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Treatment of neuropathic pain

Treatment of neuropathic pain is dictated by its severity and natural history. Most patients require a meticulous history and detailed neurological examination, a clear explanation of the problem, investigation of any underlying cause if needed, and graded treatment with selected regular analgesics and adjuvant agents for the time that pain is present. However, some patients have a history of severe unrelenting pain, requiring empathetic long-term management.

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Neuropathic pain has recently been defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.[1] Once recognised, the treatment approach is relatively straightforward, with the use of regular analgesics and adjuvant agents in a trial format agreed to by the patient and physician before treatment begins. However, the results of treatment are often disappointing to both patients and doctors. Hence, a careful explanation of the problem and the approach to treatment is needed from the outset.

Some of the more common causes of neuropathic pain are listed in Table 1. Patients may describe the pain of these conditions as spontaneous, stimulus-evoked or a combination of both. An often overlooked form of neuropathic pain is that provoked by a transient nociceptive stimulus (such as an injury) to tissues innervated by a damaged somatosensory system.

Mechanisms of pain

Most forms of neuropathic pain are due to sensitisation of neurons in the central pathways that are normally associated with the transmission of

IN SUMMARY

- **Neuropathic pain has recently been defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.**
- **Neuropathic pain is under-recognised and therefore undertreated.**
- **Most forms of neuropathic pain are due to sensitisation of neurons in the central pathways. This sensitisation is normally associated with the transmission of noxious stimuli.**
- **Treatment is largely empirical with no clear evidence for selective benefits of medications on spontaneous and stimulus-evoked pain.**
- **The main treatments of neuropathic pain are adjuvant analgesics, mainly those from antidepressant and antiepileptic drug classes. Regular opioid analgesics also result in improvement in some patients.**
- **Outcomes are often unsatisfactory in patients with severe persistent pain. These patients may benefit from specialist referral.**

Table 1. Common causes of neuropathic pain

Peripheral nervous system

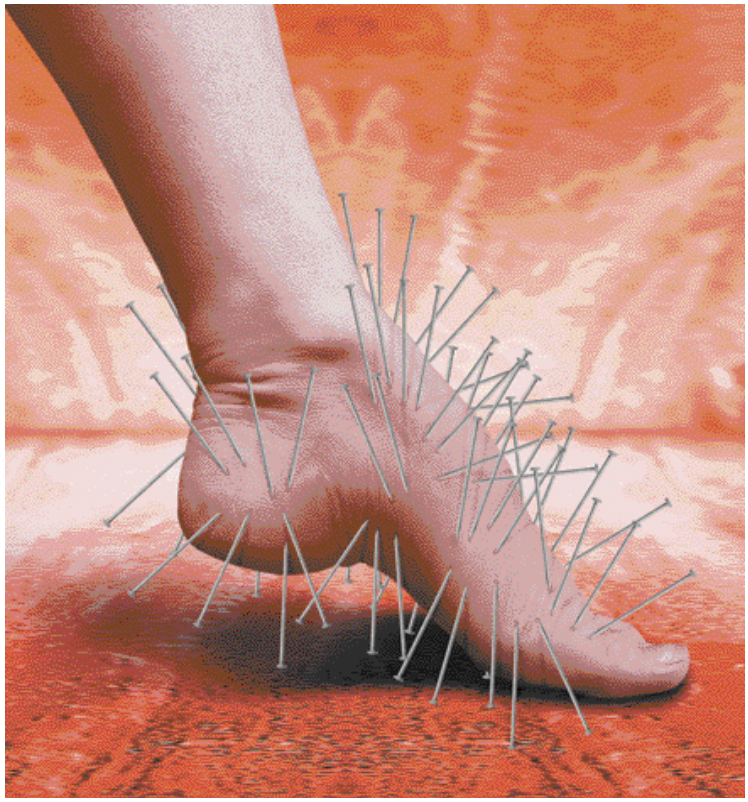
- Blunt trauma (5%)
- Radiculopathy
- Surgery (10%)
- Ischaemia
- Entrapment
- Polyneuropathy
  - hereditary
  - metabolic (diabetes 10%)
  - toxic
  - immune
  - infections
  - paraneoplastic syndromes
  - nutritional
- Amputation (stump and phantom pain)
- Postherpetic neuralgia
- Neoplastic
  - tumour invasion
  - radiation
  - surgery
  - chemotherapy

Central nervous system

- Stroke (8%)
- Multiple sclerosis (60%)
- Spinal cord injury (50%)
- Syringomyelia/bulbia (75%)

The percentages are approximate proportions of patients with each condition who have neuropathic pain.

Treatment of neuropathic pain



Neuropathic pain is a common clinical problem that is under-recognised. It requires a meticulous and time-consuming approach to history taking and examination. Some patients have unrelenting severe pain with poor treatment outcomes; referral to a pain physician or multidisciplinary pain clinic may therefore be needed.

COMPOSITE ILLUSTRATION BY DIANE PAOLO. PERMISSION FOR REPRINT BY PRACTICAL PAIN MANAGEMENT JOURNAL.

noxious stimuli. The sensitisation of neurons is characterised by increased background activity, a lowered threshold for activation (e.g. by non-noxious stimuli) and the spread of receptor fields. This is generally referred to as 'windup' and is usually associated with partial denervation in the presence of continuously active afferent input (peripheral or central). Pain in the presence of complete deafferentation (so-called anaesthesia dolorosa) is rare and usually unresponsive to any form of treatment.

'Functional' pain syndromes (e.g. fibromyalgia and irritable bowel syndrome) and pain associated with autonomic nervous system activation (e.g. complex regional pain syndrome type 1) are not discussed further in this article.

Clinical evaluation

Generally accepted clues that pain may be neuropathic in origin are its continuous nature (as opposed to movement-induced pain) and its burning, shooting or electrical qualities. There may also be associated symptoms (derived from irritation to non-noxious afferent neurons) such as numbness, dysaesthesia and formication in anatomically recognised patterns.

Important components of the assessment are the examination of the patient for evidence of stimulus-evoked pain[2] (this usually indicates central sensitisation) and routine neurological examination for neural afferent system dysfunction in recognisable anatomic patterns. The most confusing

Table 2. Examination findings in patients with neuropathic pain

Not painful

- Hypoaesthesia (normally decreased sensitivity, particularly to touch)
- Hypoalgesia (decreased sensitivity to pain)

Painful

- Hyperalgesia (an increased response to a stimulus that is normally painful; usually associated with a lowered threshold of response)
  - punctate (e.g. pinprick)
  - nerve tap/stretch
  - static (e.g. soft tissue pressure)
- Allodynia (pain in response to a stimulus that does not normally produce pain)
  - mechanical (e.g. brushing)
  - thermal (e.g. cold)
- Hyperpathia (increasing pain to a repetitive stimulus and 'after response' when stimulus is ceased; associated with an increased threshold of response)

element is the extension of areas of stimulus-evoked pain beyond the anatomical boundary of the area receiving the stimulus. This occurs because central sensitisation does not respect these boundaries. Clinical features that should be sought are summarised in Table 2. Validated tools are used to help determine the likelihood of a patient having neuropathic pain, but evidence of their benefit is mostly restricted to epidemiological studies. However, use of these validated tools as an aide-memoire in the clinic may be helpful.[3]

The investigation of neuropathic pain varies according to the suspected cause of each syndrome. A cause should be sought in each case, and treatment of that cause may contribute to alleviation of symptoms and may slow down progression of the condition.

Treatment

Treatment of neuropathic pain is generally far from satisfactory. There are very few randomised, double-blinded, controlled trials of any medication for neuropathic pain that are adequately powered, and those that have been undertaken are generally of a short duration (i.e. eight to 12 weeks). This is unsatisfactory for a condition that is likely to be prolonged. In addition, these trials have not separately considered responses of medication to spontaneous pain and stimulus-evoked pain.

Large studies have been undertaken predominantly in patients with pain from diabetic neuropathy and postherpetic neuralgia. The results of these studies are then extrapolated to other neuropathic pain states. For example, there is no convincing literature on the use of adjuvant agents in patients with radicular pain who do not have neurological signs; however, their use in this context is widespread. When one considers that a successful outcome is deemed to be a 50% reduction in pain, it is easy to appreciate that we have a long way to go before we have highly effective treatments for neuropathic pain. Unfortunately, the costs of trials are high and generally only undertaken by large pharmaceutical companies. This limits the likelihood of head-to-head trials and trials of drug combinations.[4]

The literature on the treatment of neuropathic pain is diffuse and difficult to synthesise into practical advice given the cautions noted above. Unfortunately, early trials were undertaken with few patients, showing limited reports of effectiveness on spontaneous and stimulus-evoked pain, and incomplete records of dropouts. This makes calculations of efficacy and numbers needed to treat (NNT) and to harm difficult to determine and compare. Nevertheless, the concept of referring to the number of patients we need to treat with a medicine to obtain one patient with at least 50% pain relief is the most practical way of comparing the efficacy of different treatments.

Agents used to treat neuropathic pain can be conveniently divided into two types: regular analgesics and adjuvant analgesic agents (medications used to treat other conditions but which have been found to be useful in reducing pain from nervous system damage). Given the difficulties noted above, there is literature to support the use of some antidepressants, some antiepileptic drugs, opioids and a few miscellaneous medicines for the treatment of neuropathic pain.

Antidepressants

Antidepressants of the tricyclic type have long been used to treat all forms of neuropathic pain. Clinical experience would suggest that the tricyclics are often very helpful, especially in cases of peripheral neuropathic pain, as long as the initiating dose is low (e.g. 10 to 12.5 mg at bedtime) and is increased slowly at intervals of a few days to a week. Amitriptyline has a number of sites of action apart from acting as a monoamine reuptake inhibitor and this may account for its high incidence of side effects as well as its greater therapeutic benefit.

The mean NNT to obtain a beneficial outcome as calculated in the early studies of amitriptyline was impressive at 2 to 3, but failed to take account of high dropout rates. The maximum effective dose is disputed, but usually 75 mg at night is sufficient, as higher doses become increasingly associated with anticholinergic side effects on the brain, bladder, bowel and blood pressure control. Dry mouth is inevitable but weight gain is uncommon. If a benefit is obtained, it occurs within a few days of starting amitriptyline at the prescribed doses.

Sometimes nortriptyline (Allegron) is preferred, although the evidence for its efficacy is less well established and it is a restricted benefit medication on the PBS for use in major depression.

Evidence for the use of antidepressants other than the tricyclics is very limited. It is generally agreed that selective serotonin reuptake inhibitors are not useful (NNT of 6.8), but serotonin norepinephrine reuptake inhibitors may be useful (venlafaxine [Efexor-XR; restricted benefit for major depressive disorders] has a NNT of 4.5). Again, the dosing advice is to start low and go slow. The effective dose may be as high as 225 mg daily. Duloxetine (Cymbalta; restricted benefit for major depressive disorders) is used widely overseas for neuropathic pain and may soon be approved for this purpose in Australia.

Antiepileptic drugs

There is a long tradition of using antiepileptic drugs in the treatment of neuropathic pain, but until recently there was

almost no trial evidence of efficacy. This changed with the introduction of gabapentin (Gabahexal, Gabaran, Gabatine, Gantin, Neurontin, Nupentin, Pendine) and more recently pregabalin (Lyrica) as treatments for pain in patients with diabetic neuropathy and postherpetic neuralgia. These two agents modify the action of voltage-gated calcium channels of primary afferents through their action on the A2delta component of the channels. This appears to interfere with the release of substance P, noradrenaline and the excitatory amino acid neurotransmitter glutamate. The side effects of all antiepileptic drugs tend to be similar and include drowsiness, dizziness and ataxia.

Gabapentin (PBS authority required for epilepsy only; RPBS authority required for pain) has been used for the treatment of neuropathic pain for some years[5,6] and has a NNT of between 4 and 5. Gabapentin is often commenced at a dose of 300 mg daily but this should be reduced to 100 mg in frail and elderly people. The dose is increased every few days to achieve symptomatic relief of pain. The effective dose ranges widely, and may be as high as 4000 to 6000 mg daily in some patients.

Pregabalin has had more trial exposure than any other adjuvant analgesic.[7,8] Although it is available for treatment of all forms of neuropathic pain, the trials were undertaken in patients with postherpetic neuralgia and painful diabetic neuropathy. It has also been shown to be of benefit in spinal cord injury pain. A trial investigating pregabalin in poststroke pain has been completed but is not yet published. Pregabalin appears to act through an identical mechanism to gabapentin.

The major advantage of pregabalin is the relatively short interval needed to find out whether it is useful or not; the trials all showed a benefit within one week with regimens commencing at 75 mg daily but increasing within a few days to 150 mg twice daily. The maximum doses used in the trials were 600 mg daily. The NNT for pregabalin is given in the drug company literature as 3.4. Caution is needed with the elderly and frail, and a slow increment from 75 mg daily to 75 mg twice daily by the end of the first week is likely to be better tolerated. Patients rarely want to exceed 150 mg twice daily because of side effects common to antiepileptic drugs, plus blurred vision and unexplained oedema.

Pregabalin and gabapentin should only be used after determination of renal function, preferably by calculated creatinine clearance, because they are renally excreted. Careful dose titration from an initial once daily low dose is required in patients whose renal function is impaired. Both medications have the advantage of limited interference with other drugs because of the lack of protein binding and direct excretion through the kidneys. Pregabalin is expensive and subsidised

only by the RPBS when used for pain. Thus, a well-supervised two-week trial needs to be undertaken to ensure efficacy before long-term implementation. Fortunately, many third-party payers will offset the cost in many situations.

Evidence is very limited for the use in neuropathic pain states of other antiepileptic drugs such as lamotrigine, carbamazepine, topiramate and sodium valproate.

Opioids

Opioids are useful for all neuropathic pain states, albeit at high doses and therefore with the likelihood of more side effects.[9] Slow-release forms of medication used in a time-contingent manner are preferred, although prophylactic use is sometimes warranted. Constipation will almost invariably need to be treated.

Tramadol (Durotram XR, Tramahexal SR, Tramal, Tramedo, Zydol) has been trialled successfully in patients with neuropathic pain and has a NNT of 3.8 as reported in one meta-analysis.[10] Again, the doses used have been relatively high.

Medicine combinations

The usual approach to the medical treatment of neuropathic pain is to trial therapies seriatim, trying to find the best balance of maximum effectiveness and minimum side effects. In patients who receive no useful benefit from this approach a combination of treatments can be tried. The literature in this regard is very limited. The most usual combination is a regular opioid analgesic with an adjuvant agent.[11] Medicine combinations are probably best undertaken by physicians with experience in this approach.

Other approaches

There is a limited role for the use of other medications when the above therapeutic options have been exhausted, as often occurs during exacerbations of pain. Medications include ketamine (Ketalar), an N-methyl-D-aspartate antagonist delivered by parenteral and nasal routes, clonidine (Catapres) delivered by the intrathecal and epidural routes (not approved routes under the PBS), and local anaesthetics delivered by topical, oral, parenteral, epidural, nerve root sleeve injection and intrathecal routes. Use of these modalities should be deferred to pain physicians and anaesthetists or other specialists experienced in their use.

There are very few indications for surgery, apart from patients with trigeminal neuralgia, although specialised neurosurgical centres do undertake lesioning of appropriate afferent pathways in some situations.

Neuralgia

Treatment of neuralgias (e.g. trigeminal and glossopharyngeal neuralgia but not including postherpetic neuralgia) can be considered separately as they have a

Role of the GP in treating neuropathic pain

- It is important to believe all patients who complain of pain and to dissect the contributing factors.
- Take a detailed history, especially if the origin of the pain is obscure; neuropathic pain does not always conform to usual anatomical boundaries.
- A comprehensive sensory examination (including presence of thermal sensitivity, hypoalgesia, hyperalgesia, allodynia and hyperpathia) is vital when considering a neuropathic cause for the pain; if all of these are normal then neuropathic pain is very unlikely.
- Before commencing therapy, explain the treatment plan to the patient by:
  - writing out dose schedules
  - making it clear that seriatum medications will be taken to near tolerance
  - explaining side effects and costs of medications
  - explaining that the aim is to attenuate pain, not abolish it
  - undertaking regular review.
- Keep meticulous progress notes.
- Offer to refer the patient for specialist advice if he or she perceives that there is lack of improvement.
- It is best to avoid combination therapies and invasive procedures unless you are experienced in their use.
- Ensure detailed notes accompany any patient who is referred to a specialist.

somewhat different pathophysiology associated with paroxysmal pain in the absence of clinical signs apart from pain precipitation by non-noxious stimuli. Thus, there is no neurological deficit to sensory or motor testing, and no hyperalgesia or hyperpathia.

These syndromes are generally responsive to carbamazepine (Tegretol, Teril), which is presumably acting as a sodium channel blocker. Carbamazepine is used in doses sufficient to alleviate paroxysms without producing unacceptable side effects. The starting dose varies but should usually be 50 or 100 mg per day because patients with neuralgia are often elderly and frail. Carbamazepine may be effective at this dose, but usually needs to be increased every few days according the patient's tolerance of adverse effects. When to decrease the dose of medication once an attack is controlled is always problematic, but every attempt should be made to do so one to two weeks after control has been achieved.

If carbamazepine is unhelpful, there are several second-line drugs, none of which have been adequately trialled. Oxcarbazepine (Trileptal; PBS authority required for epilepsy only) is probably the most useful but is expensive. Early referral of the patient for surgery should be considered if control is difficult to obtain.

Conclusion

Neuropathic pain is a common clinical problem that is under-recognised. It requires a meticulous and time-consuming approach to history taking and examination. Some patients have unrelenting severe pain with poor treatment outcomes and referral to a pain physician or multidisciplinary pain clinic may be needed. Any referral to a specialist is facilitated by detailed information on treatment strategies that have already been used, including medication names, doses achieved, duration of treatment and reasons for cessation of use. The role of the GP in treating neuropathic pain is given in the box on this page.

Although treatment of this patient group is currently very challenging, in a few years it is likely that management will be broadened to include novel treatments that are currently under trial in laboratory settings. MT

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COMPETING INTERESTS: Professor Helme is a member of the medical advisory boards for Lyrica (Pfizer), Zostavax (CSL Limited) and Cymbalta (Eli Lilly).