniofacial pain: diagnosis, pathophysiology, and treatment.* Int Anesthesiol Clin, 2003. **41**(3): p. 115-50.
192. Silberstein, S., Young WB., *Headaches and Facial Pain*. 1st ed. Textbook of Clinical Neurology, ed. Goetz. 1999: WB Saunders. 1089-1105.
193. Montgomery, M.T., *Extraoral facial pain.* Emerg Med Clin North Am, 2000. **18**(3): p. 577-600, vii-viii.
194. Marbach, J.J., *Medically unexplained chronic orofacial pain. Temporomandibular pain and dysfunction syndrome, orofacial phantom pain, burning mouth syndrome, and trigeminal neuralgia.* Med Clin North Am, 1999. **83**(3): p. 691-710, vi-vii.
195. Bagheri, S.C., F. Farhidvash, and V.J. Perciaccante, *Diagnosis and treatment of patients with trigeminal neuralgia.* J Am Dent Assoc, 2004. **135**(12): p. 1713-7.
196. Katusic, S., et al., *Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984.* Ann Neurol, 1990. **27**(1): p. 89-95.
197. Turp, J.C. and J.P. Gobetti, *Trigeminal neuralgia versus atypical facial pain. A review of the literature and case report.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1996. **81**(4): p. 424-32.
198. Pruitt, A., *Management of Tic Douloureux*. 4th ed. Primary Care Medicine, ed. Goroll. 2000: Lippincott Williams & Wilkins. 973-974.
199. Gass, A., et al., *Trigeminal neuralgia in patients with multiple sclerosis: lesion localization with magnetic resonance imaging.* Neurology, 1997. **49**(4): p. 1142-4.
200. Scrivani, S.J., E.S. Mathews, and R.J. Maciewicz, *Trigeminal neuralgia.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2005. **100**(5): p. 527-38.
201. Jorns, T.P. and J.M. Zakrzewska, *Evidence-based approach to the medical management of trigeminal neuralgia.* Br J Neurosurg, 2007. **21**(3): p. 253-61.
202. Graham, J.G. and K.J. Zilkha, *Treatment of trigeminal neuralgia with carbamazepine: a follow-up study.* Br Med J, 1966. **1**(5481): p. 210-1.
203. Rockliff, B.W. and E.H. Davis, *Controlled sequential trials of carbamazepine in trigeminal neuralgia.* Arch Neurol, 1966. **15**(2): p. 129-36.
204. Nicol, C.F., *A four year double-blind study of tegretol in facial pain.* Headache, 1969. **9**(1): p. 54-7.
205. Killian, J.M. and G.H. Fromm, *Carbamazepine in the treatment of neuralgia. Use of side effects.* Arch Neurol, 1968. **19**(2): p. 129-36.
206. Dam, M., et al., *A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy.* Epilepsy Res, 1989. **3**(1): p. 70-6.
207. Beydoun A, S.D., and D'Souza J, *Oxcarbazepine versus carbamazepine in trigeminal neuralgia: a meta-analysis of three double blind comparative trials.* Neurology, 2002. **58 (Suppl 3)**(02.083).

208. Merskey, H.a.B.e., *Classification of Chronic Pain*. Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms. 1994: IASP Press.
209. Schott, G.D., *From thalamic syndrome to central poststroke pain.* J Neurol Neurosurg Psychiatry, 1996. **61**(6): p. 560-4.
210. Frese, A., et al., *Pharmacologic treatment of central post-stroke pain.* Clin J Pain, 2006. **22**(3): p. 252-60.
211. Eide, P.K., *Pathophysiological mechanisms of central neuropathic pain after spinal cord injury.* Spinal Cord, 1998. **36**(9): p. 601-12.
212. Nicholson, B.D., *Evaluation and treatment of central pain syndromes.* Neurology, 2004. **62**(5 Suppl 2): p. S30-6.
213. Vranken, J.H., et al., *Pregabalin in patients with central neuropathic pain: A randomized, double-blind, placebo-controlled trial of a flexible-dose regimen.* Pain, 2007.
214. Baldessarini, R., *Drug therapy of depression and anxiety disorders.* Goodman and Gilman's pharmacological basis of therapeutics, 2006. **Brunton LJ, Parker LK, editors**(New York, McGraw-Hill): p. 438-450.
215. Leijon, G. and J. Boivie, *Central post-stroke pain--a controlled trial of amitriptyline and carbamazepine.* Pain, 1989. **36**(1): p. 27-36.
216. Vestergaard, K., et al., *Lamotrigine for central poststroke pain: a randomized controlled trial.* Neurology, 2001. **56**(2): p. 184-90.
217. Finnerup, N.B., et al., *Lamotrigine in spinal cord injury pain: a randomized controlled trial.* Pain, 2002. **96**(3): p. 375-83.
218. Levendoglu, F., et al., *Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury.* Spine, 2004. **29**(7): p. 743-51.
219. Siddall, P.J., et al., *Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial.* Neurology, 2006. **67**(10): p. 1792-800.
220. Reuben, S.S., *Chronic pain after surgery: what can we do to prevent it.* Curr Pain Headache Rep, 2007. **11**(1): p. 5-13.
221. Mishra, S., et al., *Incidence and Management of Phantom Limb Pain According to World Health Organization Analgesic Ladder in Amputees of Malignant Origin.* Am J Hosp Palliat Care, 2007.
222. Loeser, J.D., *Pain After Amputation: Phantom Limb and Stump Pain*. 3rd ed. Bonica's Managment of Pain, ed. J.D. Loeser, Butter, SH., Chapman, CR. and Turk, DC. 2001: Lippincott Williams & Wilkins.
223. Nikolajsen, L. and T.S. Jensen, *Phantom limb pain.* Br J Anaesth, 2001. **87**(1): p. 107-16.
224. Jensen, T.S., et al., *Phantom limb, phantom pain and stump pain in amputees during the first 6 months following limb amputation.* Pain, 1983. **17**(3): p. 243-56.
225. Carlen, P.L., et al., *Phantom limbs and related phenomena in recent traumatic amputations.* Neurology, 1978. **28**(3): p. 211-7.
226. Katz, J., *Prevention of phantom limb pain by regional anaesthesia.* Lancet, 1997. **349**(9051): p. 519-20.
227. Parkes, C.M., *Factors determining the persistence of phantom pain in the amputee.* J Psychosom Res, 1973. **17**(2): p. 97-108.

228. Merskey, H., *Classification of Chronic Pain: Description of Chronic Pain Syndromes and Definitions of Pain Terms.* Pain, 1986. **3**: p. S138-139.
229. Karmakar, M.K. and A.M. Ho, *Postthoracotomy pain syndrome.* Thorac Surg Clin, 2004. **14**(3): p. 345-52.
230. Dajczman, E., et al., *Long-term postthoracotomy pain.* Chest, 1991. **99**(2): p. 270-4.
231. Foley, K.M., *Pain syndromes in patients with cancer.* Med Clin North Am, 1987. **71**(2): p. 169-84.
232. Assa, J., *The intercostobrachial nerve in radical mastectomy.* J Surg Oncol, 1974. **6**(2): p. 123-6.
233. Stevens, P.E., S.L. Dibble, and C. Miaskowski, *Prevalence, characteristics, and impact of postmastectomy pain syndrome: an investigation of women's experiences.* Pain, 1995. **61**(1): p. 61-8.
234. Tasmuth, T., K. von Smitten, and E. Kalso, *Pain and other symptoms during the first year after radical and conservative surgery for breast cancer.* Br J Cancer, 1996. **74**(12): p. 2024-31.
235. Warmuth, M.A., et al., *Complications of axillary lymph node dissection for carcinoma of the breast: a report based on a patient survey.* Cancer, 1998. **83**(7): p. 1362-8.
236. Robinson, L.R., et al., *Trial of amitriptyline for relief of pain in amputees: results of a randomized controlled study.* Arch Phys Med Rehabil, 2004. **85**(1): p. 1-6.
237. Nikolajsen, L., et al., *A randomized study of the effects of gabapentin on postamputation pain.* Anesthesiology, 2006. **105**(5): p. 1008-15.
238. Smith, D.G., et al., *Efficacy of gabapentin in treating chronic phantom limb and residual limb pain.* J Rehabil Res Dev, 2005. **42**(5): p. 645-54.
239. Bone, M., P. Critchley, and D.J. Buggy, *Gabapentin in postamputation phantom limb pain: a randomized, double-blind, placebo-controlled, cross-over study.* Reg Anesth Pain Med, 2002. **27**(5): p. 481-6.
240. Sihoe, A.D., et al., *The use of gabapentin for post-operative and post-traumatic pain in thoracic surgery patients.* Eur J Cardiothorac Surg, 2006. **29**(5): p. 795-9.
241. Solak, O., et al., *Effectiveness of gabapentin in the treatment of chronic post-thoracotomy pain.* Eur J Cardiothorac Surg, 2007. **32**(1): p. 9-12.
242. Erdek, M.A. and P.S. Staats, *Chronic pain and thoracic surgery.* Thorac Surg Clin, 2005. **15**(1): p. 123-30.
243. Kalso, E., T. Tasmuth, and P.J. Neuvonen, *Amitriptyline effectively relieves neuropathic pain following treatment of breast cancer.* Pain, 1996. **64**(2): p. 293-302.
244. Tasmuth, T., B. Hartel, and E. Kalso, *Venlafaxine in neuropathic pain following treatment of breast cancer.* Eur J Pain, 2002. **6**(1): p. 17-24.
245. Caraceni, A. and R.K. Portenoy, *An international survey of cancer pain characteristics and syndromes. IASP Task Force on Cancer Pain. International Association for the Study of Pain.* Pain, 1999. **82**(3): p. 263-74.
246. Brant, J.M., *Cancer-related neuropathic pain.* Nurse Pract Forum, 1998. **9**(3): p. 154-62.

247. Grond, S., et al., *Assessment and treatment of neuropathic cancer pain following WHO guidelines.* Pain, 1999. **79**(1): p. 15-20.
248. George, R.M. and S.H. Ahmedzai, *The management of neuropathic pain in cancer: clinical guidelines for the use of adjuvant analgesics.* Indian J Cancer, 2000. **37**(1): p. 4-9.
249. Kanner, R., *Diagnosis and management of neuropathic pain in patients with cancer.* Cancer Invest, 2001. **19**(3): p. 324-33.
250. Wilkie, D.J., et al., *Nociceptive and neuropathic pain in patients with lung cancer: a comparison of pain quality descriptors.* J Pain Symptom Manage, 2001. **22**(5): p. 899-910.
251. Berger, A., et al., *Use of antiepileptics and tricyclic antidepressants in cancer patients with neuropathic pain.* Eur J Cancer Care (Engl), 2006. **15**(2): p. 138-45.
252. Fields, H.L.M., J., *Pain: Pathophysiology and Managment*. 14th ed. Harrison's Priniciples of Internal Medicine, ed. A. Fauci, Braunwald, E., Isselbacher, KJ., Wilson, JD., Martin, JB., Kasper, DL., Hauser, SL. and Longo, DL. 1998: McGraw-Hill.
253. Bonica, J., *The Management of Pain*. Vol. 1. 1990, Philadelphia: Lea & Febiger.
254. Polomano RC, F.J., *Pain and Neuropathy in Cancer Survivors.* American Journal of Nursing, 2006. **Mar; 106**(3 Suppl): p. 39-47.
255. Jacox, A., Carr, DB. and Payne, R. et all, *Management of Cancer Pain: Clinical Practice Guidelin No. 9.* , U.S. Department of Health and Human Services. Agency for Healthcare Policy and Research, Editor. 1994.
256. Levy, M.H., *Pain control in patients with cancer.* Oncology (Williston Park), 1999. **13**(5 Suppl 2): p. 9-14.
257. Zech, D.F., et al., *Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study.* Pain, 1995. **63**(1): p. 65-76.
258. Azevedo SLF, K.M., Jacobsen Teizeira M, *The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it?* Support Care Cancer, 2006.
259. Portenoy, R.K. and P. Lesage, *Management of cancer pain.* Lancet, 1999. **353**(9165): p. 1695-700.
260. Portenoy, R.K., K.M. Foley, and C.E. Inturrisi, *The nature of opioid responsiveness and its implications for neuropathic pain: new hypotheses derived from studies of opioid infusions.* Pain, 1990. **43**(3): p. 273-86.
261. Arner, S. and B.A. Meyerson, *Lack of analgesic effect of opioids on neuropathic and idiopathic forms of pain.* Pain, 1988. **33**(1): p. 11-23.
262. Kupers, R.C., et al., *Morphine differentially affects the sensory and affective pain ratings in neurogenic and idiopathic forms of pain.* Pain, 1991. **47**(1): p. 5-12.
263. Stute, P., et al., *Analysis and treatment of different types of neuropathic cancer pain.* J Pain Symptom Manage, 2003. **26**(6): p. 1123-31.
264. Bennett, M.I. and K.H. Simpson, *Gabapentin in the treatment of neuropathic pain.* Palliat Med, 2004. **18**(1): p. 5-11.
265. Rice, A.S. and S. Maton, *Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study.* Pain, 2001. **94**(2): p. 215-24.

266. Ross, J.R., et al., *Gabapentin is effective in the treatment of cancer-related neuropathic pain: a prospective, open-label study.* J Palliat Med, 2005. **8**(6): p. 1118-26.
267. Bennett, M.I., *Gabapentin significantly improves analgesia in people receiving opioids for neuropathic cancer pain.* Cancer Treat Rev, 2005. **31**(1): p. 58-62.
268. Freynhagen, R., et al., *Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens.* Pain, 2005. **115**(3): p. 254-63.
269. Stanton-Hicks, M., *Complex regional pain syndrome: manifestations and the role of neurostimulation in its management.* J Pain Symptom Manage, 2006. **31**(4 Suppl): p. S20-4.
270. Wasner, G., et al., *Complex regional pain syndrome--diagnostic, mechanisms, CNS involvement and therapy.* Spinal Cord, 2003. **41**(2): p. 61-75.
271. Schwartzman, R.J. and J. Kerrigan, *The movement disorder of reflex sympathetic dystrophy.* Neurology, 1990. **40**(1): p. 57-61.
272. Rosen, P.S. and W. Graham, *The shoulder-hand syndrome: historical review with observations on seventy-three patients.* Can Med Assoc J, 1957. **77**(2): p. 86-91.
273. Poplawski, Z.J., A.M. Wiley, and J.F. Murray, *Post-traumatic dystrophy of the extremities.* J Bone Joint Surg Am, 1983. **65**(5): p. 642-55.
274. Kingery, W.S., *A critical review of controlled clinical trials for peripheral neuropathic pain and complex regional pain syndromes.* Pain, 1997. **73**(2): p. 123-39.
275. Sharma, A., K. Williams, and S.N. Raja, *Advances in treatment of complex regional pain syndrome: recent insights on a perplexing disease.* Curr Opin Anaesthesiol, 2006. **19**(5): p. 566-72.
276. Veldman, P.H., et al., *Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients.* Lancet, 1993. **342**(8878): p. 1012-6.
277. Frade, L.C., et al., *The antinociceptive effect of local or systemic parecoxib combined with lidocaine/clonidine intravenous regional analgesia for complex regional pain syndrome type I in the arm.* Anesth Analg, 2005. **101**(3): p. 807-11, table of contents.
278. Christensen, K., E.M. Jensen, and I. Noer, *The reflex dystrophy syndrome response to treatment with systemic corticosteroids.* Acta Chir Scand, 1982. **148**(8): p. 653-5.
279. Braus, D.F., J.K. Krauss, and J. Strobel, *The shoulder-hand syndrome after stroke: a prospective clinical trial.* Ann Neurol, 1994. **36**(5): p. 728-33.
280. Grundberg, A.B., *Reflex sympathetic dystrophy: treatment with long-acting intramuscular corticosteroids.* J Hand Surg [Am], 1996. **21**(4): p. 667-70.
281. Dellemijn, P., *Are opioids effective in relieving neuropathic pain?* Pain, 1999. **80**(3): p. 453-62.
282. Mackey, S. and S. Feinberg, *Pharmacologic therapies for complex regional pain syndrome.* Curr Pain Headache Rep, 2007. **11**(1): p. 38-43.
283. Serpell, M.G., *Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial.* Pain, 2002. **99**(3): p. 557-66.

284. van de Vusse, A.C., et al., *Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1 [ISRCTN84121379].* BMC Neurol, 2004. **4**: p. 13.
285. Gobelet, C., M. Waldburger, and J.L. Meier, *The effect of adding calcitonin to physical treatment on reflex sympathetic dystrophy.* Pain, 1992. **48**(2): p. 171-5.
286. Perez, R.S., et al., *Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials.* J Pain Symptom Manage, 2001. **21**(6): p. 511-26.
287. Varenna, M., et al., *Intravenous clodronate in the treatment of reflex sympathetic dystrophy syndrome. A randomized, double blind, placebo controlled study.* J Rheumatol, 2000. **27**(6): p. 1477-83.
288. Manicourt, D.H., et al., *Role of alendronate in therapy for posttraumatic complex regional pain syndrome type I of the lower extremity.* Arthritis Rheum, 2004. **50**(11): p. 3690-7.
289. Robinson, J.N., J. Sandom, and P.T. Chapman, *Efficacy of pamidronate in complex regional pain syndrome type I.* Pain Med, 2004. **5**(3): p. 276-80.
290. Adami, S., et al., *Bisphosphonate therapy of reflex sympathetic dystrophy syndrome.* Ann Rheum Dis, 1997. **56**(3): p. 201-4.
291. Rowlingson, J., *Epidural steroids in treating failed back surgery syndrome.* Anesth Analg, 1999. **88**(2): p. 240-2.
292. Fiume, D., et al., *Treatment of the failed back surgery syndrome due to lumbo-sacral epidural fibrosis.* Acta Neurochir Suppl, 1995. **64**: p. 116-8.
293. Long, D.M., et al., *Clinical features of the failed-back syndrome.* J Neurosurg, 1988. **69**(1): p. 61-71.
294. North, R.B., et al., *Failed back surgery syndrome: 5-year follow-up after spinal cord stimulator implantation.* Neurosurgery, 1991. **28**(5): p. 692-9.
295. Skaf, G., et al., *Clinical outcome of surgical treatment of failed back surgery syndrome.* Surg Neurol, 2005. **64**(6): p. 483-8, discussion 488-9.
296. Kumar, K., et al., *Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome.* Pain, 2007. **132**(1-2): p. 179-88.
297. Birbara, C.A., et al., *Treatment of chronic low back pain with etoricoxib, a new cyclo-oxygenase-2 selective inhibitor: improvement in pain and disability--a randomized, placebo-controlled, 3-month trial.* J Pain, 2003. **4**(6): p. 307-15.
298. Reuben, S.S., et al., *The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery.* Anesth Analg, 2006. **103**(5): p. 1271-7.
299. Airaksinen, O., et al., *Chapter 4. European guidelines for the management of chronic nonspecific low back pain.* Eur Spine J, 2006. **15 Suppl 2**: p. S192-300.
300. van Tulder, M., Scholten, RJ., Koes, BW. and Deyo, RA, *Non-steroidal Anti-inflammatory Drugs for Low Back Pain*. 3rd ed. The Cochrane Library. 2004: John Willey & Sons.
301. Salerno, S.M., R. Browning, and J.L. Jackson, *The effect of antidepressant treatment on chronic back pain: a meta-analysis.* Arch Intern Med, 2002. **162**(1): p. 19-24.

302. Staiger, T.O., et al., *Systematic review of antidepressants in the treatment of chronic low back pain.* Spine, 2003. **28**(22): p. 2540-5.
303. Maier, C., et al., *Morphine responsiveness, efficacy and tolerability in patients with chronic non-tumor associated pain - results of a double-blind placebo-controlled trial (MONTAS).* Pain, 2002. **97**(3): p. 223-33.
304. Howe, J.F., J.D. Loeser, and W.H. Calvin, *Mechanosensitivity of dorsal root ganglia and chronically injured axons: a physiological basis for the radicular pain of nerve root compression.* Pain, 1977. **3**(1): p. 25-41.
305. Anderson, S.R., *A rationale for the treatment algorithm of failed back surgery syndrome.* Curr Rev Pain, 2000. **4**(5): p. 395-406.
306. Onesti, S.T., *Failed back syndrome.* Neurologist, 2004. **10**(5): p. 259-64.
307. North, R.B., et al., *Dorsal root ganglionectomy for failed back surgery syndrome: a 5-year follow-up study.* J Neurosurg, 1991. **74**(2): p. 236-42.
308. Shah, R.V., et al., *Targeting the spinal nerve via a double-needle, transforaminal approach in failed back surgery syndrome: demonstration of a technique.* Pain Physician, 2004. **7**(1): p. 93-7.
309. Schofferman, J., et al., *Failed back surgery: etiology and diagnostic evaluation.* Spine J, 2003. **3**(5): p. 400-3.
310. van Akkerveeken, P.F., *The diagnostic value of nerve root sheath infiltration.* Acta Orthop Scand Suppl, 1993. **251**: p. 61-3.
311. Dreyfuss, P., et al., *The value of medical history and physical examination in diagnosing sacroiliac joint pain.* Spine, 1996. **21**(22): p. 2594-602.
312. Van Goethem, J.W., P.M. Parizel, and J.R. Jinkins, *Review article: MRI of the postoperative lumbar spine.* Neuroradiology, 2002. **44**(9): p. 723-39.
313. Devulder, J., et al., *Nerve root sleeve injections in patients with failed back surgery syndrome: a comparison of three solutions.* Clin J Pain, 1999. **15**(2): p. 132-5.
314. Hesla, E. and H. Breivik, *[Epidural analgesia and epidural steroid injection for treatment of chronic low back pain and sciatica].* Tidsskr Nor Laegeforen, 1979. **99**(19-21): p. 936-9.
315. Revel, M., et al., *Forceful epidural injections for the treatment of lumbosciatic pain with post-operative lumbar spinal fibrosis.* Rev Rhum Engl Ed, 1996. **63**(4): p. 270-7.
316. Winnie, A.P. and P.W. Hartwell, *Relationship between time of treatment of acute herpes zoster with sympathetic blockade and prevention of post-herpetic neuralgia: clinical support for a new theory of the mechanism by which sympathetic blockade provides therapeutic benefit.* Reg Anesth, 1993. **18**(5): p. 277-82.
317. van Wijck, A.J., et al., *The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial.* Lancet, 2006. **367**(9506): p. 219-24.
318. Rowbotham MC, P.K., Davies PS, and Fields HL, *Spectrum of Pain Mechanisms Contributing to PHN*. 2nd ed. Herpes Zoster and Postherpetic Neuralgia, ed. G.A. Watson CPN. 2001: Elsevier Science.

319. Kotani, N., et al., *Intrathecal methylprednisolone for intractable postherpetic neuralgia.* N Engl J Med, 2000. **343**(21): p. 1514-9.
320. Pasqualucci, A., et al., *Prevention of post-herpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone.* Acta Anaesthesiol Scand, 2000. **44**(8): p. 910-8.
321. Wu, C.L., A. Marsh, and R.H. Dworkin, *The role of sympathetic nerve blocks in herpes zoster and postherpetic neuralgia.* Pain, 2000. **87**(2): p. 121-9.
322. Rowbotham, M.a.T., K., *Herpes Zoster and Postherpetic Neuralgia*. Anesthesia: Biologic Foundations, ed. T.L. Yaksh, Lynch, C., Zapol, WM., Maze, M., Biebuyck, JF. and Saidman, LJ. 1998: Lippincott-Raven Publishers.
323. Dworkin RH, J., RW, *A Belt of roses from Hell: Pain in Herpes Zoster and Postherpetic Neuralgia*. Handbook of Pain Syndromes: Biopsychosocial Perspectives, ed. A. Block, Kremer, EF and Fernandez, E. 1999: Erlbaum.
324. Christo, P.J., G. Hobelmann, and D.N. Maine, *Post-herpetic neuralgia in older adults: evidence-based approaches to clinical management.* Drugs Aging, 2007. **24**(1): p. 1-19.
325. Steiger, H.J., *Prognostic factors in the treatment of trigeminal neuralgia. Analysis of a differential therapeutic approach.* Acta Neurochir (Wien), 1991. **113**(1-2): p. 11-7.
326. Han, K.R., et al., *Efficacy and safety of high concentration lidocaine for trigeminal nerve block in patients with trigeminal neuralgia.* Int J Clin Pract, 2007.
327. Goto, F., et al., *The long lasting effects of peripheral nerve blocks for trigeminal neuralgia using high concentration of tetracaine dissolved in bupivacaine.* Pain, 1999. **79**(1): p. 101-3.
328. Niguma, T., Matsumoto, M., Yaida, Y., Okawa, M., Sato, K., Sanae, K., *A Patient with Acute Painful Diabetic Neuropahty Successfully Treated by Lumbar Sympathetic Ganglion Block.* J Jap Soc Clin Anes, 2002. **22**(9): p. 344-347.
329. Barolat, G., *Spinal cord stimulation for chronic pain management.* Arch Med Res, 2000. **31**(3): p. 258-62.
330. Burchiel, K.J., et al., *Prospective, multicenter study of spinal cord stimulation for relief of chronic back and extremity pain.* Spine, 1996. **21**(23): p. 2786-94.
331. Erdek, M.A. and P.S. Staats, *Spinal cord stimulation for angina pectoris and peripheral vascular disease.* Anesthesiol Clin North America, 2003. **21**(4): p. 797-804.
332. Grabow, T.S., P.K. Tella, and S.N. Raja, *Spinal cord stimulation for complex regional pain syndrome: an evidence-based medicine review of the literature.* Clin J Pain, 2003. **19**(6): p. 371-83.
333. Kemler, M.A., et al., *Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy.* N Engl J Med, 2000. **343**(9): p. 618-24.
334. Taylor, R.S., *Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis.* J Pain Symptom Manage, 2006. **31**(4 Suppl): p. S13-9.

335. Harke, H., et al., *Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain.* Anesth Analg, 2002. **94**(3): p. 694-700; table of contents.
336. Melzack, R. and P.D. Wall, *Pain mechanisms: a new theory.* Science, 1965. **150**(699): p. 971-9.
337. Oakley, J.C. and J.P. Prager, *Spinal cord stimulation: mechanisms of action.* Spine, 2002. **27**(22): p. 2574-83.
338. Stiller, C.O., et al., *Release of gamma-aminobutyric acid in the dorsal horn and suppression of tactile allodynia by spinal cord stimulation in mononeuropathic rats.* Neurosurgery, 1996. **39**(2): p. 367-74; discussion 374-5.
339. Cui, J.G., et al., *Adenosine receptor activation suppresses tactile hypersensitivity and potentiates spinal cord stimulation in mononeuropathic rats.* Neurosci Lett, 1997. **223**(3): p. 173-6.
340. Petrakis, I.E. and V. Sciacca, *Epidural spinal cord electrical stimulation in diabetic critical lower limb ischemia.* J Diabetes Complications, 1999. **13**(5-6): p. 293-9.
341. Daousi, C., S.J. Benbow, and I.A. MacFarlane, *Electrical spinal cord stimulation in the long-term treatment of chronic painful diabetic neuropathy.* Diabet Med, 2005. **22**(4): p. 393-8.
342. Tesfaye, S., et al., *Electrical spinal-cord stimulation for painful diabetic peripheral neuropathy.* Lancet, 1996. **348**(9043): p. 1698-701.
343. Law, J.D., R.A. Lehman, and W.M. Kirsch, *Reoperation after lumbar intervertebral disc surgery.* J Neurosurg, 1978. **48**(2): p. 259-63.
344. North, R.B., et al., *Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial.* Neurosurgery, 2005. **56**(1): p. 98-106; discussion 106-7.
345. Lehmann, T.R. and H.S. LaRocca, *Repeat lumbar surgery. A review of patients with failure from previous lumbar surgery treated by spinal canal exploration and lumbar spinal fusion.* Spine, 1981. **6**(6): p. 615-9.
346. Hirsch, C.a.N., A, *The Reliability of Lumbar Disc Surgery.* Clin Orthop, 1963. **29**: p. 189-195.
347. Wilkinson, H., *The Failed Back Syndrome: Etiology and Therapy*. 2 ed. 1991: Harper and Row.
348. de la Porte, C. and J. Siegfried, *Lumbosacral spinal fibrosis (spinal arachnoiditis). Its diagnosis and treatment by spinal cord stimulation.* Spine, 1983. **8**(6): p. 593-603.
349. Siegfried, J. and Y. Lazorthes, *Long-term follow-up of dorsal cord stimulation for chronic pain syndrome after multiple lumbar operations.* Appl Neurophysiol, 1982. **45**(1-2): p. 201-4.
350. North, R.B., D.H. Kidd, and S. Piantadosi, *Spinal cord stimulation versus reoperation for failed back surgery syndrome: a prospective, randomized study design.* Acta Neurochir Suppl, 1995. **64**: p. 106-8.
351. Ochoa, J.L., *Essence, investigation, and management of "neuropathic" pains: hopes from acknowledgment of chaos.* Muscle Nerve, 1993. **16**(10): p. 997-1008.
352. Schwartzman, R.J. and T.L. McLellan, *Reflex sympathetic dystrophy. A review.* Arch Neurol, 1987. **44**(5): p. 555-61.

353. Subbarao, J. and G.K. Stillwell, *Reflex sympathetic dystrophy syndrome of the upper extremity: analysis of total outcome of management of 125 cases.* Arch Phys Med Rehabil, 1981. **62**(11): p. 549-54.
354. Stanton-Hicks, M., et al., *Complex Regional Pain Syndromes: guidelines for therapy.* Clin J Pain, 1998. **14**(2): p. 155-66.
355. Barolat, G. and A.D. Sharan, *Future trends in spinal cord stimulation.* Neurol Res, 2000. **22**(3): p. 279-84.
356. Fogel, G.R., S.I. Esses, and O. Calvillo, *Management of chronic limb pain with spinal cord stimulation.* Pain Pract, 2003. **3**(2): p. 144-51.
357. Harke, H., et al., *Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study.* Eur J Pain, 2005. **9**(4): p. 363-73.
358. Harbour, R. and J. Miller, *A new system for grading recommendations in evidence based guidelines.* Bmj, 2001. **323**(7308): p. 334-6.
359. Meglio, M., Cioni, B., Prezioso, A. and Talamonti, G, *Spinal Cord Stimulation (SCS) in the Treatment of Postherpetic Pain.* Acta Neurochir (Wien), 1989. **46**: p. 65-6.
360. Onofrio, B.M., T.L. Yaksh, and P.G. Arnold, *Continuous low-dose intrathecal morphine administration in the treatment of chronic pain of malignant origin.* Mayo Clin Proc, 1981. **56**(8): p. 516-20.
361. Knight, K.H., et al., *Implantable intrathecal pumps for chronic pain: highlights and updates.* Croat Med J, 2007. **48**(1): p. 22-34.
362. Wang, J.K., L.A. Nauss, and J.E. Thomas, *Pain relief by intrathecally applied morphine in man.* Anesthesiology, 1979. **50**(2): p. 149-51.
363. Portenoy, R.K., *Cancer pain: pathophysiology and syndromes.* Lancet, 1992. **339**(8800): p. 1026-31.
364. Bonica, J., *Treatment of Cancer Pain: Current Status and Future Needs*. Advances in Pain Research, ed. H.L. Fields, Dubner, R. and Cervero, F. Vol. 9. 1985: Raven.
365. Lamer, T.J., *Treatment of cancer-related pain: when orally administered medications fail.* Mayo Clin Proc, 1994. **69**(5): p. 473-80.
366. Smith, T.J., et al., *Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival.* J Clin Oncol, 2002. **20**(19): p. 4040-9.
367. Sloan, P.A., *Neuraxial pain relief for intractable cancer pain.* Curr Pain Headache Rep, 2007. **11**(4): p. 283-9.
368. Anderson, V.C., B. Cooke, and K.J. Burchiel, *Intrathecal hydromorphone for chronic nonmalignant pain: a retrospective study.* Pain Med, 2001. **2**(4): p. 287-97.
369. Van Dongen, R.T., B.J. Crul, and M. De Bock, *Long-term intrathecal infusion of morphine and morphine/bupivacaine mixtures in the treatment of cancer pain: a retrospective analysis of 51 cases.* Pain, 1993. **55**(1): p. 119-23.
370. Rauck, R.L., et al., *Long-term intrathecal opioid therapy with a patient-activated, implanted delivery system for the treatment of refractory cancer pain.* J Pain, 2003. **4**(8): p. 441-7.

371. Miyoshi, H.a.L., SG, *Systemic Opioid Analgesics*. 3rd ed. Bonica's Management of Pain, ed. J.D. Loeser. 2001: Lippincott Williams & Wilkins.
372. Cohen, S.P. and A. Dragovich, *Intrathecal analgesia.* Med Clin North Am, 2007. **91**(2): p. 251-70.
373. Anderson, V.C. and K.J. Burchiel, *A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain.* Neurosurgery, 1999. **44**(2): p. 289-300; discussion 300-1.
374. Kumar, K., M. Kelly, and T. Pirlot, *Continuous intrathecal morphine treatment for chronic pain of nonmalignant etiology: long-term benefits and efficacy.* Surg Neurol, 2001. **55**(2): p. 79-86; discussion 86-8.
375. Turner, J.A., J.M. Sears, and J.D. Loeser, *Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications.* Clin J Pain, 2007. **23**(2): p. 180-95.
376. Ossipov, M.H. and F. Porreca, *Challenges in the development of novel treatment strategies for neuropathic pain.* NeuroRx, 2005. **2**(4): p. 650-61.
377. Ilse, W., *Neuropathic pain: Mechanisms, diagnosis and treatment.* Can J Continuing Med Education, 2002. **19**: p. 99-108.