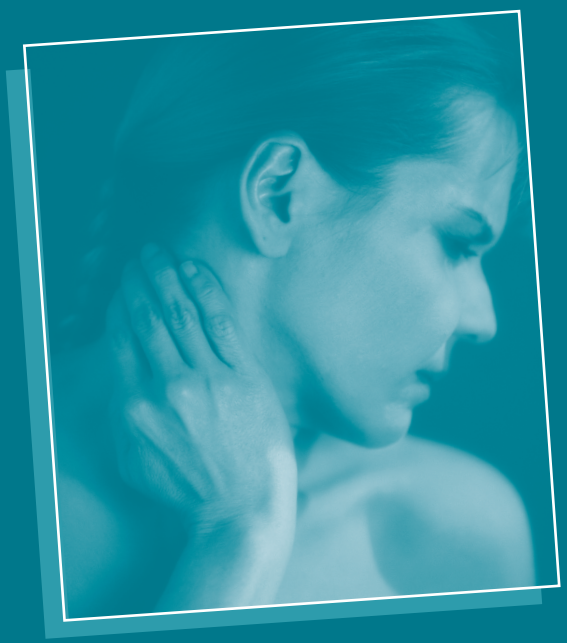
Practical Guide to **Chronic Pain Syndromes**



Edited by

Gary W. Jay

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Foreword

Pain specialists, noninterventionalists, primary care physicians, medical specialists, fellows, residents, and medical students all want to make clinical decisions about pain efficiently, often with an incomplete knowledge of underlying pathophysiology, while addressing global needs of their patients. Pain management is not part of the routine training for most physicians, yet the majority of patients seek medical attention because they have pain. Pain is typically addressed by primary care practitioners on an acute, time-limited basis, but when first- and second-level strategies fail, patients are referred to pain specialists and/or disease or body system specialists for more thorough evaluation and management. Primary care physicians, typically the first stopping point for patients in pain, as well as specialists from anesthesiology, internal medicine subspecialties, neurology, physical medicine, and psychiatry must be prepared to help people suffering with chronic pain disorders.

Pain and other medical specialists as well as primary care physicians managing patients having chronic pain know that usual acute pain management strategies do not address complex needs of people having many years of continuous pain. Interventionalists focus on performing procedures intended to interrupt pain processing, while medically oriented practitioners skillfully blend multiple medications, many of which primary care physicians are not comfortable prescribing (especially methadone). The field of modern pain management has become highly procedural, often relying upon opioids, involving the use of polypharmacy and the management of patients within multidisciplinary pain clinics.

Dr. Gary Jay and contributors to this book, *Practical Guide to Chronic Pain Syndromes*, have collectively demystified chronic pain, bringing the management of people with persisting pain into the understanding of pain medicine and other specialists. The chapter authors have prepared essential reviews focusing on the information most needed by specialists, fellows, residents, and medical students to confidently and competently manage complex people in pain. In the various pain disorder sections, chapters focus on common, but potentially vexing painful disorders: soft tissue pain syndromes, neuropathic pain, rheumatologic pain, urologic pain, back pain, cancer pain, end-of-life pain, and pain from other causes. In the second section, pharmacologic options are discussed: nonopioid analgesics and adjuvants, opioids, antidepressants, and anticonvulsants, with special attention to the legal aspects for prescribing controlled substances.

Today's specialists evaluating and treating people in pain are medical detectives. They make sense out of painful complaints by following clues, seeing patterns, laying their hands upon their patients, using scientific methods, while

balancing clinical suspicion, intuition, and compassion. People living with chronic pain may wish for absolute pain relief, but they are grateful for any pain relief and the opportunity to receive care from clinicians demonstrating concern and ability.

Practical Guide to Chronic Pain Syndromes is a "go to" book when information is needed concisely about some aspect of chronic pain. This book focuses on what matters most for busy clinicians: presentation of chronic pain syndromes, common causes and underlying pathophysiologic mechanisms, differential diagnosis, diagnostic assessment methods (e.g., laboratory studies, imaging, and electrodiagnostic testing), and recommended treatments. While much is said about the importance of evidence-based treatment, for many chronic pain syndromes there are limited well-controlled and randomized studies. The contributors have taken care to keep their messages practical, and readers are sure to find this book one they will keep close at hand.

B. Eliot Cole, MD, MPA
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Preface

Chronic pain syndromes (CPS) are complex problems that present a major challenge to health care providers. They are biological, psychological, and sociological in nature, may have an unclear etiology, and, frequently, poor responses to therapy. CPS, if treated in a typical mono- or bimodality manner may not give the patient the best treatment outcome, but as things are now, that may be the best that can be done for these difficult patients. Even the definition of a CPS (of any kind) may be considered unsettled, as some look at it as pain that persists more than three months, while others consider chronic pain to begin after six months. Pain that persists after physiological healing has occurred, typically in three months, posttreatment, for example, tells us nothing new—it becomes an entity in and of itself. The best way to treat it is to understand the complex interactions of the pathophysiology of pain as well as the issues of the psychological and sociological aspects of an individual patient's pain, and deal with it all as best as one can.

The purpose of this book is to give the practitioner the basics and more regarding a number of important, not uncommon, CPS that pain specialists, as well as other medical specialists see. Sometimes the most difficult issue is diagnosis—Clinically speaking, pain is what the patient says it is, and it is up to the clinician to determine what the patient means. Then the treatment phase begins and this may engender the use/need of chronic opioids, physical therapy, and psychological therapy—whatever it may take to help your patient's chronic pain problems.

Chronic pain can be considered to be like diabetes or hypertension—a disease that can be treated and controlled, but not necessarily cured.

Practical Guide to Chronic Pain Syndromes has been written for the noninterventional pain specialist as well as for other physicians who treat chronic pain of one, two, or multiple types. All of the pain syndrome chapters have information on a specific disorder, the pathophysiology, the treatment, any evidence-based medicine issues and, of course, up to date references.

I have elected to place the largest section, "Neuropathic Pain," first. This is followed by a section on probably the most common pain problems: the soft tissue pain syndromes including myofascial pain and fibromyalgia. One of the most frequently missed problems in my longer than a quarter century of patient care is the piriformis syndrome, which is also discussed in detail. Mechanical and neuropathic low back pain are also discussed in detail.

Many times, pain specialists are asked to deal with visceral pain syndromes such as interstitial cystitis and vulvovestibulitis, which are discussed by experts, along with prostatitis.

Cancer pain and palliative care are ever-growing issues and separate chapters dealing with both are included.

The section titled "Other Pain Syndromes" includes chapters on osteoarthritis, electrical injury, and neurogenic thoracic outlet syndrome.

Finally, no book would be complete, practical, and useful if it did not include a medications section.

I want to thank the many erudite, patient focused, and excellent contributors to this textbook. It was an honor and a pleasure to work with you!

It was a long road to get to here, and I believe it has been well worth it for the pain specialists, neurologists, anesthesiologists, physiatrists, urologists, rheumatologists, oncologists, general practitioners, internists, psychologists, nurses, physical therapists, as well as the residents and fellows and others who may benefit from the knowledge contained in these books.

Most of all, our patients should receive the ultimate benefit of this work.

Gary W. Jay, MD

Acknowledgments

First, as always, I want to thank my wonderful wife Suzanne and my incredible daughter Samantha for their love and patience with me during the extended period of time I spent working on this book. Many thanks also go to Byron Scott, R.Ph., my brother by choice, and one of the smartest and best people in the world to talk to; David Longmire, MD, another brother by choice, for his rather droll wit and strange ability to look just like my doppelganger with neither ability getting in the way of his amazing knowledge of neurology (with, of course, special attention to the Autonomic Nervous System); to my new friends at Pfizer (you know who you are) and, of course, to the thousands of patients I had the good fortune to meet, diagnose and treat- you were all my best teachers. After 25 years of clinical practice, when I made the choice to go into Pharma, I knew I would miss you all and I do.

Finally, this book is dedicated to Jim Kapp, who left us all too soon.

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1 Diabetic Peripheral Neuropathy

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THE DISORDER

Diabetes is currently on the rise around the globe. In 2007, the estimated total prevalence of diabetes (diagnosed and undiagnosed) in the United States was 7.8%, with the majority of affected individuals being 60 years and older. As the rate of diabetes has increased there has been an associated rise in prevalence of diabetic neuropathy (1).

Diabetic peripheral sensory polyneuropathy is one of the most common ailments associated with diabetes. Although it is possible to reverse the effects if treated early, diabetic neuropathy often results in permanent loss of function and death of the small nerve fibers, most commonly affecting the feet. It affects approximately 50% of the patients who have diabetes mellitus.

Despite its prevalence, the onset of symptoms is often mild and can go unnoticed for long periods of time, with most patients not experiencing any pain. However, approximately 11% experience chronic, painful symptoms (2).

Painful diabetic peripheral neuropathy (DPN) is associated with substantial patient burden due to interference with daily function, especially in those with suboptimal pain management. The severity of neuropathic pain is significantly associated with overall patient burden, employment disruption, and productivity. Not surprisingly, most interference is reported to result from reduced walking ability (3). The medical costs of DPN may account for up to 27% of the direct medical costs of diabetes, although the proportion due to pain is unclear (2).

Neuropathy is present in over 80% of diabetic patients with foot ulcers. Ulcers are more common because of decreased sensation perception of pressure and impairment of the microcirculation and integrity of the skin. Muscle imbalances may lead to anatomic deformities. Once an ulcer has occurred, aggressive therapy and protective measures should be taken to avoid secondary infection. The risk of lower limb amputation is high if there is a history of a previous foot ulcer, neuropathy, peripheral vascular disease, or poor glycemic control (4).

DIAGNOSIS

The diagnosis of DPN is based on the history. The pain may be spontaneous, continuous, or intermittent and is often worse at night. It affects the long nerve fibers

of the extremities, so the pain tends to be felt first in the toes and may progress to the hands. The pain is usually described as burning, stabbing, tingling, numb, hot, cold, or itchy.

General Examination of the Feet

Visual inspection may reveal several abnormalities such as claw toes due to atrophy of the small intrinsic muscles, allowing unopposed action of the larger muscles. Charcot arthropathy may be present and is characterized by a collapse of the midfoot arch and bony prominences. Sweating may be diminished or absent resulting in dry, scaly, cracked skin, allowing access to infection.

The feet or hands may reveal sensory abnormalities with diminution or heightened perception to touch, pinprick sensation, or hot and cold. Allodynia (nonpainful stimulation perceived as painful) may be present with patient complaints of being unable to have their feet under the bedclothes at night as the pressure of the sheet irritates them.

Testing Methods

- The Semmes-Weinstein monofilament is a simple calibrated nylon filament. It is inexpensive, easy to use, and rapid and reproducible, with a specificity of 90%. It should be placed at right angles to the skin and the pressure increased until it buckles. This indicates that a 10-g pressure has been applied. Unfortunately, the sensitivity has been reported to be only 44% to 71% depending on how many skin areas are tested, and the prevalence between examiners varied between 3.4% and 29.3% (5).
- Vibration testing is done with a 128-Hz tuning fork placed at the bony prominence at the base of the first toe and is quick and easy to do. The sensitivity and specificity have been reported to be 53% and 99%, respectively (6). If no vibration is felt, the diagnosis is probably DPN. Loss of vibration sense predicts a high probability of foot ulceration and has been suggested as predicting mortality from diabetic complications (7, 8).

Pain Scales

There are several neuropathic pain scales, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale and the Neuropathic Pain Scale, that have been devised to aid the diagnosis. Young et al. described the simple patient-completed questionnaire below (9).

1. What is the type of sensation felt? (maximum 2 points)
   a. Burning, numbness, or tingling (2 points)
   b. Fatigue, cramping, or aching (1 point)
2. Where is the location of symptoms? (maximum 2 points)
   a. Feet (2 points)
   b. Calves (1point)
   c. Elsewhere (no points)
3. Have the symptoms ever awakened you at night?
   a. Yes (1 point)
4. When is the pain worse? (maximum 2 points)
   a. At night (2 points)
   b. Day and night (1 point)
   c. Present only during the day (0 points)

5. What makes the pain better? (maximum 2 points)
   a. Walking around (2 points)
   b. Standing (1 point)
   c. Sitting or lying or no relief (0 points)

Total score:

0–2: Normal
3–4: Mild
5–6: Moderate
7–9: Severe

Additional Tests

Nerve conduction velocity (NCV) tests may be normal, as they only measure large fiber function and the majority of abnormalities are at the small fiber level.

Thermal thresholds in isolation or as part of quantitative sensory nerve testing may be more appropriate indicators of dysfunction of small-diameter sensory nerve fibers but are not widely available. Nerve or skin biopsies are useful only where the etiology is unclear or for research purposes.

Corneal confocal microscopy is a noninvasive evaluation of the middle layer of the cornea at a depth of 62 μm. Pictures taken of the corneal fiber density in this layer have been reported to closely correlate with the peripheral fiber density as measured by the much more invasive skin biopsy (10).

If the presentation of neuropathy is not symmetrical, another cause should be considered. Other differential peripheral neuropathic pain diagnoses to consider include the following:

- Entrapment neuropathy
- Alcoholism
- HIV infection
- Paraneoplastic syndrome
- Monoclonal gammopathy
- Vitamin deficiencies
- Amyloidosis
- Drugs and toxins: vincristine, cisplatin, isoniazid, arsenic, thallium
- Vasculitic neuropathy
- Fabry disease

PATHOPHYSIOLOGY

The pathophysiology of DPN is complex and not fully understood. Most theories involve interactions between metabolic and ischemic factors have been shown to create nerve damage. Several studies have begun to uncover the specific pathogenesis of diabetic neuropathy.

Hyperglycemia

By comparing animal axonal models that mimic the human disorders, it has become clear that hyperglycemia, or insulin deficiency, is a major culprit of DPN (11). The resulting damage occurs in DPN for both type 1 and type 2 diabetics. Common metabolic factors include the following:

- *Advanced glycosylation end products*—Glycosylation of tissue and plasma proteins can result in advanced glycosylation end products, which tend to

increase in concentration in diabetic patients. These end products are thought to play a major role in diabetic microvascular complications.
- *Sorbitol*—Glucose metabolism is more pronounced in patients with hyperglycemia. Accumulation of sorbitol interferes with cell metabolism by raising cell osmolarity and decreasing intracellular myoinsitol.
- *Oxidative stress*—Reduced antioxidants and prolonged exposure to reactive oxygen species lead to peripheral nerve damage and degeneration.

In the more severe type 1 DPN, insulin and C-peptide deficiencies augment the deficits in Na^+/K^+-ATPase and endothelial nitric oxide. These deficiencies result in gene regulatory abnormalities of neurotrophic factors, their receptors, and cell-adhesive proteins (12).

Disease Progression

In both experimental models and human diabetic subjects, there is an initial metabolic phase that is responsive to metabolic corrections. During this initial phase, damage, as caused by the processes described above, can often be reversed (13).

Progression of disease leads to a structural phase that is increasingly nonresponsive to therapeutic interventions. Abnormalities during the structural phase add to the severity of axonal pathology and result in severe consequences with respect to nerve function (14).

Metabolic Changes

One of the earliest metabolic abnormalities is shunting of excessive glucose through the polyol pathway, resulting in intracellular accumulation of sorbitol and fructose with depletion of other osmolytes such as taurin and myoinositol. The latter interferes with phosphoinositide turnover, resulting in insufficient diacylglycerol for activation of Na^+/K^+-ATPase. In type 1 DPN, the more severe effect on Na^+/K^+-ATPase is accounted for by additional insults caused by insulin and C-peptide deficiencies (15).

Unmyelinated fiber abnormalities occur early and are reflected in thermal hyperalgesia and allodynia. Damage to small myelinated Aδ and unmyelinated C-fibers underlies these functional abnormalities, which translate to abnormal pain sensation—a common symptom in diabetic patients with DPN. Damage to the axonal membranes of C-fibers induces increased formation of Na^+ channels and α-adrenergic receptors, facilitating ectopic discharges (16, 17).

The initial damage to small peripheral fibers appears to be coupled with impaired neurotrophic support by nerve growth factor and insulin, itself, both of which are specifically neurotrophic for small nociceptive ganglion cells of the dorsal root ganglia. This may explain the more severe degenerative changes of these fibers in type 1 versus type 2 diabetes (18).

TREATMENT

Prevention of Progression of DPN

Currently, DPN is treated symptomatically, but studies have shown a link between glycemic control and microvascular complications such as neuropathy.

Although there does not appear to be a close link to pain control, getting the HbA1c down to 7or less should be a priority.

Encouraging the patient to develop a list of achievable goals may assist with lifestyle changes. These goals should include, where relevant, smoking cessation, weight loss, and regular exercise. Getting the patient to want to change and to believe he or she can change may require a different type of therapeutic approach such as motivational interviewing (19).

Described in this section are several nonpharmacological and pharmacological treatments that have been shown to be effective in a number of trials. By one estimate, most therapies for DPN result in a 30% to 50% reduction in pain. This level of improvement may be disappointing to patients (20).

Nonpharmacological Treatment

There are several nonpharmacological treatments that have been shown to have some efficacy in small trials. Treatment should also include foot care.

Transcutaneous Electrical Nerve Stimulation

TENS versus sham stimulation had positive results in 31 patients (21). Pain, numbness, and allodynia improved significantly in a small, randomized, double-blind study of 19 patients with mild to moderate DPN in the group treated with TENS (22).

Acupuncture

There have been no large placebo-controlled studies evaluating the efficacy of acupuncture for DPN, but small open-label trials have reported some benefit (23).

Spinal Cord Stimulation

Spinal cord stimulation has been reported to provide long-term relief for some patients with DPN, but there have been no placebo-controlled studies (24).

Transcranial Magnetic Stimulation

TMS is a noninvasive technology whereby an electric current is passed through an insulated circular or figure-eight coil to produce a magnetic pulse. When the coil is applied to the head, the magnetic pulse is capable of passing uninterrupted through the skin, skull, and ultimately to the cortex.

Repetitive transcranial magnetic stimulation (rTMS) has been shown to produce long-lasting effects in some small-scale clinical trials. According to one trial, it might be effective in alleviating DPN (25).

Foot Care Advice

When discussing the care of the DPN foot, advice should include the following:

1. Avoiding walking barefoot.
2. Wearing well-fitted, not tight shoes.
3. Feeling the inside of the shoes before putting them on in case there is a stone or anything that may cause skin damage.
4. Washing feet twice a day to ensure that patients examine their feet at least that often.

5. The importance of careful nail cutting, even having a podiatrist do the cutting to avoid cutting the skin.
6. Treating all blisters and abrasions early.

Pharmacological Treatment

Frequently, patients take more than one drug for their pain. A cross-sectional, community-based survey of 255 patients with DPN found that a majority of patients (79.2%) had taken at least one medication and more than half (52.1%) had taken at least two for DPN during the preceding week (26).

Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most commonly used medications, with 46.7% reporting their use, although there is little evidence to support their efficacy. NSAIDs have a high potential for renal impairment in patients with diabetic neuropathy. Other frequently used medications were short- and long-acting opioids (43.1%), anticonvulsants (27.1%), second-generation antidepressants (18%), and tricyclic antidepressants (TCAs) (11.4%) (26).

Acetyl-L-Carnitine

Acetyl-L-carnitine (ALC) has reported beneficial effects on the metabolic abnormalities underlying the acute nerve conduction velocity slowing in experimental diabetes, such as Na^+/K^+-ATPase activity, endoneurial blood flow, and oxidative stressors (27).

A European and North American multicenter trial of 1346 patients with type 1 and type 2 diabetes and DPN received ALC, either 1500 or 3000 mg/day. None of the NCV or amplitude measures showed any significant improvement, but vibratory perception in the lower and upper extremities showed highly significant improvements. Pain also improved significantly in patients taking ALC 3000 mg/day both at 26 weeks and at the end of the trial at 52 weeks. Sural nerve biopsies also demonstrated increased nerve fiber regeneration (28).

ALC has a good safety profile and should be considered early in the disease, as results appear to be better the earlier the patient is treated (29).

ACE Inhibitors

The ACE inhibitor trandolapril was shown to improve peripheral neuropathy even in normotensive patients with diabetes. In general, the ACE inhibitor class of medications appears to have some protective effect against microvascular complications and organ damage from diabetes (30).

Lipid-Lowering Agents

Hypertriglyceridemia is a risk factor for development of diabetic neuropathy, and there is evidence that lipid-lowering agents may prevent DPN microvascular complications (31).

The lipid-lowering HMG-CoA reductase inhibitors (statins) may also possess neuroprotective properties in their own right (32).

Aldose Reductase Inhibitors

Metabolism of blood glucose via the polyol pathway, where aldose reductase is a key enzyme, may be important in the development of diabetic neuropathy. Therefore, blocking aldose reductase may reduce this risk of diabetic neuropathy.

In a one-year, placebo-controlled study, the aldose reductase fidarestat has been reported to be superior to placebo for reducing pain as well as the progression of peripheral diabetic neuropathy (33).

A postmarketing surveillance of more than 5000 patients on epalrestat, another aldose reductase inhibitor, was reported to show improvement of subjective symptoms, including spontaneous pain, in patients with DPN (34). In a three-year study, epalrestat was effective in slowing down the development of neuropathy as measured by changes in median nerve conduction velocity compared with controls. However, there was no significant difference in pain between the treated and untreated group (35).

α-Lipoic Acid

A meta-analysis of 1258 patients with DPN reported that infusions of α-lipoic acid (600 mg/day intravenously) ameliorated neuropathic symptoms and deficits after three weeks (36).

The ALADIN III (Alpha-Lipoic Acid in Diabetic Neuropathy) study showed that oral treatment with 600 mg three times a day resulted in a favorable effect on neuropathic deficits after six months (37).

The SYDNEY 2 (Symptomatic Diabetic Neuropathy 2) trial suggests that treatment for five weeks using 600 mg of α-lipoic acid orally every day reduces the paresthesias and numbness to a clinically meaningful degree (38).

All studies have reported a highly favorable safety profile. The drug is licensed in Germany, but not in the United Kingdom or the United States, for the treatment of DPN; however, it is sold as a food supplement in the latter two countries.

Tricyclic Antidepressants

Despite their widespread use, none of the TCAs has been approved by the FDA for treatment of DPN or any type of pain. A review found the total number of patients in clinical trials of the various TCAs for treatment of DPN to be less than 200, with no single study having more than 50 patients (39). That review found no difference in efficacy among the various kinds of TCAs, with an number needed to treat (NNT) of 3 (95% CI, 2.4–4.0) for improvement of pain of 50% or more. A 2005 Cochrane Collaborative analysis of five diabetic neuropathic pain trials of antidepressants reported that the NNT for amitriptyline's effectiveness was 1.3 (95% CI, 1.2–1.5; relative risk, 12.4; 95% CI, 5.2–29.2) (40).

Amitriptyline is the best studied TCA in DPN; other agents in this class include imipramine, clomipramine, desipramine, and nortriptyline. Their analgesic effect is independent of their antidepressant effect. Analgesia is thought to be the result of the inhibition of serotonin and norepinephrine reuptake, as well as sodium channel modulation.

The pain-relieving effect of amitriptyline is correlated with the total plasma concentration. If the plasma concentration exceeded 300 nmol/L, 70% of patients were responders on the daily rating of pain and 90% were responders on the global rating. Only 20% were responders at plasma concentrations below 300 nmol/L. This is lower than the reported corresponding level for the treatment of depression, which is 500 nmol/L (41).

Because of variable absorption, blood levels of amitriptyline should be taken. In a randomized controlled trial (RCT) of amitriptyline, it was found that total plasma levels of amitriptyline at a daily dose of 75 mg/day ranged from 56 to 925 nmol/L (42).

TCAs have a considerable adverse event burden. Ray et al. reported a slight increase in sudden cardiac death with TCA doses greater than 100 mg/day. There was no evidence that TCA doses lower than 100 mg increased the risk of sudden cardiac death (43). This is of obvious concern in the patient with diabetes who has a higher risk of heart disease. Some authors recommend baseline and follow-up electrocardiograms (ECGs) throughout treatment with TCAs (44).

Serotonin Norepinephrine Reuptake Inhibitors

There is general agreement that serotonin norepinephrine reuptake inhibitors (SNRIs) such as duloxetine, velafaxine and the newer SNRI's milnacipran, desvenlafaxine and venlafaxine are safer to use than TCAs and are a better option in patients with cardiac disease. However, the risk of hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is thought to be greater in elderly patients using selective serotonin reuptake inhibitors (SSRIs/SNRIs) than in those using TCAs (45). Hyponatremia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.

Venlafaxine

Results for the primary end point of pain intensity on the VAS showed that the 150 to 225 mg of venlafaxine ER significantly reduced pain intensity compared with placebo at week 6. Results with 75 mg were not different from those with placebo (46).

Another trial compared venlafaxine with imipramine for treatment of painful neuropathies. Treatment with either venlafaxine or imipramine significantly reduced pain compared with placebo; no significant difference was seen between the venlafaxine and imipramine groups (47).

In a multicenter, prospective, open-label study of 97 patients older than 80 years with depressive syndrome, not DPN, extended-release venlafaxine was found to be safe and effective in the elderly. Adverse events were reported by seven patients, but no serious events were reported. The most frequent adverse events were dizziness, gastric pain, and nausea. Treatment with venlafaxine over 24 weeks did not produce any clinically significant changes in blood pressure, heart rate, or other variables. The authors suggest that venlafaxine is particularly useful in the treatment of the elderly due to a low potential for drug–drug interaction (48).

Duloxetine

The efficacy of duloxetine in the treatment of DPN was established in three double-blind, placebo-controlled RCTs that included a total of 1139 patients. Patients with comorbid depression were excluded (49, 50).

The FDA-approved dosage of duloxetine 60 mg daily demonstrated rapid onset of action (within the first week of treatment) and sustained pain relief. All doses of duloxetine were well tolerated, with no significant changes in concentrations of hemoglobin A1C or triglycerides. Adverse events that were reported more often in the duloxetine group than in the placebo group were somnolence and constipation; these were mild to moderate (51).

Milnacipran and Desvenlafaxine

There have been no studies reported as yet on the efficacy of these drugs on DPN.

Antiepileptic Drugs

In the elderly, antiepileptic drugs may cause significant central nervous system side effects, especially dizziness and drowsiness, which not infrequently lead to discontinuation of treatment. Cognitive side effects are common and may go unrecognized in older patients, particularly in patients with communication problems.

Pregabalin

The efficacy of pregabalin in DPN has been established in three double-blind, placebo-controlled RCTs that included a total of 730 patients. It demonstrated early and sustained improvement in pain and a beneficial effect on sleep with dosages ranging from 150 to 600 mg daily. The most common treatment-related adverse events in the 300- and 600-mg/day groups were dizziness (27.2% and 39%, respectively), somnolence (23.5% and 26.8%, respectively), and peripheral edema (7.4% and 13.4%, respectively) (52–54).

Gabapentin

In one randomized trial of DPN, gabapentin was initiated at a dosage of 300 mg, three times daily, and increased during a period of four weeks in increments of 300 mg (from 900 to a maximum of 3600 mg/day). Beginning at week 2 and continuing throughout the trial, patients treated with gabapentin showed statistically significant improvements in pain scores compared with those who received placebo (55).

Sodium Channel Blockers

Sodium channel blockers have not been shown to be effective in patients with painful diabetic neuropathy. Carbamazepine cannot be recommended due to inadequate evidence in painful diabetic neuropathy. The successor drug, oxcarbazepine, has been withdrawn from clinical trials because of lack of efficacy (56). Neither topiramate nor lamotrigine has been shown to be effective (57, 58).

Opioids

The weak opioid, tramadol, is effective in painful DPN, but more severe pain often requires stronger opioids such as oxycodone (59). Two trials over four and six weeks have demonstrated significant pain relief and improvement in quality of life following treatment with controlled-release oxycodone, in a dose range of 10 to 100 mg (mean 40 mg/day). In these trials, antidepressants and anticonvulsants were not discontinued throughout the trial. As expected, adverse events were frequent and typical of opioid-related side effects (60, 61).

Combination therapy is common in treating DPN but has been poorly researched. In a study that titrated the maximum tolerable dose of a combination treatment of gabapentin and morphine compared with monotherapy of each drug, the maximum tolerable dose was significantly lower but efficacy was better, suggesting an additive interaction between the two drugs (62).

Isosorbide Dinitrate Spray

In a study of 22 DPN patients, 11 patients using topical isosorbide dinitrate had benefit and continued with the spray before bedtime compared with only four patients receiving placebo. There were virtually no adverse effects (63).

TABLE 1 Pharmacological Treatment Tier Recommendations

Drug	Dworkin et al. (66)	Attal et al. (67)	Argoff et al. (68)	Moulin et al. (69)
Antidepressants				
TCA	1	1	1	1
Duloxetine	NR	2	1	2
Venlafaxine	2	2	2	2
Bupropion	2	NR	—[a]	NR
Paroxetine	2	NR	NE	NR
Citalopram	2	NR	NE	NR
Antiepileptics				
Gabapentin	1	1	2	1
Pregabalin	1	1	1	1
Lamotrigine	NR	NR	2	NR
Valproate	NR	2	NR	4
Topiramate	NR	NE	NR	4
Phenytoin	NR	NR	—[a]	NR
Opioids				
Tramadol	1	2	2	3
Oxycodone/methadone	1	2	1	3
Topicals				
Lidocaine 5%	1	2	—[b]	2
Capsaicin	3	2	—[b]	3
Others				
Mexilitine	3	NE	NR	4
Clonidine	3	NE	NR	4

1 = first tier, 2 = second tier, 3 = third tier, 4 = fourth tier.
[a] >1 RCT.
[b] Mechanism of action.
Abbreviations: NR, no recommendations; NE, not considered effective.

Local Anesthetics

Lidocaine 5% patches may be effective for treating patients with DPN (64, 65). Some patients find that cutting the patch and wrapping it around their toes and then putting socks on will decrease their nighttime pain and allow a better night's sleep.

Summary of Pharmacological Treatments

There have been three published task force recommendations for pharmacological therapies in neuropathic pain and one consensus guidelines published on DPN. Drugs were evaluated and ranked based on recommendations from tier 1 to 4, with tier 1 drugs being the most recommended, as shown in Table 1.

Comorbidities

When deciding which medication to choose, other factors must play a role.

- Obesity: Avoid or monitor carefully TCAs or a gabapentinoid (gabapentin, pregabalin), all of which have significant risk of weight gain.
- Poor sleep: Consider any of the tier 1 medications in Table 1.
- Smoking: To encourage smoking cessation consider bupropion to assist in decreasing withdrawal symptoms.

- Polypharmacy: Consider a gabapentinoid and/or venlafaxine.
- Depression or anxiety: Consider duloxetine, venlafaxine, or TCAs because of fewer drug to drug interactions.

Surgical Treatment

If the presentation of pain is atypical, with pain felt over individual nerve dermatomes, entrapment neuropathy should be considered. A Tinel sign should be looked for over the deep peroneal or posterior tibial nerve. The superficial peroneal nerve, as it goes around the head of the fibula, may also be tender to touch, leading to a possibility of entrapment at this site. Although there are advocates of decompression in these cases, there is controversy as to whether surgical nerve decompression surgery is effective (70, 71).

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2 HIV/AIDS Neuropathy

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THE DISORDER

There are several forms of peripheral neuropathy related to HIV/AIDS, but the most common is distal sensory polyneuropathy (DSP). DSP has become the most frequent neurologic syndrome associated with HIV infection, and the pain associated with this condition can be debilitating. Several factors such as age, use of antiretroviral medication (ARV), severity of HIV infection, diabetes, and alcohol abuse have been related to an increased risk of developing DSP (1). However, studies of subgroups who received highly active antiretroviral therapy (HAART) have not shown a relationship between virologic and immunologic status, and the development of symptomatic sensory neuropathies (2). There are two subtypes of DSP: the type solely associated with HIV infection and the type associated with antiretroviral treatments, sometimes referred to as antiretroviral toxic neuropathy (ATN) (3). When caused by ARV, the clinical presentation may be the same except for a temporal relationship with ARV use. Neuropathy in HIV can also result from other causes, such as chronic hepatitis C infection, vitamin deficiency, or chemotherapy.

Occurring in the middle and late stages of HIV infection, DSP commonly presents as painful feet. Neuropathy related to ARV toxicity may occur at any stage of HIV infection. When DSP is caused by medications, the most common culprits are antiretroviral agents, but medications such as dapsone, isoniazid, and chemotherapeutic agents have also been implicated. Nucleoside reverse transcriptase inhibitors (NRTIs) are the class of drugs most frequently associated with peripheral neuropathy.

Prevalence

The prevalence of DSP varies from 9% to 63% in different series (4). Although the incidence has progressively decreased since the introduction of HAART (5), DSP has become more prevalent. This increase in prevalence is most likely due to the increased survival of those infected with HIV, the occurrence of comorbidities with similar complications, and the use of antiretroviral therapy (6).

DIAGNOSIS

The diagnosis of the peripheral neuropathy syndrome in HIV-infected patients is generally based upon the clinical picture.

DSP commonly presents as tingling and numbness in the toes bilaterally, and then gradually spreads proximally from the lower extremities, rarely involving the upper extremities. Early painful dysesthesias of the lower extremities are common, but patients may also complain of numbness. These symptoms

are typically most severe on the soles of the feet and are worse at night or after walking (7). There is sensory loss in a stocking distribution, and ankle jerks are decreased or absent. Knee jerks are occasionally decreased and may be absent in severe cases. Vibratory, pain, and temperature sensation is usually decreased, but muscle weakness is not a prominent symptom of DSP and generally occurs only in advanced disease.

Compared with DSP that is related to HIV infection, that related to antiretroviral toxicity is indistinguishable, except for the temporal relationship of ARV use with onset, and eventual resolution with discontinuation. Whereas HIV-related DSP may take weeks to months to develop, ATN generally occurs shortly after exposure and may not be related to cumulative exposure to ARV (8). Specific agents in the NRTI class are most commonly associated with DSP, particularly the so-called "d" drugs: ddI (didanosine), ddC (zalcitabine), and d4T (stavudine). As a result of the frequency of ATN, and other adverse drug reactions, prescribing patterns in the developed world have changed to limit the use of these agents. In developing countries, however, ARV regimens still commonly contain stavudine. Concern about a possible relationship of ATN and the class of ARV known as protease inhibitors led to a recent study by Ellis and colleagues. The investigators concluded that the independent risk of DSP attributable to protease inhibitors, if any, is very small (9).

It can be clinically difficult to distinguish between HIV-associated and drug-induced neuropathy. Numbness, tingling, and pain are common in both types. Both predominantly affect the distal extremities, mostly in the lower limbs. The upper extremities may become involved late in the course and may be more commonly affected with drug toxicity. A beneficial response after withdrawal of the offending agent can help identify ARV as the cause. It has been noted that a transient intensification of symptoms ("coasting") can occur for four to eight weeks after drug withdrawal and before improvement begins (6).

In patients with significant weakness, or an asymmetric presentation, additional diagnoses should be considered. Electrodiagnostic studies including electromyography and nerve conduction studies may be helpful when there is doubt about the diagnosis (4). Nerve biopsy is rarely indicated, and a skin biopsy may be helpful in some cases. A careful history of antiretroviral therapies with a review of other medications should be done to exclude possible iatrogenic causes.

Laboratory evaluation in DSP is relatively unrevealing, but it should exclude other causes of this type of neuropathy. Testing should include the following:

Vitamin B_{12} and folate levels
Thyroid-stimulating hormone assay
Fasting blood sugar
Liver function tests
Blood urea nitrogen and creatinine
Serum protein electrophoresis and immunoelectrophoresis
Screening test for syphilis

Electrophysiologic findings show small or absent sural sensory nerve activation potentials. Nerve conduction studies usually confirm a length-dependent

axonal polyneuropathy. Needle electromyography shows acute or chronic partial denervation of distal lower limb muscles.

Nerve biopsy is rarely indicated to exclude other neurologic diagnoses. Features include loss of myelinated and unmyelinated fibers with axonal degeneration and macrophage activation (10).

Skin biopsy may be positive in some patients with negative electrodiagnostic studies (4).

The presence of a low epidermal nerve fiber density (<11 fibers/mm) has been noted in persons with DSP. This finding was associated with an increased likelihood of developing DSP in one study (11).

PATHOPHYSIOLOGY

The pathogenesis of DSP is not well understood and is thought to be multifactorial.

There is little evidence to support direct infection of the neurons by HIV-1, suggesting that this is not likely to be an important mechanism for neuronal injury (12). In vitro studies suggest roles for viral proteins such as gp120 in the indirect stimulation of axonal degeneration and/or cell death (3).

The envelope glycoprotein gp120 may produce neurotoxicity within the dorsal root ganglion, and in vitro studies have suggested that gp120 induces apoptosis in rodent dorsal root ganglion cultures and lowers the threshold for excitation (7).

Neuropathologic changes of the dorsal root ganglia include inflammatory infiltrates of lymphocytes and activated macrophages and low numbers of neurons. The amount of macrophage activation in the dorsal root ganglion relates with symptomatic DSP (7).

The prominent presence of proinflammatory cytokines including TNF-alpha, interferon alpha, interleukin 6, and other inflammatory mediators including nitric oxide has been shown in dorsal root ganglia in AIDS. This may lead to neuronal hyperexcitability as has been seen in animal models (7).

In patients receiving NRTIs, therapy interferes with DNA synthesis and causes mitochondrial abnormalities (13). These abnormalities are thought to underlie the pathogenesis of antiretroviral-related DSP. This view is supported by the evidence showing increased serum lactate concentrations and decreased serum concentrations of acetylcarnitine in patients with this condition (7). Elevated blood lactate levels occurred in 90% of those with DSP who were using stavudine (14).

A prospective study of 509 patients again identified older age and receipt of stavudine and didanosine as being more frequent in those developing DSP, but the mitochondrial haplogroup T was also more frequent in this group (15).

TREATMENT

Distal Sensory Polyneuropathy

Management of DSP is largely symptomatic and usually aimed at ameliorating the painful dysesthesias. Correcting nutritional and metabolic abnormalities when present may be helpful. Various classes of medication have been used in the treatment of DSP.

Tylenol/NSAIDs

Acetaminophen or nonsteroidals (NSAIDs) are the initial treatment for mild pain. If this is inadequate, other treatment should be considered.

Tricyclic Antidepressants

Tricyclic antidepressants are still used for the treatment of HIV-associated neuropathies, despite the absence of efficacy noted in two small studies (16, 17). Either nortriptyline or amitriptyline may be used. In patients who experience nighttime pain primarily, amitriptyline is a sound alternative. Treatment may be initiated with lower doses to reduce possible side effects such as sedation, urinary retention, dry mouth, and orthostatic hypotension. A starting dose of 25 mg at night is gradually increased to 75 mg or as high as 100 to 150 mg if needed. For patients with daytime pain, oral nortriptyline is often used, since it has a less sedative effect. A starting dose of 10 mg/day is gradually increased to 30 mg three times a day.

Anticonvulsants

Gabapentin

Gabapentin has been widely used in the treatment of DSP. The use of gabapentin for the treatment of painful HIV-related neuropathy was found to reduce pain better than placebo in small groups of patients in two studies (18, 19). Beneficial effects begin with higher doses. The usual starting daily dose is 300 mg/day in three divided doses, but doses can be increased to a maximum of 3600 mg/day. Slow escalation of doses should allow for tolerance to side effects such as somnolence and dizziness.

Pregabalin

Pregabalin is an anticonvulsant designed as a more potent successor to gabapentin. Although pregabalin may be used for the treatment of patients with HIV-associated painful peripheral neuropathy, a randomized, double-blind, placebo-controlled study (20) showed no long-term difference in end point mean pain score between pregabalin and placebo groups. Important to note is that there was a larger-than-usual placebo effect in this study compared with similar studies, possibly negating the effect of pregabalin.

Lamotrigine

Lamotrigine has also been studied in HIV-DSP. In a randomized, placebo-controlled trial (21), lamotrigine alone showed improved pain control over placebo, but only in patients receiving neurotoxic antiretroviral therapy. There was a seven-week dose escalation phase, followed by a maintenance phase. In a different double-blind, placebo-controlled trial (22), lamotrigine, 200 to 400 mg daily, when used in combination with other medications for neuropathic pain, did not demonstrate medication efficacy better than placebo.

Other Agents

Memantine

The use of memantine for the treatment of HIV-associated peripheral neuropathy was evaluated in a placebo-controlled study enrolling 45 subjects. This

N-methyl-d-aspartate (NMDA) receptor antagonist used in the treatment of Alzheimer's disease was not effective at reducing HIV-associated peripheral neuropathy (23).

Prosaptide
A randomized trial evaluating the polypeptide prosaptide for HIV-associated sensory neuropathies (24) showed that, although prosaptide was safe, it is not an effective agent in the treatment of HIV-associated peripheral neuropathy.

Tramadol
Tramadol 50 mg po bid or narcotics are reserved for those with breakthrough pain, as part of a broader treatment regimen. In refractory cases of peripheral neuropathy, the patient may respond to combinations of medications.

Topical

Lidocaine gel
In a double-blind, placebo-controlled multicenter study, lidocaine 5% gel was a safe but ineffective agent in the treatment of pain in HIV-associated DSP (25). The gel was applied once daily to skin over the area of pain.

Capsaicin patch
A double-blind multicenter study randomized 307 subjects with HIV-related peripheral neuropathy to compare high-concentration capsaicin patch versus a low-concentration capsaicin patch. The high-concentration patch had a greater reduction of pain intensity over a 12-week period, 23% versus 11% (26), when applied for 30 to 90 minutes once daily.

Cannabis
Cannabis may be useful in the management of painful HIV-associated sensory neuropathy. A prospective, randomized, placebo-controlled trial of 50 patients with painful HIV-associated sensory neuropathy (27) showed that smoked cannabis reduced daily pain better than placebo (34% vs. 17%). Fifty-two percent of the group treated with cannabis reported a reduction in pain greater than 30% as opposed to the placebo group who experienced a 24% reduction in pain. The first cannabis cigarette reduced chronic pain by a median of 72% vs. 15% with placebo ($p < 0.001$). The patients smoked up to one cigarette three times a day, containing approximately 1 g of cannabis with 3.56% tetrahydrocannabinol (THC).

Acupuncture
In a case series, 21 subjects with HIV-related neuropathy received acupuncture treatment, which demonstrated that subjective pain and symptoms of neuropathy were reduced during the period of acupuncture. The total subjective peripheral neuropathy summary score was reduced by approximately 50% (28).

Healing Touch
A review of anecdotal reports of healing touch (29) found that there are many positive outcomes, but none of the findings were conclusive.

Plasmapheresis/Intravenous Gamma Globulin

Kiprov et al. (30) treated HIV neuropathy with plasmapheresis and intravenous gamma globulin. It appears that the combination of plasmapheresis and intravenous gamma globulin was a potent immunomodulatory therapy for patients with HIV-related neuropathy.

It has been recognized that unhealthy behaviors may be employed by HIV-positive patients suffering from DSP. As part of a larger study on self-care and HIV (31), investigators identified specific unhealthy self-care behaviors such as cigarette smoking, alcohol consumption, and illicit drug use which were employed to alleviate pain. It was concluded that the clinician must partner with the patient to address any unhealthy behavior that may exacerbate DSP.

Antiretroviral Toxic Neuropathy

Treatment of ATN should include the discontinuation of drugs that cause peripheral neuropathy. About two-thirds of these patients will eventually respond to the NRTI discontinuation.

Two large studies (32, 33) demonstrated the beneficial effect of using lamotrigine in patients with ATN rather than DSP. Dose escalation occurred over seven weeks to reach a maximum of 400 to 600 mg/day in two divided doses.

Acetyl-L-carnitine has been used as treatment for painful ATN in HIV patients. In an open-label study (34), acetyl-L-carnitine was found to be effective in symptomatic treatment of painful neuropathy but had no observable effect on neurophysiologic parameters. In another double-blind, placebo-controlled, multicenter study (35), investigators looked at acetyl-L-carnitine in the symptomatic treatment of ATN. Using the Visual Analog Scale, acetyl-L-carnitine was found to significantly reduce the subject's pain rating in comparison to placebo.

Amitriptyline, mexiletine, topical capsaicin, 5% lidocaine, and gabapentin may also be useful therapeutic modalities for treating ATN.

In a prospective study (36), 11 HIV/AIDS patients with a drug-induced neuropathy were enrolled. Noninvasive skin electrodes were placed on the leg, and low-voltage current was passed for 20 minutes every day for 30 days. Although only seven individuals completed the study, the results support the notion that low-voltage electroacupuncture improves the condition of the neuropathic HIV/AIDS patient.

General Measures

Podiatrist evaluation (to develop plan of care, including exercise, care of feet, etc.)

Loose shoes or no shoes
Soak feet
Short walks
Blanket bridge to protect feet while sleeping

Initiation of HAART may help in DSP
Vitamin supplements may be considered—mainly B_1, B_{12}, and folate
Other supplements including magnesium, α-lipoic acid, γ-linolenic acid
Avoidance of alcohol
Control blood sugar if applicable
Alternative therapy: massage, yoga, hypnosis, and meditation

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3 Central Poststroke Pain

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THE DISORDER

Central poststroke pain (CPSP) was originally thought to be "thalamic" pain, as described by Dejerine and Roussy (1), although it was described even earlier in 1883 (2). Dejerine and Roussy (1) characterized their eponymous thalamic pain syndrome as including hemiplegia; hemiataxia and hemiastereognosis; difficulties with both superficial and deep sensation; persistent, paroxysmal, typically intolerable pain; and choreoathetoid movements. This syndrome is now known as central poststroke pain syndrome.

DIAGNOSIS

The reported incidence of CPSP varies widely from 2% (3) to 8% (4) in stroke patients and to 25% (5) in patients with lateral medullary infarctions (Wallenberg's syndrome).

CPSP is broadly defined as central neuropathic pain, secondary to lesions or dysfunction in the central nervous system. It is typically characterized by constant or intermittent pain and sensory abnormalities, most commonly of thermal sensation (6).

The pain is typically described as burning, scalding, or freezing and burning. Early diagnosis can be difficult, as the patients who develop CPSP may develop the problem long after their cerebral vascular accident (CVA), causing misdiagnosis or significant delay prior to treatment. Also, as these patients may have cognitive or speech difficulties, as well as depression, anxiety, and sleep problems, diagnosis may be further complicated. They may also develop spontaneous dysesthesias and stimulus-evoked sensory disturbances including dysesthesia, hyperalgesia, and allodynia (6, 7).

The onset of the pain may be immediate or be delayed for months to years (7–9). In 40% to 60% of CPSP patients, the onset of their centrally related pain post stroke may occur more than one month after the CVA (10). The pain may encompass a large part of the contralateral body, but it may also involve only a small area.

Sensory abnormalities are also associated with CPSP. These may include altered sensory processing: warm and cold stimulation applied to the skin may be perceived as paresthesias or dysesthesias rather than cold or warm (4,7). Allodynia is found in 55% to 70% of patients (11, 12). Hyperalgesia and dysesthesia are also frequently seen (13).

Evaluation of the CPSP patient may be more complex than that of the typical pain patient, at least in part for reasons noted above. The pain history must be accompanied by a pain-specific sensory examination, musculoskeletal and

myofascial evaluation, and basic psychological evaluation. Specialized sensory testing may also be needed, something that a neurologist can easily learn but may need specialized tools (14).

PATHOPHYSIOLOGY

Locations of the lesions inducing the CPSP have been demonstrated to be referable to the spinothalamocortical tract/pathway, typically associated with abnormal evoked sensations in the peripherally affected area (10,15,16). While at least three thalamic regions, which directly or indirectly receive spinothalamic projections, appear to be involved in the development of CPSP—the ventroposterior thalamus including the posteriorly and inferiorly located nuclei bordering on that region, the reticular nucleus, and the medial intralaminar region—it is the ventroposterior thalamic region that is proposed to be most significantly involved in central pain (17–19). It should also be noted that cerebrovascular lesions located above the diencephalon, that is, in the parietal lobe, may also induce CPSP (11,17,20).

While damage to the spinothalamocortical pathway appears to be a necessary condition in CPSP, it is thought that the spontaneous pain linked to CPSP is secondary to hyperexcitability or spontaneous discharges in thalamic or cortical neurons that have lost part of their normal input (21).

CPSP is most typically associated with a single lesion, associated with either a focal gray or white matter lesion; the lesion may be at the spinal, brain stem, or cerebral level, but it is always contralateral to the pain of CPSP; CPSP is associated with abnormal somatic senses, particularly thermal and/or pain sensations—most commonly, a loss of sensation is seen, but one may also see an exaggerated sensation of pain or temperature. The pain of CPSP may unilaterally involve the contralateral (to the lesion) face, body, and extremities, or it may be focal, involving only a limb, part of a limb, or the face; it is almost always within the region of somatic motor or sensory impairment; it may begin at the time of the CVA or be delayed for months (22).

Studies using magnetic resonance imaging and positron emission tomography (PET) scan have demonstrated anatomical lesions and associated information. One study using functional magnetic resonance imaging and diffusion tensor imaging found that in CPSP, there is an important role of damage of lateral nociceptive thalamoparietal fibers, along with release of activity of anterior cingulate and posterior parietal regions (23). An older study using single-photon emission computerized tomography found a contralateral relative hyperactivity in a central region corresponding with the thalamic region in patients with CPSP (24).

The "disinhibition hypothesis" of CPSP suggests that there is an excessive response (including dysesthesias/hyperalgesia/allodynia) associated with a loss of sensation secondary to a lesion of a "lateral nucleus" of the thalamic or "corticothalamic pathways." It was also thought that injury to a cool-signaling lateral thalamic pathway disinhibits a nociceptive medial thalamic pathway, producing both burning, cold, ongoing pain and cold allodynia. Using quantitatively evaluated sensory testing, it was found that, in CPSP, tactile allodynia occurs in disturbances of thermal/pain pathways that can spare the tactile signaling pathways, and that cold hypoesthesia itself is not necessary or sufficient for cold allodynia (25).

Another way of evaluating CPSP using PET scan technology revealed a striking loss of opioid receptor availability widely distributed throughout a great deal of the hemisphere contralateral to the pain (especially in the thalamus, anterior and posterior cingulate cortex, insula, S2, and lateral prefrontal cortex) (26).

It has previously been pointed out that decreased opioid receptor binding can also indicate the release of endogenous opioids during pain (27). The authors of the previous study (26) found that the location and distribution of the diminished receptor binding was more extensive and showed little overlap as compared to the other group (27). It is thought possible that the loss of opioid receptor availability in CPSP may be secondary to a reduction or downregulation of opioid receptors, resulting in a reduction of effectiveness of endogenous, opioid-mediated, analgesic mechanisms (26).

A later study looked at peripheral versus central neuropathic pain (28). The authors used PET scans to evaluate patients with peripheral ($n = 7$) and CPSP ($n = 8$) neuropathic pain patients. They found that in CPSP patients, interhemispheric comparison indicated a significant decrease in opioid binding in posterior midbrain, medial thalamus, and the insular, temporal, and prefrontal cortices contralateral to the painful side. The patients with peripheral neuropathic pain did not show any lateralized decrease in opioid binding. The authors concluded that decreases in opioid binding were much more extensive than anatomical cortical lesions and were not colocalized with the lesions: metabolic depression (diaschisis) and/or degeneration of opioid receptor–bearing neurons secondary to central lesions appears to be a likely mechanism (28).

Sympathetic dysfunction has also been felt to play a role in central pain secondary to signs of abnormal sympathetic activity: edema, hypohidrosis, trophic skin changes, changes in skin color, and decreased skin temperature (12,29). It is also noted that some or many of these changes may be secondary to "movement allodynia," which makes the patient keep the affected limb motionless (9).

Reports of CPSP associated with abnormal "epileptiform" activities in thalamic cells may be involved with central pain (30, 31). This would also indicate that some aspects of the problem may be secondary to cortical involvement, as epileptiform discharges are associated with that region, typically. Another group also noted that central pain may be a manifestation of partial epileptic seizures (32).

TREATMENT

Treatment of the CPSP is difficult and options are limited.

The most common first-line drug is amitriptyline, with other drugs including opiates treated as second line (10). Amitriptyline is thought to be helpful, secondary to its reuptake inhibition of serotonin and norepinephrine (33). In a controlled trial of amitriptyline and carbamazepine, only patients on amitriptyline reached a statistically significant reduction in pain compared to placebo. Patients on carbamazepine did not but had "some pain relief" and more side effects (34).

Aside from amitriptyline, anticonvulsants including lamotrigine and gabapentin have been reported to provide pain relief with better safety than carbamazepine and phenytoin (35–39). In spite of the articles suggesting lamotrigine provided good relief of CPSP, a Cochrane review found that lamotrigine had only limited evidence that it would be useful, and it was, in fact, unlikely to be of benefit for the treatment of neuropathic pain (40).

Other antidepressants and anticonvulsants have also been tried in the treatment of CPSP, but none has become a primary or gold-standard treatment (41–46).

Intravenous lidocaine appeared to be helpful in patients with CPSP (47, 48). Intravenous naloxone was not helpful in CPSP (49), while intrathecal baclofen, an agonist of GABA-B receptors, did provide relief for CPSP patients (50).

Stimulation of the primary motor cortex for intractable deafferentation pain, as well as central stroke pain, has been used successfully. The mechanism of pain relief by this form of electrical stimulation of MI is uncertain (51, 52). However, motor cortex stimulation is felt to be the treatment of choice in poststroke pain, thalamic pain, or anesthesia dolorosa of the face (53).

One group looked at the effectiveness of chronic subthreshold stimulation of the contralateral precentral gyrus in patients with intractable neuropathic pain for more than 15 years. They found that patients with trigeminal neuralgia had a greater positive effect than those with CPSP. They note that positive effects can last for 10 years in long-term follow-up (54).

Repetitive transcranial magnetic stimulation of the primary motor cortex has also been used successfully, as long as the postcentral gyrus (M1) is stimulated (55). Another group found this modality to give good but transient relief (56).

Transcutaneous electrical nerve stimulation (TENS), both high and low frequency, was tested on patients with CPSP ($n = 15$). Four patients obtained pain relief. Three patients continued to use TENS ipsilaterally with good effect at 23 to 30 months, while in one-third of the patients, TENS temporarily increased their pain (57).

One undesirable effect of repetitive deep brain stimulation (DBS) is the reduction of the seizure threshold, known as kindling (58–62). An associate of the author (personal communication) described a patient whose pain was only partially reduced with the original stimulus parameters of DBS. In an attempt to improve pain control, that individual used the external controller to increase the amount of stimulation above the amount used by the attending neurosurgeon. After several days of this maneuver, the patient suffered a first-ever focal onset, secondarily generalized seizure. To the author's knowledge, this patient may represent the first case of self-induced kindling of seizures in a human patient using DBS for pain control. Other treatments include sympathetic blockade, as well as surgical interventions including cordotomy, dorsal root entry zone lesions, thalamotomy, or cortical and subcortical ablation (63–69).

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