Peripheral neuropathic pain: an approach to management

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Chapter 40

Introduction

Pain is characteristic of some peripheral neuropathic diseases (e.g., diabetic and alcohol-deficiency neuropathies and herpes zoster). There are two broad classes of patients with painful peripheral nerve disease: focal and multifocal (e.g., traumatic, ischaemic, inflammatory) or generalized (e.g., toxic/metabolic, hereditary, or inflammatory). Although our knowledge of the mechanisms of peripheral neuropathic pain has grown, treatment remains largely empirical. This chapter outlines a systematic approach to management.

Diagnosis

Peripheral neuropathic pain has several distinct clinical characteristics. First, there is almost always an area of abnormal sensation and the patient’s maximum pain is topographically coextensive with an area of sensory deficit. The sensory deficit is usually to noxious and thermal stimuli, indicating damage to small-diameter afferent fibres. Second, there is often a hyperpathic state characterized by allodynia, summation, and radiation of pain. Allodynia is present when gentle mechanical stimuli evoke pain. Summation is the progressive worsening of pain evoked by slow repetitive stimulation with mildly noxious stimuli. Third, neuropathic pain commonly has a burning and/or shooting quality with numbness, tingling, crawling, or electrical sensations (dysesthesiae). When these features are present, the diagnosis of neuropathic pain is likely.

Mechanisms that may contribute to neuropathic pain (See Chaps. 16–21)

Peripheral mechanisms

Sensitization and ectopic impulse generation in primary afferent nociceptors

Injured peripheral nerves develop spontaneous activity and exquisite mechanical sensitivity (Wall and Gutnick 1974, Scadding 1981, Kajander and Bennett 1992). Primary afferent axons need not be transected to become hyperactive. Intact primary afferent nociceptors in a partially damaged nerve become spontaneously active (Bennett 1993, Ali et al 1999). Furthermore, ectopic impulses may be generated at sites other than the damaged and regenerating distal axon terminals. For example, when a peripheral nerve is damaged, a region near the dorsal root ganglion (which is distant from the site of injury) becomes capable of generating

There is evidence that hyperactive nociceptors contribute to pain in patients with postherpetic neuralgia (PHN). In some PHN patients pain relief can be produced by cooling the skin, applying local anaesthetics or cyclooxygenase inhibitors topically (De Benedittis and Lorenzetti 1996, Rowbotham et al 1996), or inactivating C nociceptors by repeated application of capsaicin (Watson et al 1993). These observations indicate that sensitized C fibres can generate an ongoing discharge that contributes to neuropathic pain.

**Sympathetically maintained pain**

Causalgia is the classic example of a sympathetically maintained pain associated with nerve injury. It is characterized by autonomic changes, severe allodynia, and a distal burning sensation exacerbated by cold and strong emotions (Mitchell 1865). Early in the course of the disease, most patients obtain virtually complete relief with sympathetic blocks. Damaged primary afferents including nociceptors acquire adrenergic sensitivity (Devor and Janig 1981, Scadding 1981, Janig et al 1996). For example, electrical stimulation of the sympathetic trunk can activate C nociceptors that have regenerated following nerve injury (Habler et al 1987). Furthermore, after partial nerve injury, electrical stimulation of the sympathetic trunk (Sato and Perl 1991) and local application of adrenergic agonists can activate or sensitize intact unmyelinated nociceptors (Ali et al 1999). Sympatholytic procedures can alleviate rodent pain behaviours that develop after partial nerve injury (Shir and Selitzer 1991).

These animal studies are supported by human research demonstrating that adrenaline (epinephrine) applied directly to a neurone produces severe burning pain (Chabal et al 1992). Furthermore, intraoperative stimulation of the sympathetic chain increases spontaneous pain in patients with causalgia (Walker and Nilsen 1948). In post-traumatic neuralgias, intracutaneous application of noradrenaline (norepinephrine) into a symptomatic area rekindles spontaneous pain and mechanical hyperalgesia after they are relieved by sympathetic blockade (Torebjork et al 1995). Thus, damage to a peripheral nerve induces a novel state of sensitivity to sympathetic activity and noradrenaline (norepinephrine) in primary afferent nociceptors.

**Inflammation of the nerve trunk**

Because the connective tissue sheath surrounding a peripheral nerve is innervated by nociceptive primary afferents (nervi nervorum) (Hromada 1963, Bahrn et al 1986, Bove and Light 1995), peripheral nerve can be a source of pain in conditions with an inflammatory component. Consistent with this idea, certain diseases are associated with localized pain and tenderness along the trunk of the nerve, rather than pain referred to its innervation territory. The acute pain of a herniated inflamed disc, or that seen with brachial neuritis or acute inflammatory demyelinating neuropathy (Guillain–Barré syndrome), probably represents pain mediated by nociceptive *nervi nervorum* (Asbury and Fields 1984).

In experimental animals, activation of macrophages and a proliferation of endoneurial blood vessels have been demonstrated in injured peripheral nerve (Sommer and Myers 1996). The cytokine tumour necrosis factor alpha (TNFα) produced by activated macrophages is a potential cause of pain (Sommer et al 1998, Wagner et al 1998) by inducing ectopic activity in primary afferent nociceptors (Sorkin et al 1997). Consistent with this view, the TNFα inhibitor thalidomide is reported to reduce pain in inflammatory lepromatous neuropathy (Partida-Sanchez et al 1998).

**Central mechanisms**

**Central sensitization**

Prolonged or repeated activation of nociceptive C fibres produces central sensitization so that innocuous stimuli produce pain (allodynia) and noxious stimuli produce more intense pain (hyperalgesia). Central sensitization occurs in any situation with prolonged or intense C-fibre input. In neuropathic pains like postherpetic neuralgia, where there is evidence of ongoing C-fibre activity, central sensitization seems to play a significant role in maintaining pain and allodynia (Koltzenburg et al 1992, Petersen et al 2000). Glutamate acting at the N-methyl-D-aspartate (NMDA) receptor contributes to central sensitization, and thus NMDA antagonists are potential therapeutic targets in some patients with neuropathic pain (Dougherty et al 1994, Dickenson 1997).

**Deafferentation hyperactivity**

Following dorsal rhizotomy or peripheral nerve damage, many dorsal horn cells begin to fire spontaneously at high frequencies (Lombard and Larabi 1983, Laird and Bennett 1993). Such a mechanism may underlie the pain that occurs following extensive denervating injuries. For example, pain is a characteristic sequela of the deafferentation produced by brachial plexus avulsion (Wysocki-Farr 1980), and this pain seems to respond to surgical procedures that destroy...
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Pericellular dorsal horn neurons (Nashold and Ostdahl 1979).

Reorganization of the central connections of primary afferents
In models of peripheral nerve injury, loss of the central terminals of unmyelinated primary afferents to dorsal horn neurons leads to sprouting of large-diameter primary afferents. These afferents, which respond maximally to gentle mechanical stimulation, sprout to directly innervate the deafferented nociceptive dorsal horn neurons (Shortland and Woolf 1993). Although it is difficult to prove that this is a mechanism of pain in any clinical situation, some patients with postherpetic neuralgia have exquisite allodynia in a region of skin that shows a profound nociceptive deficit (Baron and Sagué 1993).

Loss of large-fibre afferent inhibition
Because selective blockade of large-diameter myelinated sensory axons increases pain, Melzack and Wall (1965) proposed that these axons normally inhibit pain-transmitting spinal-cord neurons and that the pain of nerve injury is due to selective damage to these large axons. This hypothesis predicts that selective activation of large-diameter, non-nociceptive myelinated primary afferents, for example by electrical stimulation of a peripheral nerve, would decrease pain. In fact, there are cases of dramatic pain relief produced by transcutaneous electrical nerve stimulation (TENS) in patients with painful traumatic mononeuropathies (Meyer and Fields 1972). Furthermore, there are reports that dorsal column stimulation, which would selectively activate the central branches of large-diameter primary afferents, is effective for some patients with neuropathic pain (Broggi et al 1994, Kumar et al 1996). Thus it seems likely that release of dorsal horn pain transmission cells from inhibition by myelinated axons contributes to the pain that occurs in some cases of peripheral nerve injury.

The treatment of neuropathic pain
Except for trigeminal neuralgia, which responds reliably and specifically to anticonvulsant medications, the treatment of neuropathic pain is largely empirical and often unsatisfactory. Fortunately, data from clinical trials have led to improvements in the medical management of neuropathic pain (Kingery 1997).

Pharmacological approaches
Antidepressants
Tricyclic antidepressants (TCAs) are currently the best documented therapy for neuropathic pain (Onghena and Van Houdenhove 1992, McQuay et al 1996, Kingery 1997). These compounds are inhibitors of the reuptake of monoaminergic transmitters. They are believed to potentiate the effects of biogenic amines in CNS pain-modulating pathways. On the other hand, the effectiveness of TCAs in neuropathic pain may depend on their broad range of pharmacological actions. In addition to blocking serotonin and noradrenaline (norepinephrine) reuptake, these drugs block voltage-dependent sodium channels (Jett et al 1997) and α-adrenergic receptors. All three of these actions could contribute to their analgesic effect.

Of the TCAs, amitriptyline is currently the best established for the treatment of chronic pain. Amitriptyline produces pain relief in diabetic neuropathy and postherpetic neuralgia (McQuay et al. 1996, Sindrup and Jensen 1999). The mean dose required for pain reduction (75-150 mg/day) is usually smaller than the doses necessary to achieve antidepressant effects. Improvement of sleep, mood, and anxiety are an added benefit of antidepressant therapy. Amitriptyline and other TCAs have significant side effects (Richelson 1990). They can produce orthostatic hypotension, due largely to an α-adrenergic blocking action. Because of its histamine receptor blockade, amitriptyline is also a potent sedating drug, which can be a desirable action if patients are having difficulty sleeping. Other significant problems include urinary retention, memory loss, and cardiac conduction abnormalities (largely due to the muscarinic anticholinergic actions of the drug). Patients, especially the elderly, who are to be treated with this drug should be started at a very low dose, even as low as 10 mg, and built up slowly by about 25 mg every fourth day until optimal pain relief is achieved.

Desipramine and nortriptyline, both of which have predominant noradrenaline (norepinephrine) reuptake blocking action, appear to be almost as effective as amitriptyline in postherpetic neuralgia and painful diabetic neuropathy. Patients respond to desipramine and nortriptyline at doses comparable to those of amitriptyline but with fewer anticholinergic side effects and significantly less sedation.

All patients undergoing treatment with any TCA should have a cardogram at the onset of treatment. Cardiac conduction defects are a contraindication to their use. Plasma drug levels and repeated cardigrams should be taken if the dose
is pushed above 100 mg/24 h, especially in elderly or cognitively impaired patients.

There are very few studies of antidepressants other than TCAs for pain management. Serotonin selective reuptake inhibitors (SSRIs) are currently the most commonly used drugs for the treatment of depression. SSRIs may have some efficacy for neuropathic pain but are significantly less effective than TCAs (Max et al 1992, McQuay et al 1996, Sindrup and Jensen 1999). Furthermore, there is evidence that noradrenaline (norepinephrine) reuptake blockade is more effective in producing analgesia than pure serotonin reuptake blockade (Atkinson et al 1999). On the other hand, SSRIs have virtually none of the serious side effects common with desipramine or amitriptyline. They are non-sedating, and devoid of the adrenergic-, histaminergic-, and muscarinic-antagonist-induced side effects. Thus, even if SSRIs are less effective for neuropathic pain per se, they are effective antidepressants and some patients report an improvement in pain as their depression clears. Thus, when using antidepressants, especially in patients with clinically significant depression, the drug dose should be pushed until limiting side effects ensue or the maximum recommended plasma concentration is achieved.

There are some newer antidepressants that are neither TCAs nor SSRIs. Venlafaxine is an example of such a drug. It blocks both serotonin and noradrenaline (norepinephrine) reuptake (Lang et al 1996). There are some early positive reports on the usefulness of this drug (Gumpston and Moulin 2001). However, above a daily dose of 300 mg it has a tendency to elevate blood pressure and to cause headaches.

Anticonvulsants and antirhythmics
In contrast to the antidepressants, anticonvulsants such as phenytoin and carbamazepine are helpful for a more restricted group of neuropathic pain patients. Carbamazepine is very effective in trigeminal neuralgia (McQuay et al 1995, Fields 1996). However, carbamazepine is less helpful in other types of neuropathic pain. These anticonvulsants are more likely to be helpful if a patient reports pain with a sharp shooting or electric shock-like component.

Gabapentin is an interesting drug that was originally developed and marketed for seizure control. Its mechanism of action is unknown; however, recent placebo-controlled trials show that it is effective in diabetic neuropathy (Backonja et al 1998) and postherpetic neuralgia (Rowbotham et al 1998). Its relatively benign side-effect profile compared to TCAs has encouraged many physicians to use it as a first-line drug for nerve injury pain.

The antirhythmic drugs lidocaine ( lignocaine), mexiletine, and tocainide block voltage-dependent sodium channels. Caution should be exercised when administering these compounds. Contraindications include electrocardiac abnormalities, reduced left ventricular function, and coronary heart disease.

Lidocaine (lignocaine) by intravenous infusion produces significant relief for patients with postherpetic neuralgia (Rowbotham et al 1991), diabetic neuropathy (Kastrap et al 1987), and a variety of other neuropathic pain syndromes (Glazer and Portenoy 1991). Mexiletine has been shown to be effective for pain in diabetic neuropathy (Dejgard et al 1988) and other peripheral neuropathic conditions (Chabal et al 1992, Wallace et al 2000). A positive response to intravenous lidocaine (lignocaine) significantly predicts longer-term relief with oral mexiletine (Galer et al 1996).

Drugs that affect gamma-aminobutyric acid receptors
Several drugs that enhance or mimic the effects of the inhibitory transmitter gamma-aminobutyric acid (GABA) are clinically available (Dickerson et al 1997). Baclofen is an agonist of the GABA-B receptors and in the spinal cord acts presynaptically to prevent the release of excitatory neurotransmitters. Baclofen is useful in trigeminal neuralgia (Fields 1996). Some GABA receptor modulating agents may have a place in the treatment of painful muscle spasms, particularly when these are associated with spasticity. In some cases of neuropathic pain clonazepam has been shown to be effective (Bartushe et al 1996).

Opioid analgesics
Opioids are clearly effective in postoperative, inflammatory, and cancer pain. However, the use of narcotic analgesics for patients with chronic neuropathic pain is highly controversial, even among experts in the field of pain management. Acute infusions of morphine or fentanyl give significant relief to patients with postherpetic neuralgia (Rowbotham et al 1991) and a mixed group of neuropathic pain patients respectively (Dellern et al 1997). Furthermore, sustained efficacy has been demonstrated for oral oxycodone (Watson and Babul 1998) and tramadol (Harati et al 2000) in postherpetic neuralgia and painful diabetic neuropathy respectively.

Our (anecdotal) experience and that of others (Portenoy et al 1990) is that many patients with pain due to central and peripheral nerve injury can
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**N-methyl-D-aspartate-receptor antagonists**
Clinically available substances with N-methyl-D-aspartate (NMDA) receptor blocking properties include ketamine, dextromethorphan, memantine, and amantadine. Typical side effects include sedation, nausea, disagreeable psychological disturbances, and even frank hallucinations.


**Topical medications**
Several topical agents have been used for neuropathic pain, particularly when patients have cutaneous hypersensitivity. Capsaicin is an agonist of the vanilloid receptor, VR1, which is present on the sensitive peripheral terminal of primary nociceptive afferents (Lynn 1990, Caterina et al 1997). On initial application it has an excitatory action and produces burning pain and hyperalgesia, but with repeated or prolonged application it inactivates the receptive terminals of nociceptors (Bjerring et al 1990). Therefore, this approach may help patients whose pain is maintained by anatomically intact, sensitized primary nociceptors.

Capsaicin extracts are commercially available in a 0.025% and a 0.075% preparation (Rains and Bryson 1998). Both preparations have been reported to reduce the pain of postherpetic neuralgia (Bernstein et al 1988, Watson et al 1993) and postmastectomy pain (Watson et al 1992). The 0.075% preparation has also been advocated for pain in diabetic neuropathy (Group 1991). However, these capsaicin preparations often produce intolerable burning so that many patients discontinue their use. There is anecdotal evidence that application of relatively high concentrations (greater than 5%) of capsaicin can produce prolonged pain relief in some patients with neuropathic pain (Robbins et al 1998). This produces burning so severe that spinal anaesthesia is required for the patients to tolerate the procedure.

A second promising topical medication for neuropathic pain is local anaesthetics. The rationale is similar to that discussed above in the section on anticonvulsants and antiarrhythmics. Efficacy for a 5% patch preparation has been established (Rowbotham et al 1995, 1996). Topical application of aspirin in either a chloroform or ethyl ether suspension has been reported to produce profound pain relief for some patients with postherpetic neuralgia (King 1988, De Benedittis and Lorenzetti 1996).

In summary, the medical management of neuropathic pain consists of four main classes of oral medication (serotonin/noradrenaline (norepinephrine) reuptake blockers, anticonvulsants, antiarrhythmics, opioids) and several categories of topical medications for patients with cutaneous hyperalgesia (cyclooxygenase inhibitors, capsaicin in either 0.025 or 0.075% preparations, and local anaesthetics).

**Non-pharmacological approaches**

**Transcutaneous electrical nerve stimulation**
The advantages of peripheral nerve stimulation techniques are the lack of side effects and complications and the fact that the treatment can be easily repeated (see Chap. 30). Furthermore, efficacy can be determined rapidly. Therefore, a trial should be performed when feasible (Meyer and Fields 1972, Kumar and Marshall 1997, Finsen et al 1998). Invasive techniques, i.e., epidural spinal cord stimulation (SCS) and deep brain stimulation, may be effective in special cases of neuropathic pain (Broggi et al 1994, Tasker and Vilenski Filho 1995, Kumar et al 1996). Complications include dislocation of the electrodes, infection of the system, and occasionally bleeding.

**Neurosurgical destructive techniques** (see Chap. 29)

Techniques such as neurectomy, rhizotomy, dorsal root entry zone lesions (DREZ), cordotomy, and thalamotomy may provide short-term pain relief. Because destructive techniques increase the amount of deafferentation, sometimes even more severe pain will result from the procedure. Outside of trigeminal neuralgia there are no surgical approaches with established efficacy in neuropathic pain (Fields 1996).
A systematic approach to patients with neuropathic pain

The ideal in medicine is to treat the cause of the disease rather than the symptom. Since neuropathic pain is often multifactorial and its causes are usually uncertain, a treatment algorithm is required (Fig. 40.1). Entrapment neuropathies can be treated by neurolysis, transposition, or decompression (Dawson et al 1983). If scar-induced mechanical traction is a factor, this approach is particularly worthwhile. Transcutaneous electrical stimulation of nerves (TENS) is a viable option for some patients with focal nerve injury, particularly if the nerve trunk can be stimulated proximal to the site of injury. The majority of patients, however, require medical management. When cutaneous hypesthesia and/or allodynia are present, topical agents are a good starting point, with either local anaesthetic, cyclooxygenase inhibitor, or capsaicin.

In patients with focal neuropathies, a sympathetic block can be a useful procedure (Dellon et al 1994, Baron and Maier 1996). We use a local anaesthetic block of the sympathetic chain early if there is evidence of a sympathetically maintained component to the patient’s problem (see Chap. 18). Such evidence includes unilateral distal extremity pain, swelling, and vasomotor and sudomotor asymmetries. Patients with sympathetically maintained pain may obtain relief from a series of sympathetic blocks combined with vigorous physical therapy; provided this is done early in the course of the disease. In general, if sympathetic blocks are going to be helpful, they will provide sustained or at least increasing durations of post-block relief. If local anaesthetic blocks achieve sympatholysis as indicated by skin temperature change or a Horner’s syndrome but no relief beyond 6 h, this approach is not promising. Furthermore, we have seldom found that surgical sympathectomy is helpful.

There are two serious interpretive problems with sympathetic blocks (Dellon et al 1994). The first is systemic absorption of lidocaine (lidocaine), because even low plasma concentrations can relieve neuropathic pain independent of a sympathetic component to the problem. The second is the production of a somatic block by diffusion of local anaesthetic to the nearby nerve plexus.

If there is no strong evidence of sympathetically maintained pain or sympatholytic interventions do not provide significant relief, we proceed to systemic medication. General treatment principles are the individualization of therapy and the titration of a given drug depending on effect on the one hand and side effects on the other. Non-response should not be accepted unless a sufficient dose has been given and until a sufficient period of time has passed to judge the drug’s benefit. A rigorous systematic sequential approach is useful, if progression of the disease and pain profile are stationary.

Once the decision is made to pursue systematic medical management, we currently use the algorithm illustrated in Fig. 40.1. Because of the extensive literature supporting their use, we usually begin with TCAs; however, in some patients we begin therapy with gabapentin, especially in elderly patients or those with evidence of cardiac conduction block. With TCAs patients must be warned about side effects such as drowsiness, dry mouth, and orthostasis and then therapy should be initiated with an appropriately low dose (e.g., 10–25 mg). It is equally important to increase the dose gradually to optimize pain relief. In some patients it is necessary to raise the dose into the antidepressant range (over 200 mg/day). It is essential to check...
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