Neuropathic Pain:

Mechanisms, Diagnosis and Treatment

Many physicians face the challenging responsibility of treating chronic pain. Such treatment requires flexibility, determination and persistence on the part of the physician.

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Treatment of chronic pain is a common and challenging responsibility that crosses the boundaries of most medical and surgical specialties. Although the 21st century has seen a progressive increase in the number of specialty pain clinics, the individual family practitioner remains responsible for pain management in most patients. Treatment of chronic neuropathic pain (neuralgia) requires specific and unique strategies, and often tests the physician's flexibility, determination and persistence. This review discusses basic mechanisms and principles of diagnosing and treating neuralgia with the principal origin in the peripheral nervous system.

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Diagnosis

Systematic treatment depends on an accurate diagnosis. This is particularly important in rare instances where definitive treatment remedying the pathophysiologic process is available (*i.e.*, carpal tunnel syndrome). Definitive treatment always supersedes symptomatic/prophylactic treatment.

Neuropathy, the fundamental denominator of peripheral neuropathic pain, may be of focal, multifocal (rare) or diffuse distribution. Focal, discretely localized neuralgia may be of the nerve, root, or, occasionally, plexus origin. More prevalent causes of focal neuropathy are listed in Table 1. Occasionally, central processes (cord or brain) also may cause focal pain. In the developed world, this is most commonly seen in cases of demyelination. Primary central pain is not further discussed in this article.

Neuralgia of radicular origin tends to follow a dermatomal distribution and shares nerve territories. Typically, it is relatively discrete in its distribution. Pain that crosses a major joint (*e.g.*, elbow or knee) supports the diagnosis of radiculopathy. It is less common for pain due to a solitary peripheral nerve lesion to cross a major joint. If such pain is found within a body area, however, it tends to show a more extensive distribution than does radicular pain, and it crosses dermatomal boundaries. Plexopathies may be focal or multifocal. Pain of the plexus origin, unless highly localized, crosses both nerve and dermatomal boundaries.

Pain distribution is, however, not always a reliable indicator of its origin. A good example is carpal tunnel syndrome (CTS). In CTS, the pain is often on the hand dorsum, but it is not supplied by the median nerve. Although numbness is useful for making a diagnosis, its distribution is highly unreliable as an indicator of the source of neuropathic symptomatology. Distribution of paraesthesiae is often the most reliable indicator of the origin of localized neuralgia. Paraesthesiae are further discussed below.

Diffuse neuropathic processes theoretically may cause generally distributed, whole body/multifocal pain, and some occasionally do. In practice, however, most neuropathies with

Summary

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- Neuropathy, the fundamental denominator of peripheral neuropathic pain, may be of focal, multifocal (rare) or diffuse distribution. Occasionally, central processes (cord or brain) also may cause focal pain. Diffuse neuropathic processes theoretically may cause generally distributed, whole body/multifocal pain, and some occasionally do.
- Theoretically, neuropathic pain is principally, if not exclusively, dependent on dysfunction of unmyelinated (C-type), and thinly-myelinated (Aδ) axons.
- Definitive treatment of chronic neuropathic pain always supersedes symptomatic/prophylactic treatment. Where such treatment is unavailable, or some element of chronic neuropathic pain nevertheless remains, systematic symptomatic/prophylactic treatment is required.
- Virtually all patients will experience some residual pain/discomfort, and the most realistic goal is the elimination of the intolerable component of the pain.
- Sometimes multiple treatment modalities or combinations of therapeutic agents are required.

Table 1

Causes of Focal Neuropathy and Associated Neuralgia

• Chronic pressure/trauma	(*e.g.,* carpal tunnel syndrome, focal ulnar neuropathy at elbow) (*e.g.*, meralgia paresthetica)
• Mechanical or medical (mostly diabetic) radiculopathy	
• Diabetic mononeuropathy (other than radicular)	
• Direct acute trauma — blunt or penetrating, or traction	
• Inflammatory (*e.g.*, tuberculosis, leprosy, syphilis, polyarteritis, toxoplasma, sarcoid root sleeve fibrosis [failed back syndrome])	
• Post-infectious (*e.g.*, post-herpetic neuralgia)	
• Idiopathic (*e.g.*, trigeminal neuralgia)	
• Post-traumatic (*e.g.*, phantom nerve pain after nerve section)	

sensory involvement demonstrate so-called length-dependent symptomatic distribution ("glove and stocking"). This reflects the fact that longer nerves tend to bear the brunt of most injurious processes, particularly in axonopathies (as opposed to myelinopathies). These commonly, though not always, show a "dying-back" pattern of behaviour.

Most neuralgias are predicated on axonopathy rather than myelinopathy. Even in disorders such as classical Guillain-Barré syndrome (GBS), significant peripheral neuropathic pain most commonly reflects an associated component of axonopathy. The typical back pain associated with GBS is popularly considered to reflect radicular inflammation, and in the peripheral constituents of neuropathy, exuberant inflammation is commonly associated with significant pain. This is the case, for example, in necrotizing, vasculitic and eosinophilic syndromes.

Diffuse neuropathies more commonly associated with neuralgia are listed in Table 2. Among these diabetic, idiopathic and ethanolic neuropathy are most prevalent. Early in the course of the evolution of foot neuralgia, pain and numbness may be restricted to one or two toes, or a discrete area of the foot, and unilateral occurrence is not uncommon. This should not be misconstrued as a focal syndrome. Over time, the diffuse distribution becomes progressively more apparent and gross asymmetries tend to disappear, though minor asymmetries may remain.

Orthopedic and soft tissue causes of foot pain may be difficult to distinguish from neuropathic pain, but are not associated with well-defined numbness or paraesthesiae. Orthopedic causes of localized neuropathy are uncommon, except in cases of significant trauma and Morton's neuroma. Tarsal tunnel syndrome, an exceedingly rare entity, for example, is grossly overdiagnosed. Diffuse neuropathy associated with neuralgia, in most instances, shows slow evolution over years. Very rapid evolution should provoke consideration of a spinal-cord cause of foot neuralgia. Tendon reflexes and plantar responses may be helpful in this differential diagnosis. Typically, some inflammatory, vasculitic and toxic causes of neuropathy also may cause rapid evolution of neuropathy and associated neuralgia. With respect to the length dependence phenomenon,

hand digital symptoms typically only develop once lower extremity symptoms reach the knees. A considerably earlier appearance of hand symptoms suggests these symptoms may be of independent local origin, due to CTS or focal ulnar neuropathy at the elbow, for example.

Not only are the distribution and chronology of the evolution of neuralgia, and its associated numbness important in the definition of origin and pathophysiology of the neuralgia, but the presence or absence of sensory ataxia, true muscular weakness and the types of paraesthesiae may be helpful in forming the diagnosis. Disproportionate gait instability with the eyes closed, or in the dark, defines sensory ataxia (rombergism).

Exercise caution when interpreting patient testimony to "weakness." Additional enquiry is required. Remarkably, some patients, especially elderly individuals, equate "weakness" with numbness. Consider the statement: "This severe weakness grips my legs, doctor, but my strength is good. In fact, its about as good as when I was 30."

Commonly reported paraesthesiae include tingling, burning, compression or tightness, a sense of having stones or marbles under the feet, scalding, lancinating, running water, tearing and formications. Other abnormal sensory phenomena include hyperesthesia, dysesthesia (altered or exaggerated sensation) and allodynia (permutation of a sensation, for example, from coldness to a burning sensation).

Mechanisms of Neuropathic Pain

Theoretically, neuropathic pain is principally, if not exclusively, dependent on dysfunction of unmyelinated (C-type), and thinly-myelinated (A∂) axons. Evidence for all of the following mechanisms exists based on human and laboratory animal data as follows:

- Spontaneous ectopic axon discharge;
- Increased ephaptic (electrical) transmission between adjacent axons;
- Abnormal nerve terminal sensitivity to pressure, thermal, and chemical stimuli;
- Enhanced expression of mRNA for certain voltage-gated Na-channels, resulting in lowering membrane action potential thresholds, and likely causing the first two points above;
- Enhanced sensitivity in the region of the dorsal root ganglion (DRG), causing increased spontaneous discharges;
- Catecholamine receptors develop on primary afferent cutaneous nociceptor fibres where they are not normally expressed, resulting in susceptibility to excitatory influence from noradrenaline;
- Sympathetic vasoconstrictor fibres in the area of the DRG sprout to enclose cell bodies of primary sensory afferents, resulting in increased activation;
- The DRG receptive fields of secondary sensory afferents expand, and, as a result, low threshold non-pain mechanosensitive fibres begin to activate secondary sensory fibres;
- Surviving A∂ fibres sprout to terminate in spinal cord areas normally supplied by (damaged/destroyed) C-fibres;
- With the loss of some A∂ fibres that normally collaterally inhibit the C-fibre pain response to cold, the surviving C-fibres are permitted central transmission in response to cold, yielding a burning sensation (allodynia); and
- With pure peripheral nerve injury and no primary central pathology, some increased primary spontaneous activity may occur in the thalamus and even in the parietal sensory cortex.

Table 2

Causes of Diffuse Neuropathy and Associated Neuralgia

- Diabetes mellitus
- Ethanol
- Idiopathic (small fibre) neuropathy
- Clonal gammopathy — associated
- Other paraneoplastic neuropathy
- Microvasculitic (*e.g.*, Churg-Strauss syndrome)
- Distal symmetrical painful polyneuropathy of acquired immune deficiency syndrome
- Inflammatory neuropathies — CIDP, GBS variants, others
- Nutritional (*e.g.*, pyridoxine deficiency or excess)
- Hypothyroidism
- Hereditary neuropathies with sensory involvement
- Amyloidosis
- Aliphatic hydrocarbon-associated neuropathy (*e.g.*, caused by gasoline, solvents)
- Toxic agents other than ethanol and aliphatic hydrocarbons
  (*e.g.*, Environmental: lead, arsenic, thallium, germanium, acrylamide
  Therapeutics: vinca alkaloids, cis-Pt, paclitaxel, metronidazole, gold)
- Neuroborreliosis

Treatment of Neuropathic Pain

Definitive treatment of chronic neuropathic pain always supersedes symptomatic/prophylactic treatment. Where such treatment is unavailable, or some element of chronic neuropathic pain nevertheless remains, systematic symptomatic/prophylactic treatment is required. Realistic goals and expectations of treatment are fundamental for both the patient and the physician. Except in very mild cases, which arguably warrant treatment, no single treatment is effective in more than 70% of patients, and no therapeutic approach completely relieves pain in any patient. Virtually all patients experience some residual pain/discomfort, and the most realistic goal is eliminating the intolerable component of the pain. This eventually can be achieved in most patients.

Carefully discussing the details of the treatment plan and expectations with patients is a time investment that pays considerable dividends in compliance and adequacy of response to treatment. It is vital that patients understand finding an effective treatment is a trial-and-error process. Failure with any agent/modality of treatment neither implies a poor choice of treatment by the physician, nor prejudices the expectation of success with other agents, even those within the same therapeutic class. Individual patient responses to various treatments/agents are highly variable, sometimes even within the same patient from time to time.

Sometimes, multiple treatment modalities or combinations of therapeutic agents are required. An adequate trial of each agent or modality of treatment is necessary. Impatience on the part of the patient and/or physician, with premature termination of treatment, commonly causes an apparent treatment "failure." Except when using conventional analgesic or anti-inflammatory agents, the response to antineuralgic agents normally shows a specific time course and a threshold effect. Benefit typically is not achieved until a threshold dose (unpredictable and defined by trial and error) is attained, and the patient has been taking the drug for several days or weeks. A corollary of this is, although a surprising number of patients report increased benefit from extra doses of an antineuralgic, taken (against medical advice) on days when they experience more pain, there is no theoretical basis for this other than a probable placebo effect.

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The following paragraphs describe and compare individual types of therapeutic agents and modalities. The systematic approach to treatment, dosages of individual agents, and possible adverse effects are discussed separately, in summary, after the description of the classes of therapeutic agents. Most interpretable trials of therapeutic agents have been conducted only in postherpetic neuralgia (PHN) or in painful diabetic neuropathy (PDN). Treatment of neuralgias of other origin, therefore, is based largely on extrapolation from these latter studies.

Tricyclic Antidepressants. Use of tricyclics for neuralgia was first described in 1965, and since that time has gained popularity to become the first choice of most pain specialists.[1] Several well-controlled trials have reported good results in treatment of post-herpetic neuralgia (PHN) and painful diabetic neuropathy (PDN) with amitriptyline, yielding success rates of up to 70%. This agent, a nonselective serotonin and catecholamine reuptake inhibitor, has become the principal tricyclic in use.[2,3]

Nortriptyline, another nonselective reuptake inhibitor, has recently been demonstrated to show comparable effectiveness to amitriptyline, with fewer side effects.[4] Desipramine, a selective noradrenaline reuptake inhibitor also has gained popularity, though its use has not been satisfactorily studied. Within its class, only maprotiline has been subjected to controlled trials. These drugs have shown benefit in some patients with PHN and with PDN, including some instances where amitriptyline has been ineffective.

Except occasionally in diabetics, where clomipramine and citalopram have shown some antineuralgic benefit, the selective serotonin reuptake inhibitors, including trazodone, nefazodone and fluoxetine, have been found to be generally ineffective in attempted treatment of neuralgia.

Anticonvulsants. Although some recent reports have been interpreted to suggest that anticonvulsants are as effective as tricyclics, with fewer side-effects in treating neuralgia, this has not been the conventional experience. In fact, a recent Cochrane review concluded there is little evidence for effectiveness of anticonvulsants in general, and carbamazepine in particular. Moreover, the increasingly popular gabapentin is no better in this regard than carbamazepine.[5,6] Most of the latter conclusions do not agree with

current popular specialty view. Except in the treatment of trigeminal neuralgia, however, carbamazepine enjoys little popularity in treatment of chronic neuropathic pain, at least in the Canadian context.

Phenytoin is rarely used to treat neuropathic pain, and, in the experience of many, is mostly ineffective. Several studies have been interpreted to show considerable effectiveness for gabapentin, but, in regular use, this certainly has not been a universal observation. Though an attractive choice with respect to its minimal interaction with other therapeutic agents, gabapentin generally shows a side-effect profile that differs little from that of the tricyclics. Regrettably, at the somewhat high doses required for therapeutic effectiveness (2,400 mg to 4,800 mg daily), it may show more prominent side-effects. In the author's experience, it has been regarded as intolerably expensive by a majority of patients. Many have discontinued it of their own accord, due to a perception of insufficient benefit for the price paid.

Where an option for definitive treatment is unavailable or only partially effective, chronic neuropathic pain should be treated symptomatically/prophylactically.

A recent Cochrane review concluded valproic acid is ineffective in treating neuralgia.[6] This may, however, be a circumstantial conclusion. Several entirely satisfactory studies have found valproic acid to be highly effective in treating migraine, and certainly the anecdotal experience of the author and others has been that it is typically highly effective as a second- or third-line agent for treatment of chronic neuralgia. Significant side-effects are rare, when used at typical anticonvulsant doses.

Several reports of the effectiveness of lamotrigine in the treatment of neuralgia have appeared, and a smaller number for topiramate. Both of these agents may eventually be confirmed as useful, but, currently, experience is insufficient to recommend either of these agents other than as third-line options where other, better-established agents have been ineffective.

Sodium Channel Antagonists. Of these theoretically beneficial agents, only mexiletine and lidocaine have been extensively studied. Mexiletine studies have yielded varying results, but it may be quite helpful in some patients. Unfortunately, however, side-effects (principally cardiac) tend to develop at doses lower than those required for effectiveness. The agent has, therefore, encountered a progressive decline in use. Lidocaine, as a transdermal patch, has gained popularity in the U.S., but not in Canada.

Opioids. Narcotic use has not been extensively studied in treating chronic neuralgia, except in the case of tramadol. Nevertheless, specialty experience has been that opioids, especially long-acting preparations, are highly useful for neuralgia refractory to other agents, when used systematically with appropriate controls. In conventional experience, there has been little material tendency toward physical or psychological habituation.[2] Prudence, nevertheless, dictates that well-defined guidelines be followed, and, in the author's view, narcotic treatment is best initiated by a specialty pain clinic. Subsequent administration should be under the auspices of the primary-care physician under the direct guidance of the pain clinic.[7,8]

Capsaicin. This analogue of the nonapeptide substance P first activates P-ergic C-fibres, and thereafter produces inactivation of these pain fibres. There are a number of topical preparations available. These are very popular with some patients as an adjunctive local remedy, for example, in application to the feet. Regrettably, the use of a cream is messy, not compatible with footwear or with barefoot ambulation, and, unless the feet are securely wrapped after cream application, not practical at night, when the foot neuralgia is typically most troublesome. This has reduced popularity with most patients.

Summary: Approach to the Patient

Where an option for definitive treatment is unavailable or only partially effective, chronic neuropathic pain should be treated symptomatically/prophylactically. Treatment should be initiated with a tricyclic agent (*e.g.*, amitriptyline). Usual doses are in the 10 mg to 100 mg range. Slow escalation of dosage reduces the occurrence and intensity of the usual side effects, including sedation, dry mouth, urinary retention, constipation, and permits a better definition of optimal dosage. Most patients achieve success at doses below 50 mg daily, which may be taken as a single bedtime (hs) dose. Weight gain is a variably experienced dose-dependent side effect. If amitriptyline proves ineffective, desipramine and/or nortriptyline may be tried.

Preferable second-line options are valproic acid and gabapentin in conventional anticonvulsant doses. The former requires regular monitoring bloodwork (CBC, hepatic transaminases), and patients find the high doses and cost of the latter intimidating. Lamotrigine and topiramate are gaining popularity, but have seen limited use to date.

Combinations of agents from different classes may be effective (with caution to interactions) in cases of refractory neuralgia. Long-term narcotic use is legitimate in refractory cases with appropriate guidelines, under pain clinic supervision. Capsaicin cream may be adjunctively useful. But is not highly popular due to awkwardness of use. Other treatments, such as transcutaneous electrical nerve stimulaion (TENS) and root injections, may be used in select circumstances, but are not dealt with in this article. CME

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