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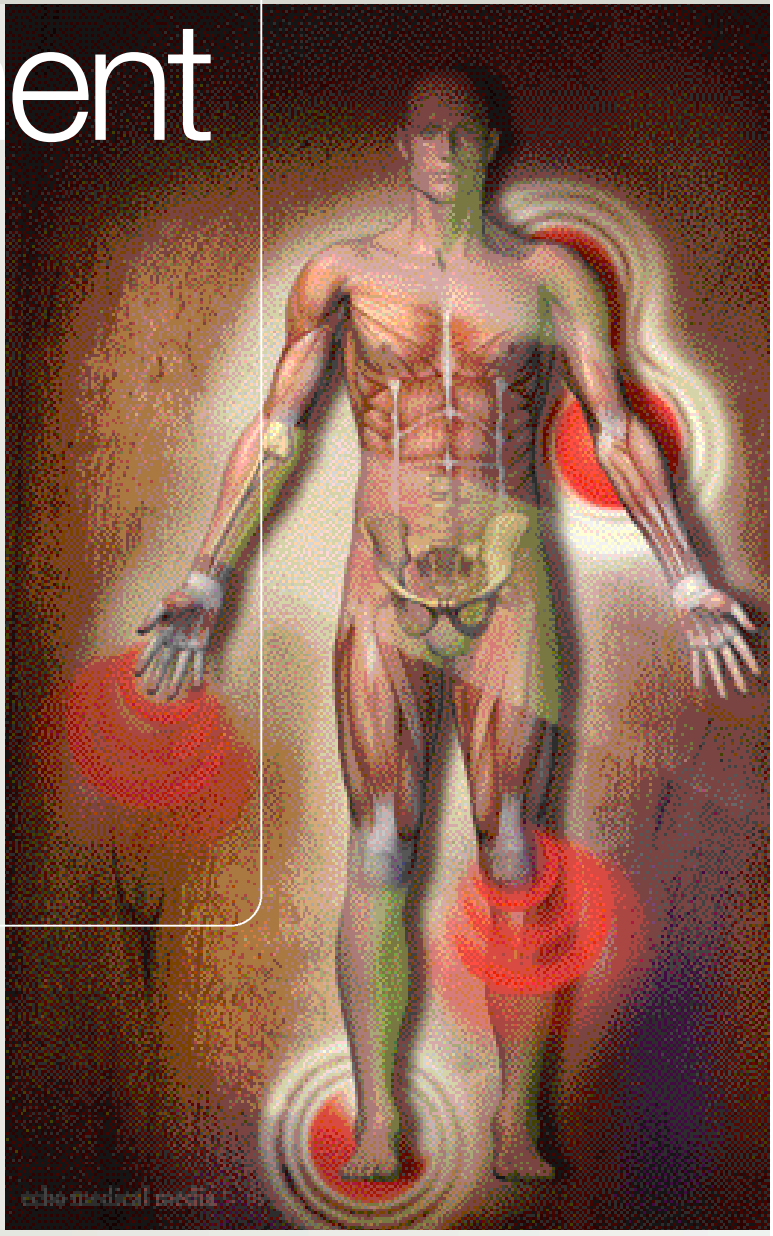

What a pain! Managing it through the continuum

Treatment of neuropathic pain

Peripheral nerve conditions in diabetes

Management of trigeminal neuralgia and its atypical variant

Formerly **MODERN MEDICINE**

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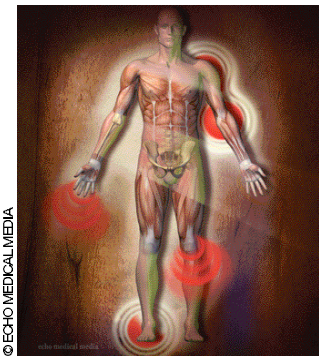
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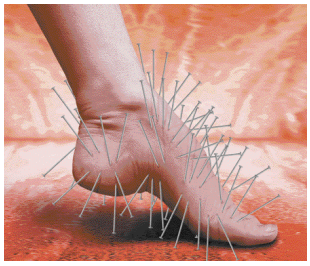
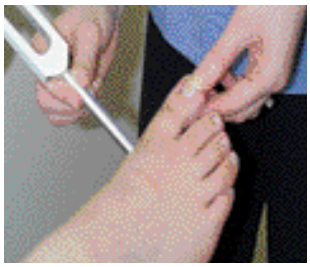

PAGE 7


PAGE 12


PAGE 22

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What a pain! Managing it through the continuum

Managing chronic pain is a challenge for all doctors. Patients need to be encouraged to take control of their pain with a self-management plan and not rely on medication alone. Low back pain is discussed in the article as a model of pain.

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Pain is a complex concept to come to terms with – not only for patients but also for health care professionals. What may be very painful and distressing to one person may be only a mild ache to another. As medical practitioners, we are familiar with the different types of behaviour seen in patients as they present their history. The language of pain varies significantly, and patients may have difficulty describing their pain, often using words such as sore, hurt, ache, throb or 'it's just pain'. Our role is to try and tease out the multiple contributors to their pain and often quite severe distress.

Recent epidemiological data analysed from the Bettering the Evaluation and Care of Health (BEACH) program estimated that osteoarthritis (14.3%), depression (12.9%), anxiety (9.5%) and chronic back pain (8.4%) are significant problems for patients attending general practice in Australia.[1] Further analysis has suggested that 'multimorbidity', where two or more of these conditions occur simultaneously, is present in 10.6% of the population attending general practice.[2]

These particular multimorbidities contain the hallmarks of patients with persisting pain. There is increasing evidence that chronic or persistent pain can be classified as a disease in its own right, something that most medical practitioners will readily recognise.[3]

How best then to manage these patients? Both acute and chronic low back pain are common presentations in general practice and can be used as models to discuss some of the issues associated with persistent pain.

IN SUMMARY

- **Pain is a complex concept to come to terms with – what may be very painful and distressing to one person may be only a mild ache to another.**
- **There is increasing evidence that chronic or persistent pain can be classified as a disease in its own right.**
- **Patients should be helped to institute an holistic, active, self-management program, something akin to a lifestyle change.**
- **Part of the management plan will include addressing patient expectations.**
- **Drug therapy should never be used alone. Address also lifestyle issues such as ensuring a healthy diet, exercising regularly, sleeping well and managing stress appropriately.**
- **Escalating doses of opioids are more likely to increase the side effect profile than improve analgesia and will often reduce functional outcomes and quality of life.**

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Acute nonspecific low back pain

Back pain can be initially classified as being due to specific or nonspecific causes. The use of 'red flags' to rapidly exclude serious (specific) pathology in patients with back pain is easy and quick (Table 1). If a red flag is identified, further investigation and referral is appropriate. Some other specific conditions, such as radicular leg or arm pain causing neurological compromise (especially weakness), will also warrant further investigation and referral.

If no specific condition or 'red flag' is present, then an approach embracing the principles of management of nonspecific low back pain is recommended.

The prognosis for patients with acute nonspecific low back pain is for resolution of symptoms over a one-month period. However, recent Australian data suggest that up to 25% of individuals will have a recurrence within the first year.[4]

Best practice guidelines

Current best practice guidelines for the management of acute nonspecific low back pain include:

- providing reassurance that there is no serious underlying pathology
- giving a simple but understandable explanation of the causes of low back pain and muscle guarding
- demonstrating simple stretching exercises
- advising against bed rest
- encouraging a return to normal activities.

Some patients will have strong beliefs about the cause of their back pain. These must be identified and discussed with the patient. A set of so-called 'yellow flags' has been developed in New Zealand to help identify abnormal beliefs (Table 2).[5] Yellow flags indicate psychosocial barriers to recovery. The clinical assessment of yellow flags may identify the risk of long-term disability, distress and work loss.

Emphasis on the benign nature of the condition should be reinforced. In the absence of red flags or clinically specific causes of the pain, investigation with x-ray or CT scanning is not necessary.

Role of medications

In acute nonspecific low back pain, use of simple analgesics (such as paracetamol 500 mg two tablets every six hours or extended-release paracetamol 665 mg two tablets three times a day) can be recommended. Low-dose short-term anti-inflammatory medications (for example, ibuprofen 200 to 400 mg three or four times daily, naproxen 250 to 500 mg twice daily or celecoxib 200 mg daily) may be of value. Although there is some evidence for the use of benzodiazepines for the treatment of 'muscle spasm', the sedating and dependency risks associated with them means that they cannot be recommended.[6] In general, the use of opioids for more than a short period of time should be avoided for the same reasons.

Recurrent, persistent or chronic low back pain

Imaging

With recurrent or chronic nonspecific low back pain, investigations with imaging are rarely helpful in terms of management. However, it is recognised that because of patient pressure a request for an x-ray or CT scan will usually be made. If performed, imaging should be used to reassure the patient that 'serious' pathology has been further excluded from the differential diagnosis.

The interpretation of findings on diagnostic imaging and its correlation with the clinical picture is not always straightforward. A careful explanation of these findings is needed, because patients may interpret relatively benign reports in an alarmist way, further reinforcing abnormal beliefs about the cause of their pain. A useful resource on diagnostic imaging is the WA government website (www.imagingpathways.health.wa.gov.au), which has diagnostic algorithms and doses of radiation from each imaging technique.

Table 1. Red flags to help identify potentially serious pathological causes of low back pain

- Features of cauda equina syndrome especially urinary retention, bilateral neurological symptoms and signs, saddle anaesthesia) – this requires very urgent referral to a specialist
- Significant trauma
- Weight loss
- History of cancer
- Fever
- Intravenous drug use
- Corticosteroid use
- Age over 50 years
- Severe, unremitting night-time pain
- Pain that gets worse when lying down

Table 2. Yellow flags to help identify potentially serious psychosocial causes of low back pain

- The belief that pain and activity are harmful
- 'Sickness behaviours' (such as extended periods of rest)
- Low or negative moods and social withdrawal
- Treatment that does not fit with best practice guidelines
- Problems with a difficult compensation claim
- A history of back pain
- Problems at work, poor job satisfaction or excessive time off work
- Heavy work or unsociable working hours
- An overprotective family or a lack of support

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continued

Table 3. Discussion points for patients with low back pain

- Address patient expectations to ensure they are realistic
- Encourage a regular 'paced' exercise program, which may include:
  - aerobic activity
  - movement instruction
  - muscle strengthening
  - postural control
  - stretching
- Discuss diet and ideal weight
- Encourage normal activity as far as possible
- Encourage the avoidance of bed rest
- Discuss general lifestyle issues, including:
  - smoking
  - sleep hygiene

Rehabilitation

As with acute low back pain, once specific causes of chronic low back pain have been excluded, management should focus on rehabilitation. Patients should be helped to institute an holistic, active, self-management program, something akin to a lifestyle change (Table 3). Excessive reliance on passive coping strategies, such as medications and interventional procedures, should be discouraged. At best these passive treatments should be viewed as providing a 'window of opportunity' for the patient to institute their self-management program.

As the patient's condition is now considered to be chronic or persistent, a range of psychological and social features will require assessment and management. Patients will often present with low mood, fear avoidance behaviour usually linked to a decreased range of movement, catastrophising thoughts, anger, frustration and a poor level of physical fitness due to deconditioning. They may also have a high body mass index, be unemployed and/or on a disability pension, and have a poor social support network. The GP is ideally suited to be the team manager and to involve allied health professionals to design a management plan.

Patient expectations

Part of the management plan will include addressing patient expectations. These must be realistic and can be difficult for patients to articulate. Patients are all individuals and will present their problems in quite different ways. For example, some patients who have good, enjoyable and challenging jobs will often accept returning to work with some degree of ongoing pain. Others who dislike their jobs and/or supervisors may insist on complete resolution of their pain symptoms before engaging in return to work programs.

For many patients, whether they have nonspecific pain issues or specific but not otherwise treatable ('curable') conditions, resolution of all pain symptoms is often impossible and patients' expectations need to reflect this. However, despite pain, an improvement in function should be possible, along with an improvement in quality of life. Again the GP is the ideal person to start a care plan that will address function and quality of life.

Role of medications

The role of medications in the management of chronic low back pain is somewhat limited and drug therapy should never be used alone. Addressing lifestyle issues is important to ensure the patient is eating a balanced diet, exercising regularly, sleeping well and managing stress appropriately.

If low mood is identified, behavioural strategies, information about depression and goal setting to overcome the depression are also important. If depressive symptoms persist, contact with a clinical psychologist within the team care arrangement and the use of a selective serotonin reuptake inhibitor (SSRI; for example, citalopram 20 mg daily, fluoxetine 50 mg daily or sertraline 50 mg daily), should be considered.

Despite the best of efforts, some patients seem to rely solely on medications and fail to engage in an appropriate rehabilitation program. In the chronic pain setting, these patients have sometimes been referred to as 'chemical copers'.[7] Frequently, benzodiazepines (for example, alprazolam, clonazepam or diazepam), opioids (for example, methadone, morphine or oxycodone) or other sedating medications are used excessively or inappropriately by these patients, often to treat their psychological distress.

Management of these patients who rely on medications should focus on harm minimisation and containment of this essentially iatrogenic problem. Clear boundaries should be set, especially with regard to requests for extra medication, with regular review to reinforce them. Care should be taken to avoid unnecessary investigations, referrals and treatments. Often the best strategy is a thorough clinical assessment and explanation of the appropriate use of medication for chronic pain. Significant support is required from the treating doctors, as well as allied health professionals, family and community services.

What about opioids?

The role of opioids in the management of chronic pain in general has waxed and waned over the past 20 years but still remains relatively controversial. Recent meta-analyses demonstrate a modest reduction (about 30%) in pain with dosages of up to 100 mg daily morphine equivalents but this is not always associated with improved function.[8,9] As discussed previously, functional improvements should be the goal when managing patients with chronic pain, rather than unrealistic reductions in pain intensity.

If opioids are to be prescribed, current Australian recommendations[10,11] are for a trial of treatment, with clear goals to improve lifestyle (for example, take a daily

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20-minute walk, socialise with friends, return to part-time work) agreed between the prescriber and the patient. These recommendations are similar to those published recently in the USA.[12]

During the trial of opioid use, the dose should be adjusted with careful monitoring of adverse effects. The trial needs to be clearly time limited, with the agreement that the opioids will be tapered and ceased if the functional goals are not met. Often verbal consent is adequate; however, written consent may be more useful in more complex patients. Agreeing the terms of the opioid trial with the patient is the most difficult aspect to implement and is frequently neglected.

Information about the side effects of medium- to long-term use of opioids (nausea, constipation, sedation, dry mouth, urinary hesitancy and depression of sex hormones) and a clear explanation that opioids are not to be used as a single treatment strategy should be given to every patient. Constipation is a common and often distressing side effect of opioid use, particularly in the elderly, and should be treated pre-emptively. Although not an absolute contraindication, the use of opioids in patients with a history of drug or alcohol abuse requires extreme caution.

Increasing doses of opioids are more likely to increase the side effect profile than improve analgesia, and will often reduce functional outcomes and quality of life. There is increasing evidence that chronic opioid therapy induces a degree of hyperalgesia, which is partly responsible for the poor outcomes in these patients. Other significant side effects include:

- opioid-induced bowel dysfunction
- suppression of the hypothalamic/pituitary axis
- suppression of the immune system and cognitive impairment.

There is some agreement that in patients already receiving regular opioid medication for persistent pain, a 'ceiling' for the total daily dose should be considered. Some authorities have suggested a ceiling of 100 mg daily morphine equivalents.[9] Functional outcomes, as agreed when the goals were set, should be the major assessment tool for these patients, because it is unlikely that there will be dramatic changes in pain scores, and tolerance is a problem for many patients.

For patients already on opioids for persistent pain, ongoing prescription can be facilitated by the introduction of a care plan including goal setting and functional outcomes. Regular review of goals and the care plan, together with assessment for side effects and overall function, should occur every time a prescription for opioids is written.

The concept of 'universal precautions' has been popularised in Canada with the suggestion that at each review consultation there is value in using a check list of the four As. These are:

- analgesia
- activities
- adverse effects
- aberrant behaviours (such as illicit drug use, lost or stolen prescriptions, consistently using increased amounts of opioids etc).[13]

Patients with chronic pain who are difficult to manage should be referred to a pain or addiction medicine specialist. If opioid use is to be withdrawn, then this should occur gradually. Generally a dose reduction of 10% per week is recommended to avoid severe withdrawal symptoms. Remember that state or territory prescribing rules about notification of Schedule 8 drugs must be followed.

Finally, in patients with some specific types of back pain, interventional procedures (such as nerve root sleeve and facet joint injections) may provide some temporary relief from pain and may have some value in encouraging engagement in rehabilitation and self-management programs. Similarly, surgery is no panacea. Surgical intervention must be combined with a comprehensive rehabilitation program if there are to be successful outcomes.

Neuropathic pain

Another often problematic but less common type of pain that is increasingly recognised is neuropathic pain, which can be defined as pain caused by damage to the peripheral or central nervous system. Words such as tingling, pins and needles, electric shock-like or burning may be used to describe the pain, and on clinical examination areas of hypersensitivity, increased pain and/or numbness can be identified. Simple screening tools are now available.[14]

The causes of neuropathic pain include:

- diabetic neuropathy
- postherpetic neuralgia
- trigeminal neuralgia
- 'sciatica'
- rarer conditions such as complex regional pain syndrome and central post-stroke pain.

Management

Management of neuropathic pain should be similar to that for other forms of chronic pain, and if the pain persists should involve the design of a care plan. There has been good international consensus on medication options for neuropathic pain.[15]

First-line treatment recommendations include tricyclic antidepressants (used off label for neuropathic pain), such as amitriptyline and nortriptyline. Effective doses of tricyclic antidepressants vary widely. They should be started at a low dose of 10 mg at night and then, to optimise acceptability, increased slowly by 10 to 25 mg every seven nights to a maximum dose of 150 mg at night.[15] Amitriptyline given at night may be helpful for sleep disturbance, while less-sedating tricyclic antidepressants such as nortriptyline can be given to patients during the day.

Adverse effects of tricyclic antidepressants include dry mouth, constipation, sweating, dizziness, sedation, drowsiness, palpitations, autonomic dysregulation with postural hypotension and urinary retention, especially when prescribed in elderly patients. Tricyclic antidepressants

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have a slow onset of effectiveness and should be trialled for at least two weeks.[16]

If tricyclic antidepressants are contraindicated, the anticonvulsants pregabalin or gabapentin can be used as first-line therapy.

Second-line treatment involves the use of anticonvulsants or serotonin-noradrenaline reuptake inhibitor (SNRI) antidepressants (used off label). Some of the newer drugs such as pregabalin and gabapentin have the best evidence of efficacy. Pregabalin may be preferable to gabapentin because of its more predictable dose–response relation, twice daily dosing and the ability to titrate quickly. Starting dosages are 75 mg twice daily, up to a maximum dosage of 300 mg twice daily, and there is now a 25 mg capsule of pregabalin, which may be useful in elderly patients.[15] They are used as second-line treatment if tricyclic antidepressants are not tolerated or found to be ineffective.

The anticonvulsant carbamazepine has good efficacy for the treatment of patients with trigeminal neuralgia. The SNRI antidepressants venlafaxine (150 to 225 mg daily) and duloxetine (60 to 120 mg daily) have shown moderate efficacy in patients with neuropathic pain.

Third-line options include tramadol, sodium valproate and opioids.[17] When third-line treatment options are reached, management is obviously more complex and a whole-person approach to the pain should be used. The previously discussed guidelines for using opioids are equally appropriate for neuropathic pain, and a telephone consultation with a pain medicine centre should be considered.

Conclusion

As the concept of describing ongoing pain as a disease in its own right gains momentum, so also is it being recognised as a true chronic condition. It is essential for patients and practitioners to understand the principals of self-management.

Pain is a complex phenomenon and can be challenging to manage, especially once it is persistent. It requires a comprehensive, co-ordinated approach that emphasises active self-management principles. GPs are ideally placed to manage chronic pain within a team environment, utilising the wide range of community services available. By employing these principles and obtaining successful outcomes managing patients with pain should no longer be 'heart sink' but may even become music to our ears. MT

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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 anticonvulsant 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.**

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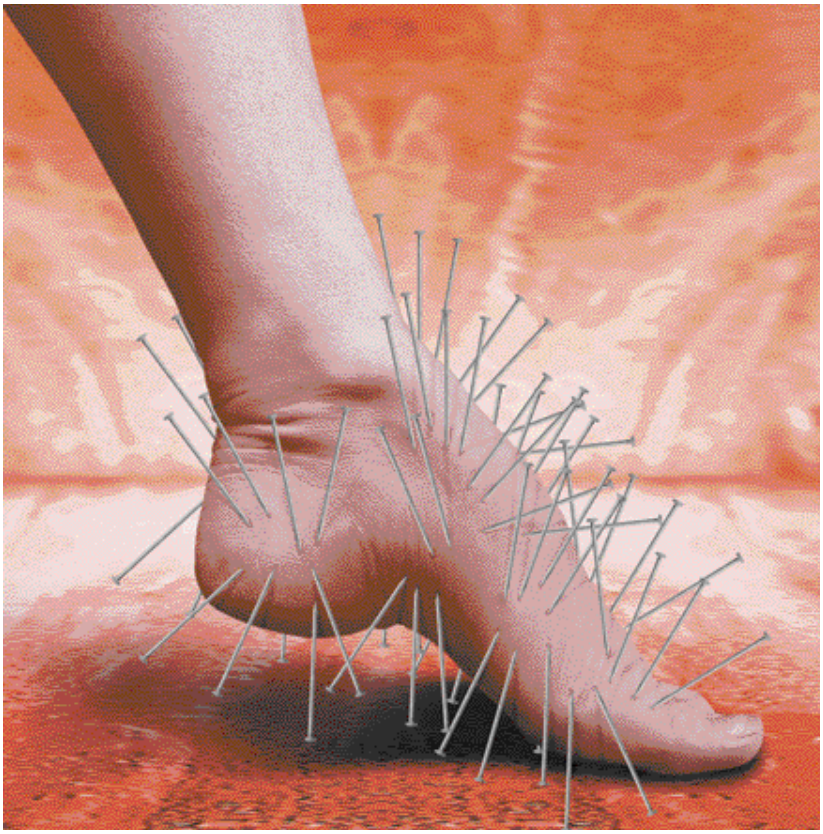
Treatment of neuropathic pain



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.

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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 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 aidememoire 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

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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 anticonvulsants, 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 (used off label). 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 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 noradrenaline reuptake inhibitors may be useful (venlafaxine [restricted benefit for major depressive disorders] has a NNT of 4.5), although their use for pain is off label. Again, the dosing advice is to start low and go slow. The effective dose may be as high as 225 mg daily. Duloxetine (restricted benefit for major depressive disorders) is used widely overseas for neuropathic pain and is approved in Australia for the treatment of patients with diabetic peripheral neuropathic pain.

Anticonvulsants

There is a long tradition of using anticonvulsants in the treatment of neuropathic pain, but until recently there was almost no trial evidence of efficacy. This changed with the introduction of gabapentin and more recently pregabalin 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 anticonvulsants 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

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)

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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 seriatim 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.

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 post-stroke 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 anticonvulsants, 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 anticonvulsants such as lamotrigine, carbamazepine, topiramate and sodium valproate (all used off label).

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 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 (used off label), an N-methyl-D-aspartate antagonist delivered by parenteral and nasal routes, clonidine (used off label) 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.

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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 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, 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 to 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 (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 page 10.

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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Peripheral nerve conditions in diabetes

Tight glycaemic control is needed to help prevent the development of diabetic peripheral neuropathy. However, once the condition has occurred patients should be protected against the development of foot ulceration. Patient education and preventive podiatric care are priorities in people with diabetic peripheral neuropathy.

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Among the different organs that are particularly susceptible to the adverse effects of diabetes, the neurological system features prominently. The parts of the nervous system affected by diabetes are the peripheral nerves, the autonomic nervous system and, more recently demonstrated, the central nervous system.

This article addresses the main clinical presentations of patients with diabetes who have peripheral neuropathy and discusses recommendations in management. The high importance of early detection of loss of protective sensation in the feet of patients with diabetes, and the consequent foot care required, is key to the prevention of foot ulceration and amputation and is emphasised in this clinical update.

Peripheral nervous system

The elevated blood glucose levels that occur in people with diabetes over time are thought to cause some degree of peripheral neuropathy in the majority of people with the condition. Neurons supplying the feet are more than one metre in length and are especially likely to be metabolically challenged. High blood glucose levels lead to toxic glucose levels in neuronal cells because

IN SUMMARY

- **The most common symptomatic clinical presentation of diabetic peripheral neuropathy is loss of sensation in the feet, which is usually bilateral and symmetrical.**
- **Many patients have no symptoms of peripheral neuropathy even when it is found to be present based on clinical signs.**
- **Detection of signs of peripheral neuropathy requires careful foot examination.**
- **Insensate neuropathy is typically due to abnormalities in small and large nerve fibres whereas painful neuropathy may be due to purely small nerve fibre involvement.**
- **Peripheral neuropathy in patients with diabetes, once established, is usually not reversible.**
- **To help prevent foot ulceration, insensate neuropathy is managed by patient education, self-care and regular podiatry care.**
- **New foot complications due to diabetic peripheral neuropathy, such as foot ulceration, require urgent medical assessment to manage any infection or ischaemia and to reduce pressure at the ulcer site.**
- **Painful diabetic neuropathy is often difficult to control adequately. Achieving adequate symptom relief may require a trial of several different therapies. Combination pharmacological therapy usually provides the best results.**

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they are obligate glucose metabolisers. The most common type of nerve damage is a metabolic 'die back' neuropathy and, because the lower limbs have longer nerve extensions, the feet are affected before the hands.

Pathologically, the injury to the peripheral nerve is a mixture of axonal loss and demyelination of some nerves. Much research is focussed on whether the toxic effects of high glucose levels are directly on neurons or whether the vessels supplying the nerves, the 'vasa nervorum', are also an initial target, with nerve hypoxia being a secondary process.

Although peripheral neuropathy in diabetes may be silent and not cause any symptoms, it may present as loss of light touch such as numbness in the feet or in other cases as pain. So-called 'insensate neuropathy' is usually due to abnormalities in small and large nerve fibres. In contrast, 'painful neuropathy' may be due to involvement of purely small fibres or a mixture

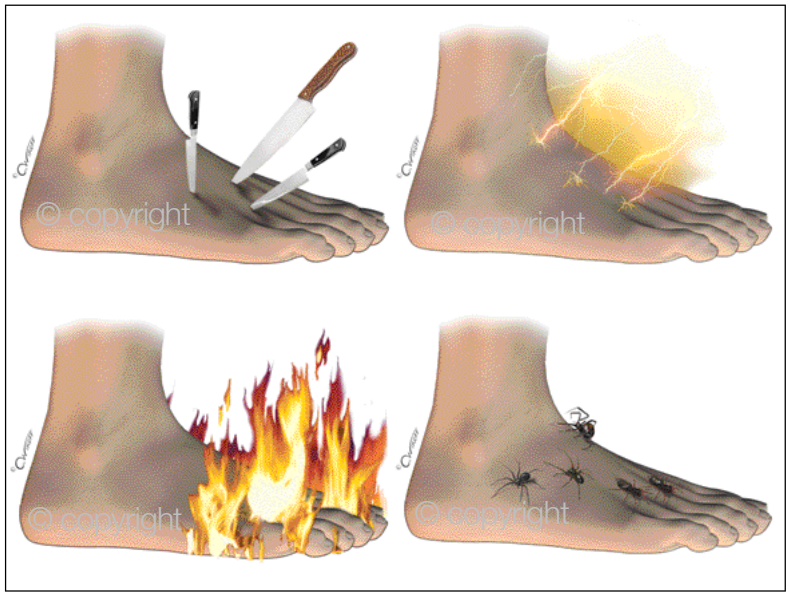

Figure 1. Visual presentations of some symptoms of painful neuropathy. Patients describe their pain as stabbing (top left), electric (top right), burning (bottom left) or crawling (bottom right).

Table 1. Symptoms and signs occurring in the two different types of diabetic peripheral neuropathy[3,4]

Insensate neuropathy (most common type)	Painful neuropathy (less common type; may also develop some features of insensate neuropathy)
Symptoms	
No symptoms Numbness	'Pins and needles' Burning Electric/lancinating, sharp Tightness Stabbing Crawling Allodynia Hyperalgaesia Nocturnal distress is typical
Signs	
Loss of ankle reflexes Reduced vibration sense (128 Hz tuning fork or elevated biothesiometer reading) Loss of the ability to feel the 10 g 5.07 gauge Semmes-Weinstein monofilament Foot deformity (motor neuropathy with 'cock-up' deformity of toes; increased pressure over the metatarsal heads with callus) Autonomic features (fissures, loss of sweating, dry cracked skin)	May be no signs

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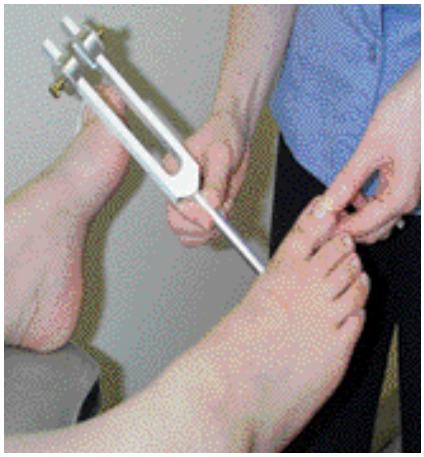

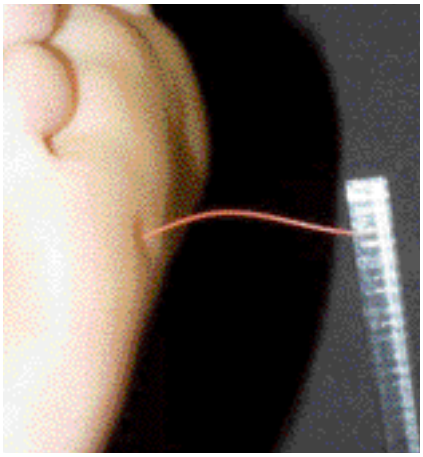

Figures 2a and b. Testing for insensate neuropathy. a (left). Tuning fork vibration testing. b (right). 10 g 5.07 gauge Semmes-Weinstein monofilament testing.

of small and large fibres. Why some people may have particular nerve fibre sizes affected and thus develop one symptom such as numbness rather than another such as pain is not well understood and currently remains in the realms of research. This article addresses clinical aspects of both types of diabetic peripheral neuropathy – the insensate form and the painful type.

Making the diagnosis of diabetic peripheral neuropathy

The first issue to determine in a patient with diabetes presenting with feet or leg symptoms is whether the condition is a peripheral neuropathy. If a neuropathy is present then the next priority to address is whether diabetes is the cause.

The most common symptomatic clinical presentation of diabetic peripheral neuropathy involves loss of sensation in the feet, which is usually bilateral and symmetrical.[1] Many patients have no symptoms at all of neuropathy, even when it is found to be present based on clinical signs. In others, a 'spongy feeling' to the toes and feet is common, with patients unable to clearly feel their feet on weight-bearing.

A less common presenting symptom in patients with diabetic peripheral neuropathy is pain.[2] The description of the pain can vary markedly, and it can have radicular elements in the legs or be distal in the feet only. Terms used to describe the pain include electric, pins and needles, burning, shooting, sharp or a tightness. Excessive pain caused by the light touch of objects (allodynia) or exaggerated pain from a noxious stimulus (hyperalgaesia) are also well recognised. A peak in pain nocturnally is typical. Some of these symptoms of painful neuropathy are shown as images in Figure 1.

In contrast to the symptoms that feature in patients with peripheral neuropathy are those that can occur due to other conditions such as musculoskeletal symptoms or peripheral arterial disease. In cases of pain, if the pain is unilateral then causes other than peripheral neuropathy, such as arthritis, vascular causes or spinal nerve compression, should be considered. For example, pain in the legs due to lumbar spondylosis is usually asymmetrical and radicular and there is also often a history of lumbar pain. Pain due to peripheral arterial disease when relatively less severe is that of claudication and when more severe occurs at rest and is accompanied by signs of major arterial insufficiency. Pain due to a form of arthritis will often occur with inflammatory features and/or deformity at the site of a joint.

The diagnosis of peripheral neuropathy ideally requires that at least two characteristic features be present: characteristic symptoms or signs, nerve conduction abnormalities, or abnormalities on quantitative sensory testing or quantitative autonomic tests.[3] Characteristic symptoms and signs are listed in Table 1.[3,4] The sensory changes tend to dominate over the motor features, which are clinically a late manifestation. Most people with diabetes who develop peripheral neuropathy will have the insensate form of the condition, whereas the painful type will develop in a minority of patients.

Detection of signs of peripheral neuropathy requires careful foot examination. Some early features on examination are loss of ankle reflexes and progressive reduction in vibration sensation as demonstrated by either a 128 Hz tuning fork or a biothesiometer, a device that delivers a vibration stimulus in a more quantitative continuous manner than a single frequency stimulus from a tuning fork (Figure 2a). The 10 g 5.07 gauge Semmes-Weinstein monofilament is a useful tool to detect severe, 'insensate' peripheral neuropathy (Figure 2b). This is a standardised filament of specific weight and gauge that will produce a standard skin sensory signal when pressure is applied to its tip. When this monofilament is applied to the foot, an inability by the patient to feel it at one or more sites on the plantar aspect of the foot is abnormal. This indicates a markedly increased risk of diabetic foot ulceration compared with the normal result of the patient feeling it at all sites tested. Typical sites tested are under the first and fifth metatarsal heads and on the plantar aspect of the hallux.[5] Although monofilaments other than the 10 g (e.g. 6 g monofilament) can detect more subtle sensory loss, ankle reflexes and a tuning fork or biothesiometer are used to detect milder changes of sensory loss because of familiarity with the

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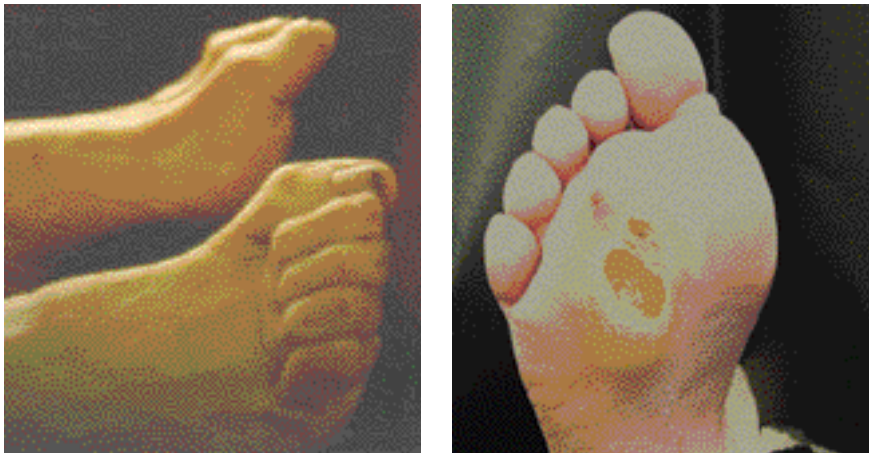
equipment and ease of access in practice.

Usually in patients with peripheral neuropathy the feet will appear normal. In more advanced cases of peripheral neuropathy, signs of peripheral neuropathy, which may be present as features of motor neuropathy, are seen with hyperextension at the metatarsophalangeal joints and flexion at the interphalangeal joints. This 'cocked-up deformity of the toes' is associated with a weakness of intrinsic foot muscles and callus formation on the plantar aspect of the feet where weight-bearing foot pressure is increased, especially under the metatarsal heads as shown in Figures 3a and b. Sites of callus development are especially prone to result in foot ulceration, and prevention and early and regular treatment of calluses are important to prevent foot ulceration. Autonomic neuropathy may appear as dry skin with fissures.



Figures 3a and b. Typical appearance of neuropathic feet in advanced insensate neuropathy. a (left). Feet with cocked-up toe deformity. b (right). Plantar haemorrhagic callus requiring debridement has formed under a metatarsal head, which is a common site of development of increased weight-bearing pressure.

In the authors' experience, almost all cases of diabetic peripheral neuropathy can be diagnosed clinically. Patients with atypical presentations, however, should receive formal laboratory-based nerve conduction studies and referral to a neurologist, especially in cases of rapidly progressive symptoms. A nerve conduction study result is shown in Figure 4. It should be noted that in cases of painful diabetic neuropathy where only small fibres may be affected, results of nerve conduction studies (which measure large

MOTOR NERVE CONDUCTION

Nerve	Stim	Rec	amp mv	lat ms	dist mm	CV m/s
L Post Tibial	Ankle	Flex Hal Brev	0.5	5.8	110	
L Post Tibial	Knee	Flex Hal Brev	0.3	19.8	420	30
R Post Tibial	Ankle	Flex Hal Brev	2.0	5.9	110	
R Post Tibial	Knee	Flex Hal Brev	0.9	20.0	430	30

SENSORY NERVE CONDUCTION

Nerve	Stim	Rec	amp uV	lat ms	dist mm	CV m/s
L Sural	Ankle	Calf	0.7	3.5	120	34
R Sural	Ankle	Calf	0.0	0.0		
R Median	Digit 2	Wrist	4.1	2.7	130	48
R Ulnar	Digit 5	Wrist	2.3	2.3	100	43

CLINICAL NEUROPHYSIOLOGY

Figure 4. Results of a nerve conduction study in a patient with diabetes and severe peripheral insensate neuropathy, showing reduced amplitude of signal (indicating axonal neuropathy) and reduced nerve conduction velocity (each relative to the median and ulnar nerves).

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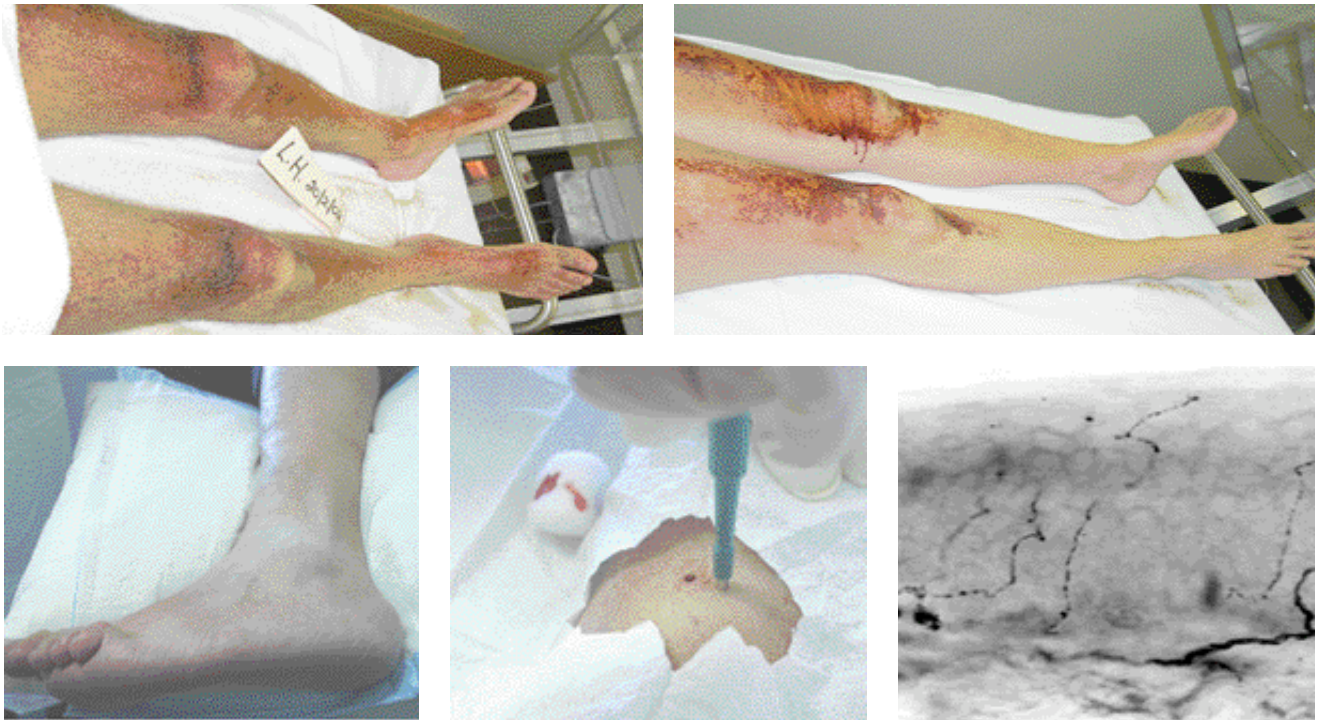

Figures 5a to e. Confirmatory tests supporting a clinical diagnosis of painful peripheral neuropathy. a and b (top left and right). Sudomotor reflex examination using sweat testing: a normal sweat test, as indicated by red colour (left), and an abnormal result with a lack of signal below the knees (right). c and d (bottom left and middle). Skin punch biopsy of the lower limbs, which is largely a clinical research tool. e (bottom right). Intraepidermal nerve fibre staining for counting following the skin biopsy.

fibre function) are often normal and therefore not helpful in diagnosis.[6]

Two nerve conduction tests that are often abnormal in patients with painful diabetic neuropathy are:

- autonomic tests of the lower limbs examining sudomotor reflexes in sweat testing[7]
- nerve fibre analysis including during skin biopsy,[8] rather than the more invasive sural nerve tests.

These tests are shown in Figures 5a to e. However, these investigations are mainly used in clinical research rather than in diagnosis. The sweat test as shown is semiquantitative and is only abnormal in the most severe cases of autonomic neuropathy.

Once peripheral neuropathy has been diagnosed careful consideration should be given as to whether diabetes is the cause, in contrast to one of many other potential causes, as shown in Table 2.[9] Indeed, a diagnosis of diabetic peripheral neuropathy is defined as the presence of neuropathy in a patient with diabetes in whom other causes have been excluded.[8] The clinical course in its presentation can be helpful. Diabetic peripheral neuropathy manifesting as sensory loss is slow or chronic in onset and distal in location. In contrast, some causes of peripheral neuropathy, such as Guillain Barré syndrome, are rapidly progressive, acute or subacute and can become proximal.

In people with diabetic peripheral neuropathy, diabetes will usually have been present for at least five years. However, it is also recognised that in up to 20 to 30% of people with type 2 diabetes, diabetic peripheral neuropathy is present at the time of diabetes diagnosis.[10] In most cases, this is because the diabetes has been present for some years before diagnosis and has not been recognised.

Peripheral neuropathy is more common in the elderly, not only related to diabetes duration but also due to age alone because some light touch sensation is lost with age. In a small minority of people with milder glucose abnormalities, such as impaired glucose tolerance, a syndrome of transient symptomatic painful neuropathy can sometimes occur: in this situation, the pain usually resolves after some months.[11]

In a patient with peripheral neuropathy, whether investigations should be undertaken to help exclude other causes of peripheral neuropathy will depend on the clinical presentation. Investigations that should be considered include measurement of vitamin B_{12} level, thyroid function tests and studies for paraproteinaemia, connective tissue disease and sarcoidosis, as listed in Table 3.

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Table 2. Differential diagnoses of underlying causes of peripheral neuropathy[9]

- Diabetes
- Alcohol abuse
- Vitamin deficiency (B_1, B_{12})
- Thyroid hormone excess or deficiency
- Vitamin excess (B_6)
- Monoclonal gammopathy
- Carcinoma – paraneoplastic phenomena
- Infection (HIV/AIDS, hepatitis C, diphtheria)
- Exposure to toxins and heavy metals (arsenic, thallium, lead, mercury)
- Hereditary
- Autoimmune
- Coeliac disease
- Sarcoidosis
- Guillain Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Amyloidosis
- Porphyria
- Vasculitis – may be threatening to the limbs

Prevention of peripheral neuropathy

Among the various metabolic and haemodynamic disturbances that occur in patients with diabetes, hyperglycaemia is the key factor that contributes to diabetic peripheral neuropathy. Intervention studies in patients with type 1 diabetes (the Diabetes Control and Complications Trial [DCCT]) and in patients with type 2 diabetes (the United Kingdom Prospective Diabetes Study [UKPDS]) have clearly demonstrated that the onset of insensate peripheral neuropathy can be prevented in more than 50% of cases by tight glycaemic control – for example, at a glycosylated haemoglobin (HbA_{1c}) level of 7%, compared with a level of 8 or 9%.[12,13] These data relate to longer term, chronic glycaemic control. Although it is less well studied, there is a body of anecdotal evidence indicating that minimising fluctuations in blood glucose levels can help to reduce symptoms of painful diabetic neuropathy in some people.

On the basis of animal models of diabetic neuropathy and *in vitro* cell studies, it has been concluded that high glucose levels act through multiple intermediates in cells to cause neuronal dysfunction and death. Over the years, many medications have been studied in the hope that they can prevent the damage of peripheral nerves by the mediators of high glucose. Medications that have been examined in clinical trials include aldose reductase inhibitors, inhibitors of protein kinase beta II isoforms and nerve growth factors. However, results overall have been disappointing and targeting tighter blood glucose control remains the main metabolic intervention in preventing diabetic neuropathy.[14]

Other factors present in diabetes may be important in helping to prevent the worsening of neuropathy. Although blood pressure control was not associated with neuropathy in the UKPDS, more recent epidemiological and mechanistic studies are starting to implicate dyslipidaemia in the exacerbation of peripheral neuropathy.[15] Prospective studies will be required to determine whether targeting lipids can reduce peripheral neuropathy and which lipid parameters are most important.

Peripheral neuropathy in patients with diabetes is thought to be usually irreversible. The insensate form is slowly progressive with the passing of the years. If the pain is of short duration of onset (less than 12 months) then it is likely to resolve more rapidly. The chronic painful form of diabetic neuropathy present for longer than 12 months may progress, stabilise or, with time, the symptoms of pain may resolve. In one series, in 30% of cases the pain worsened and in 11% it resolved, with most patients receiving some ongoing degree of pain control.[16] Although painful neuropathy alone without sensory loss is not associated with an increased risk of foot ulceration, a slow development of sensory loss has been documented in some cases and the patient will be at increased risk of foot ulceration if sensory loss also develops over time.

Table 3. Laboratory investigations to be considered in patients with peripheral neuropathy

- Glycaemic control if diabetes is present (glycosylated haemoglobin [HbA_{1c}] and blood glucose levels including fluctuations)
- Thyroid function tests
- Measurement of vitamin B_{12} level
- Immune electrophoresis
- Coeliac disease screen (especially anti-tissue transglutaminase)
- Measurement of angiotensin converting enzyme level (sarcoidosis)
- Measurement of rheumatoid factor, antinuclear antibody, extractable nuclear antigens and antiphospholipid antibodies

Managing diabetic peripheral neuropathy

Insensate neuropathy

The main concern in patients with peripheral neuropathy is that the loss of protective sensation in the feet increases the risk of them developing foot ulceration, which can then lead to further complications such as deep tissue infection that may necessitate amputation. Indeed, up to 25% of people with diabetes will develop a foot ulcer in their lifetime, and it is estimated that every 30 seconds an amputation occurs in the world due to diabetic foot disease, with more than half of these amputations being preventable.[17] In people who have insensate neuropathy where the 10 g monofilament cannot

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continued

Table 4. Advice to give patients diagnosed with insensate diabetic peripheral neuropathy*

Area of concern	Advice
Exercise	• Focus on nonweight-bearing exercise such as swimming, water aerobics or upper body exercise • Do not undertake walking or running as exercise; stationary cycling is a reasonable option because it minimises shear stress on the feet • Avoid any activity that may lead to burns of the feet, including excessive sun exposure
Footwear	• Wear enclosed shoes with an ample toe box, flexible rubber soles, smooth seams and a wide and low heel at all times during weight-bearing activities, making sure the shoes are not too tight • Orthotics and possibly custom-made footwear may be indicated to minimise pressure sites and to protect vulnerable feet • At the beach or pool, soft surf shoes with a rubber sole are ideal • Wear new shoes in slowly to test that they match feet well • Choose socks that are made from natural fibres and that are not tight around the top
Foot hygiene and foot inspection	• Wash feet daily using warm water and mild soap, and dry between toes • Undertake foot inspection daily including between toes (a mirror may help to view the plantar aspects or inspection with the help of another person) • Avoid dry skin by using a urea-based cream • Report any persisting breach in the skin to the health carer
Health professional support	• Podiatric care should be routine, including treatment of any corn or callus, and the doctor should examine the feet at follow-up appointments • If a foot injury develops with an ulcer, wash the area gently with saline or water, pat dry and cover with a non-adhesive dressing. If there is no improvement within 24 to 48 hours or the area appears to be inflamed or infected then contact the doctor without delay for further treatment • Ulceration of feet should be rapidly assessed by the doctor for consideration of antibiotic therapy and minimisation of foot pressure at the ulcer site. Also, referral of patients with foot ulcers to a diabetes high-risk foot service, if accessible, is desirable

* Written advice for the person with diabetes is preferred and if available, education in group sessions.

be felt, the risk of foot ulceration is about 10 times higher than that of a person who has no neuropathy and occurs at an annual incidence of about 10%.[18] In a person with diabetes who has insensate neuropathy, the main priorities are therefore to prevent foot ulceration and subsequent amputation, and to preserve a functioning foot.

If a person cannot feel the 10 g monofilament they are at substantial risk of diabetic foot ulceration due to the presence of the severe insensate neuropathy. These patients require:

- intensive foot education
- regular podiatry care to manage areas of high pressure such as corns and calluses
- protection for the feet with appropriate footwear recommendations, and possibly orthotics and/or referral for custom-made footwear
- help to balance the moisture in the feet and correctly trim the nails.

Recommended patient education and self-care when insensate neuropathy is present is given in Table 4. The extended-care program with GP referral to podiatry is an appropriate path in such persons with insensate neuropathy.

Times of particularly increased risk of foot ulceration occur in a person with insensate neuropathy when new shoes are being worn or 'broken in' and/or when new intensive exercise regimens involving walking or other weight-bearing activities are commenced. Another time of particularly increased risk is the hotter summer months when patients are more likely to walk barefoot and on very hot surfaces prone to causing blisters.

Patients need to be advised about appropriate footwear and to break in new shoes slowly, for a maximum of only a few hours each day, to enable at-risk feet to accommodate the new shoes. For structured exercise programs, nonweight-bearing forms (such as swimming), upper body exercises or exercise that minimises shearing on the feet (such as cycling) are preferred. Patients should undertake regular daily inspection of the feet for any

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Table 5. Options in therapy for painful diabetic neuropathy*

Therapy type	Reason for recommendation	Drug†	Typical final dose in adults for commonly used drugs
First tier	More than two randomised controlled trials in diabetic peripheral neuropathy	*Duloxetine* *Pregabalin* *Oxycodone CR* *Amitriptyline*‡	60 mg daily 75 to 300 mg twice daily 5 to 40 mg at night 25 to 150 mg at night
Second tier	One randomised controlled trial in diabetic peripheral neuropathy; more than one randomised controlled trial in neuropathic pain	*Gabapentin* *Tramadol* *Lamotrigine*‡ *Venlafaxine XR*‡	300 to 600 mg three times daily 50 to 400 mg daily 75 to 225 mg daily
Topical	Mechanism of action	*Capsaicin 0.075% cream* Lidocaine‡ Isosorbide dinitrate‡	Administered two to three times daily
Other	More than one randomised controlled trial in neuropathic pain or other evidence	*Buprenorphine patch* *Carbamazepine*‡ Bupropion‡ Paroxetine‡ Topiramate‡ Citalopram‡ Methadone	5 to 20 µg/hour administered as a weekly patch 100 to 200 mg two to three times daily

* Adapted from Argoff CE, Backonja MM, Belgrade MJ, et al. Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. Mayo Clin Proc 2006; 81(Suppl 4): S12-25.
† Drugs in italics are more commonly used in Australia for the treatment of patients with painful diabetic neuropathy.
‡ Not TGA-indicated for use in patients with peripheral diabetic neuropathy.

skin breach and avoid excessive skin dryness.

It is beyond the scope of this article to discuss in detail acute foot ulceration in diabetes and its subsequent care. However, patients with insensate diabetic peripheral neuropathy need to be warned that any breach of the skin should lead to rapid assessment by their doctor as to whether the site is clinically infected and if antibiotic therapy should be commenced. Regimens such as dicloxacillin or clindamycin, which are directed against the most commonly involved pathogenic bacteria, *Staphylococcus aureus,* are useful.[19,20]

Assessment for peripheral arterial disease and osteomyelitis may also be appropriate. Such a patient should minimise weight-bearing on the ulcer site and not continue to use regular footwear but be promptly referred for pressure offloading approaches such as a 'postoperative shoe' and use of felt deflection. Following prompt assessment by his or her GP, a patient with diabetes who has developed a new foot ulcer should be referred in a timely manner to a multidisciplinary diabetes high-risk foot service if available.[21,22] If this service is not available, an alternative may be timely assessment by a GP and more intensive follow up by a podiatrist, co-ordinating care with a diabetes nurse educator and endocrinologist or a general physician who manages diabetic foot complications, and utilising access to surgical colleagues who manage foot complications such as vascular and orthopaedic surgeons.

Painful neuropathy

Painful diabetic neuropathy can be extremely distressing for the patient and difficult to control adequately. The pain is usually worst at night and keeps the patient awake, and a vicious cycle of insomnia, poor quality sleep and depressed mood is created.

Pharmacotherapy is generally the most effective pain control option for painful neuropathy. Table 5 lists the main pharmacotherapy options. It is important to recognise that no one treatment is effective in all patients and a trial approach needs to be used in each case.[23] Doses prescribed and duration of therapy, usually for a minimum of some weeks, need to be sufficient for an adequate therapeutic trial to be realised. Rarely is the pain fully reduced to

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continued

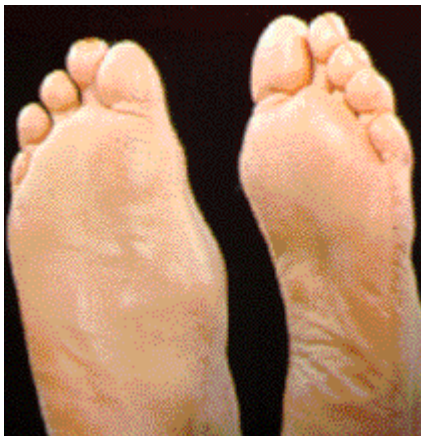

Figure 6. A case of chronic Charcot's arthropathy showing mid-foot deformity.

zero intensity; instead pain is controlled, enabling an improved patient quality of life. The placebo effect is strong in painful diabetic neuropathy, with most patients in clinical trials reporting some benefit from an oral placebo.

In cases of less severe pain, twice daily application of topical agents, such as butoxyethyl nicotinate and nonivamide cream or ointment or capsaicin cream, can be effective. Although low-dose oral tricyclic antidepressant therapy (such as amitriptyline) can be helpful, anticholinergic side effects often limit its use. The serotonin noradrenaline reuptake inhibitor (SNRI) duloxetine has recently been approved by the TGA in Australia for use in patients with painful diabetic neuropathy. It has a good evidence base from international studies for efficacy and is generally well tolerated. Other treatment options include anticonvulsants, especially gabapentin or pregabalin (both indicated for the treatment of neuropathic pain), both of which require commencement at a low dosage with uptitration. The SNRI antidepressant venlafaxine also has proven efficacy, although it is not indicated for the treatment of patients with painful neuropathy.

In the most severe cases of pain, combining agents such as an opioid (e.g. hydromorphone, morphine and oxycodone) and gabapentin can be more effective in pain control with less severe side effects than using either agent alone. Opioids are often very effective because they impact on mu receptors, which are thought to transmit signals in patients with diabetic painful neuropathy. Some patients also report benefit from using transcutaneous electrical nerve stimulation (TENS) devices, acupuncture and/or yoga, with the best evidence base to support the use of TENS.[24,25] The use of alpha lipoic acid and gamma linolenic acid have received some positive reports.[26] For intractable cases, referral to a chronic pain service, if available, may aid in patient care, and intrathecal analgesia and spinal cord stimulators are options sometimes used.

Less common forms of peripheral nerve syndromes in diabetes

Although chronic distal bilateral symmetrical peripheral neuropathy is the most common type of peripheral nerve damage in patients with diabetes, other forms can occur, as described below.

Charcot's arthropathy

A rare form of neuropathy involving diabetic feet is Charcot's arthropathy.[27] Although it occurs in less than one in 1000 people with diabetes, it is very important to recognise the condition and make the diagnosis because delay can lead to severe and progressive foot fracture with gross dislocation and consequent need for amputation.

Patients with Charcot's arthropathy will often present with a hot, inflamed foot of some days or weeks' duration, often with mid-foot bony deformity and swelling associated with rapid osteolysis in bone. Although insensate neuropathy is often present, this condition involves an autonomic neuropathy, which has an initial inflammatory phase. There may be a history of recent blunt injury to the foot as a precipitant. Charcot's arthropathy is not caused by infection, and infection can often be excluded clinically at presentation by the absence of a history of penetrating injury and no evidence of a transcutaneous entry point on foot examination. A plain x-ray of the foot will often show fracture dislocation of mid-foot bones.

In such a presentation of acute foot inflammation with deformity, rapid assessment by a diabetes high-risk foot clinic is indicated. Once the diagnosis is made, treatment involves extensive pressure off-loading using a total contact plaster cast. Regular follow up is required, with changing of the cast as foot oedema settles. The acute phase takes several months to resolve and the total duration of therapy is usually 12 months to help ensure that the foot bones fuse in a stable form, enabling a functional foot. Patients who have been treated for Charcot's arthropathy usually need custom-made footwear to support the foot deformity that persists (Figure 6).

Radiculopathies

Occasionally, sudden loss of function of a peripheral nerve can occur in a person with diabetes as a mononeuropathy.[28] Other than secondary median nerve involvement from entrapment in carpal tunnel syndrome, the nerves most commonly affected are the cranial nerves III (oculomotor), IV (trochlear) and VI (abducens), and therefore affected patients will present with ptosis and/or diplopia with squint. The cranial nerve pathology is thought to occur on the basis of occlusion of small vessels supplying the relevant nerve, which is reflected in the oculomotor nerve lesions usually having an element of papillary sparing.

With these clinical presentations, it is important to exclude other causes of the nerve palsy such as an intracranial lesion, including an aneurysm. Head scans are usually indicated, as well as neurologist review.

Diabetic amyotrophy

The rare condition diabetic amyotrophy is a lumbosacral plexopathy with patchy

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denervation rather than a peripheral nerve condition as such.[28] The patient, who is more commonly male, usually presents with severe and mainly unilateral pelvic and proximal lower limb pain with weakness. Glycaemic control is poor and the patient appears cachectic, with a recent history of many kilograms of weight loss. In the differential diagnosis it is important to exclude a pelvic mass as the cause, using imaging procedures.

Complex analgesia regimens with opioids, such as regular use of oral oxycodone or buprenorphine patches, may be required. The pain usually fully resolves after 12 to 18 months.

Conclusion

Diabetic peripheral neuropathy is a common complication among people who have diabetes. Its onset and worsening can be prevented by tight glycaemic control. Protecting patients with insensate neuropathy from the development of foot ulceration is a high priority and relies on patient education and preventive podiatric care. In contrast, control of symptoms in patients with painful neuropathy remains a major therapeutic challenge requiring individualisation of patient care typically using pharmacological regimens. MT

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Management of trigeminal neuralgia and its atypical variant

Although trigeminal neuralgia is relatively uncommon, the recurrent and sometimes chronic pain associated with the condition can result in negative psychosocial behaviours, such as anxiety and depression. Anticonvulsant drugs are first-line treatment for the classic form of trigeminal neuralgia.

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Trigeminal neuralgia is characterised by sharp, electric shock-like, paroxysmal pain that radiates through the face, teeth and jaw. It is a relatively uncommon condition with an incidence in the USA of four to five per 100,000 people per year and with a predilection for women over the age of 65 years.[1] Although very rare, the condition can occur in children and infants.

In its common presentation, patients with classic trigeminal neuralgia experience episodic pain lasting from seconds to minutes. Patients with this acute classic form of the condition are managed with anticonvulsant treatment. Subsequent surgical intervention may be required, particularly where higher doses of medications fail to relieve the pain and when vascular compression of the trigeminal ganglion is shown on magnetic resonance imaging. Classic trigeminal neuralgia is a well-recognised condition treated by medical practitioners.

The International Association for the Study of Pain (IASP) and the International Headache Society describe an additional form of trigeminal neuralgia. Leading researchers have used the term 'atypical trigeminal neuralgia' to describe the condition with persistent pain as its important distinguishing quality.[2] However, no specific diagnostic criteria have been established for atypical trigeminal neuralgia and to complicate matters the terms secondary or symptomatic trigeminal neuralgia

IN SUMMARY

- **Trigeminal neuralgia is characterised by sharp paroxysmal pain radiating through the face, teeth and jaw.**
- **Pain from classic trigeminal neuralgia is episodic in nature, whereas atypical trigeminal neuralgia has persistent pain as its distinguishing quality.**
- **Anticonvulsants are the treatment of choice for the classic form of trigeminal neuralgia, with carbamazepine being the gold standard.**
- **Amitriptyline is first-line treatment for atypical trigeminal neuralgia.**
- **Several surgical and ablative procedures can be used to treat trigeminal neuralgia.**
- **Classic trigeminal neuralgia that is initially well controlled with a single anticonvulsant may progress to a complex pain state involving neuralgic pain, neuropathic pain, sympathetically maintained pain and/or musculoskeletal pain.**

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have been proposed to describe the condition. For the sake of clarity, in this article the term atypical trigeminal neuralgia is used. A problem with defining and categorising atypical trigeminal neuralgia is its broader range of symptomatology than classic trigeminal neuralgia. There is a general consensus among pain clinicians and researchers that atypical trigeminal neuralgia is a form of neuropathic pain.

The purpose of this article is to provide a synopsis of trigeminal neuralgia management for the general medical practitioner and compare the symptoms of trigeminal neuralgia and atypical trigeminal neuralgia, which may help in distinguishing these two pain states. In addition, an overview of atypical trigeminal neuralgia nomenclature and neuropathic pain discusses the current dilemma regarding the diagnosis and classification of this type of neuralgia. A table of orofacial pain is given to assist diagnosis and medical treatment planning (Table 1).

Management of trigeminal neuralgia

Drug therapy

Adherence to medication prescribing principles and patient compliance to treatment regimens underpin the success of meaningful and sustained pain relief. Patients with uncontrolled trigeminal neuralgia will be markedly challenged by spontaneous episodes of high-intensity pain, or episodes of breakthrough pain that occur when dosage regimens are titrated or altered. Patients can quickly lose confidence in the drug used and, occasionally, in the doctor and believe they are back at 'square one'.

The typical pain-relieving medications, such as codeine, ibuprofen, aspirin or paracetamol, used by patients with acute pain are ineffective for the treatment of neuralgic pain. Patients need to be guided against the use of a quick-fix painkiller.

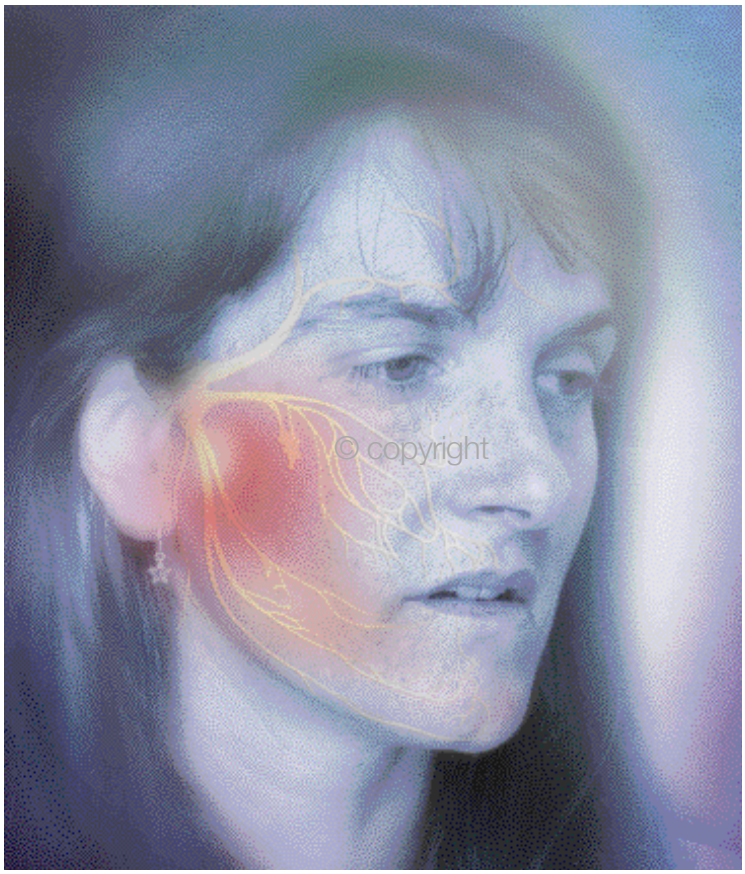
At the initial consultation, adequate time should be given to explain the variability of patient responses to medications. Then, at the follow-up appointment, there is the need to establish carefully the ratio of therapeutic benefit to side effect profile of the trialled drug.

Anticonvulsant drugs are an appropriate first-line treatment for patients experiencing pain that is sharp, shooting and paroxysmal in quality. They have a membrane-stabilising effect, causing a general reduction in the excitability of neurons.

Standard pharmacological principles apply in the use of anticonvulsants and include:

- supply an adequate dose to achieve a therapeutic effect
- titrate the dose to minimise side effects
- consider any background medical conditions that may influence the pharmacokinetic profile of the drug
- consider any potential drug interactions with other drugs and herbal/dietary supplements (for example, grapefruit juice increases plasma concentrations of carbamazepine).

Management of trigeminal neuralgia



Trigeminal neuralgia is characterised by sharp, electric shock-like, paroxysmal pain that radiates through the face, teeth and jaw. Anticonvulsants and tricyclic antidepressants are the treatments of choice for trigeminal neuralgia and its atypical variant, respectively.

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continued

Table 1. Features of trigeminal neuralgia, atypical trigeminal neuralgia and other orofacial pain conditions

Pain type	Incidence	Location of pain	Clinical description	Treatment (daily therapeutic range)
Trigeminal neuralgia	Incidence in the USA of 4 to 5 per 100,000 people per year, mainly women aged 65 years and over	Usually unilateral single trigeminal nerve division (maxillary division common)	Brief episodes of sharp, shooting, unilateral pain Triggered by cold wind, eating, shaving etc Can mimic severe toothache	Carbamazepine (200 to 1200 mg) Gabapentin (900 to 3600 mg)* Pregabalin (150 to 600 mg)* Sodium valproate (600 to 2500 mg)†
Atypical trigeminal neuralgia	Estimated incidence in Australia of 1 to 2 per 100,000 people per year, mainly women aged 65 years and over	One or more trigeminal nerve divisions	Persistent throbbing, burning, aching pain Episodes of sharp neuralgic pain	Amitriptyline (10 to 75 mg at night)† Carbamazepine (200 to 1200 mg) Gabapentin (900 to 3600 mg)* Pregabalin (150 to 600 mg)* Sodium valproate (600 to 2500 mg)†
Postherpetic neuralgia	Prevalence estimated to be 500,000 to 1 million people in the USA, and 100,000 to 200,000 people in the UK	Located in ocular, cranial, cervical, thoracic and lumbar regions	Constant, deep burning, throbbing, aching and/or intermittent sharp, stabbing, shooting, lancinating pain that may be spontaneous Evoked allodynia that usually lasts well beyond the duration of the stimulus (hyperpathia). Allodynia, seen in 70% of patients, is the most distressing symptom	Amitriptyline (10 to 150 mg at night)† Gabapentin (900 to 3600 mg)* Lignocaine gel 2% applied under occlusive patch Pregabalin (150 to 600 mg)* Tramadol (100 to 400 mg) Topical capsaicin (0.025 to 0.075% applied three to four times daily)
Glossodynia (burning mouth/tongue syndrome)	Worldwide incidence of 0.5 to 3% of the general population (mainly postmenopausal women)	Common sites are tip of tongue, palate and inside of lips	Constant burning, stinging pain Dry mouth or viscid saliva, altered or sour taste may be experienced	Amitriptyline (10 to 150 mg at night)† Clonazepam (temporary relief) (0.5 to 1 mg)† Cognitive behavioural therapy

* General indication for neuropathic pain in adults.
† The use of these drugs is not TGA approved for the condition mentioned.

continued on the next page

Anticonvulsants to be considered include carbamazepine, sodium valproate, gabapentin and pregabalin. Different levels of evidence exist for the effectiveness of the use of anticonvulsants in the treatment of patients with neuralgic pain (Table 1). The traditional gold standard for trigeminal neuralgia is carbamazepine. Newer anticonvulsants trialled routinely in pain clinics for trigeminal neuralgia include gabapentin and pregabalin.

From a long-term pain management perspective, trials of drugs can be conducted in individual patients to determine the optimal therapeutic effect, minimal side effects and most cost-effective medication. A recent evidence-based meta-analysis concluded that carbamazepine is still the first-line monotherapy treatment of choice, and should be switched to oxcarbazepine if inadequate pain relief or problematic side effects occur.[3] Combining carbamazepine with lamotrigine or baclofen is recommended as the second-line treatment (off-label use). Where possible a single anticonvulsant is used; however, some patients respond better to two or more anticonvulsants taken simultaneously at lower doses.

Carbamazepine can increase brain concentrations of serotonin (5-hydroxytryptamine). The starting dosage for carbamazepine is usually 100 mg three times a day (or 100 mg at night for elderly patients), which is gradually increased until a therapeutic effect is achieved (or side effects occur). The effective dosage may need to be as high as 400 mg three times a day, but at this dosage side effects of sedation, ataxia and gastrointestinal upset are common. Regular monitoring of blood counts is necessary because of the possibility of thrombocytopenia and bone marrow depression.

Sodium valproate can increase concentrations of gamma-aminobutyric acid (GABA) in the central nervous system. At a starting dosage of 600 mg per day, sodium valproate appears to be less toxic than carbamazepine, and is generally better tolerated by patients, although its

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Table 1. Summary of trigeminal neuralgia, atypical trigeminal neuralgia and other orofacial pain conditions – continued

Pain type	Incidence	Location of pain	Clinical description	Treatment (daily therapeutic range)
Atypical odontalgia (phantom tooth pain)	Occurs in 3 to 5% of patients worldwide after root canal therapy	Specific to treated tooth or can spread to adjacent teeth and entire quadrants of mouth; may occur in oral mucosa and supporting bone of teeth	Constant severe throbbing, burning, aching pain in teeth and jaws, with no visible or radiographic dental decay or infection Sharp neuralgic pain may be experienced Associated symptoms include masticatory muscle pain and oral dysaesthesia	Amitriptyline (10 to 150 mg at night)† Gabapentin (900 to 3600 mg)* Topical capsaicin (0.025 to 0.075%)†
Temporo-mandibular disorder	Occurs in 95% of the western population at least once during their lifetime; mainly in women aged 18 to 35 years	Jaw pain, headache, neckache	Episodic aching, cramping pain in jaw muscles Sensitive teeth Jaw clenching and teeth grinding (bruxism)	Physical therapy NSAIDs and muscle relaxants (short-term use) Stress reduction Dental occlusal splint
Facial pain of unknown aetiology	Previously termed atypical facial pain; unknown incidence, mainly in women aged 45 years and over	Widespread facial pain	Constant aching pain No radiographic / clinical pathology Unknown aetiology Thought to be associated with psychosocial factors	Amitriptyline (10 to 150 mg at night)† Cognitive behavioural therapy

* General indication for neuropathic pain in adults.
† The use of these drugs is not TGA approved for the condition mentioned.

use in patients with trigeminal neuralgia is off label. Gastrointestinal disturbance, sedation and, occasionally, alopecia are possible side effects of sodium valproate. In addition, disturbances of hepatic function may occur with sodium valproate use, and routine measurement of liver enzymes is necessary.

Phenytoin is a second-line or third-line anticonvulsant for trigeminal neuralgia (off-label use) because it has a narrow therapeutic range and a potential side effect of marked gingival hyperplasia. The anticonvulsants gabapentin and pregabalin have been introduced more recently and have improved therapeutic effect to side effect ratios. Other drugs that have been trialled include baclofen, lamotrigine, oxcarbazepine, clonazepam, capsaicin and botox; however, these drugs are not commonly prescribed by GPs for patients with trigeminal neuralgia.

Surgical and ablative procedures

Several surgical and ablative procedures are used in the treatment of patients with trigeminal neuralgia.

Surgical microvascular decompression is performed when compression of the trigeminal nerve root is suspected. For most procedures, the prognosis is good for patients with classic trigeminal neuralgia of relatively short duration and who have had no previous surgical interventions. Microvascular decompression appears to offer the best long-term outcome, particularly in noncomplex cases. The mortality rate of this procedure is 0.4%.

Ablative procedures include gamma knife stereotactic radiosurgery. Ablative techniques lesion the trigeminal nerve in different ways, and are more likely to be associated with numbness, paraesthesia or other low-grade complications. These techniques are less effective than microvascular decompression; however, they are indicated for medically compromised or high-risk surgical patients because they are associated with a lower mortality rate. Ablative techniques are sometimes performed as a diagnostic or investigative

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procedure, more commonly in patients with atypical trigeminal neuralgia.[4]

Peripheral surgical procedures include peripheral neurectomy, cryotherapy and alcohol blocks. Although less invasive than other surgical procedures, these techniques provide a shorter duration of pain relief.[5]

Atypical trigeminal neuralgia and neuropathic pain

Classification controversy

A challenge in the classification and treatment of the pain of trigeminal neuralgia can be its progression from an acute pain phase to a persistent pain phase. Patients may present initially with symptoms indicative of classic trigeminal neuralgia; however, symptomatology may change when patients report constant pain and declining efficacy of anticonvulsant medication, possibly with no pain relief whatsoever. In such cases, a diagnosis of atypical trigeminal neuralgia is likely. In terms of nomenclature the use of atypical trigeminal neuralgia as a distinct diagnostic category has been criticised with suggestions that it is based on symptom constellation and not aetiology.[6] Several authors suggest that trigeminal neuralgia, atypical trigeminal neuralgia and trigeminal neuropathic pain represent a continuous spectrum of a disease state rather than discrete entities.[4,7,8]

Clinical features consistently reported by patients diagnosed with atypical trigeminal neuralgia include pain with severe throbbing, burning, aching and sharp (neuralgic) pain qualities. These descriptors are also reported by patients with trigeminal neuropathic pain states, including postherpetic neuralgia, burning mouth syndrome (glossodynia), atypical odontalgia (phantom tooth pain), temporomandibular disorder and facial pain of unknown aetiology following injury or surgery (Table 1).[9]

Neuropathic pain

Neuropathic pain is persistent pain defined by the IASP as 'pain initiated or caused by a primary lesion or dysfunction in the nervous system'. Understanding and treating neuropathic pain is a major area of research for the IASP, a multidisciplinary group of more than 10,000 clinicians and researchers. Terms and phenomena commonly identified in neuropathic pain include allodynia (pain elicited by an innocuous nonpainful stimulus) and hyperalgesia (increased response to a painful stimulus). Neuroplasticity of the peripheral and/or central nervous systems can occur in addition to secondary activation of muscle efferents and the sympathetic nervous system via spinal cord interneurons that produce multiple, concurrent and linked pain states.

Briefly, the pathophysiology of neuropathic pain involves several key events that occur after tissue injury. Anatomical regions of high innervation, such as the orofacial region (trigeminal nerve), are particularly involved, with subsequent widespread cortical responses. In addition to releasing vascular-derived inflammatory mediators (such as bradykinin, serotonin, prostaglandin E2 or histamine), tissues rich in nerves may express neuropeptides, with resultant neurogenic inflammation (major algesic peptides studied include substance P and calcitonin gene-related peptide). Along the neuron there is reorganisation of the type and locality of sodium channels following injury. Calcium channels on the neuron also undergo change and are thought to be associated with hyperalgesia and allodynia. Treatment with anticonvulsants such as gabapentin or pregabalin attenuate mechanical hyperalgesia by blocking calcium channels.

An additional first-line antineuropathic agent is amitriptyline (dosage 10 to 75 mg at night; off-label use), which is used as first-line treatment for atypical trigeminal neuralgia.

Neuroplasticity may occur at the level of the peripheral nervous system and/or spinal cord (central nervous system), causing the original locus of pain to spread. Further developments in the course of neuropathic pain may be abnormal (ongoing) sympathetic activity, termed sympathetically maintained (or mediated) pain, and secondary myofascial pain. Sympathetically maintained pain is defined as pain that is maintained by sympathetic efferent innervation caused by emotional and psychological distress, or by circulating catecholamines. Neuronal coupling occurs between sympathetic and somatosensory pathways at the level of the peripheral and central nervous systems (at between three and 20 days after surgery in animal models). Clinical symptoms include sudomotor activity and episodes of swelling and/or redness. Secondary muscle spasm occurs via spinal cord interneurons.

In summary, classic trigeminal neuralgia that is initially well controlled with a single anticonvulsant may progress to a complex pain state involving neuralgic pain, neuropathic pain, sympathetically maintained pain and/or musculoskeletal pain.

Integrative therapies

Recurrent pain and chronic pain ultimately result in negative and maladaptive psychosocial behaviour involving anxiety, depression, frustration and anger.[10] Medical management, in turn, must be adaptive and include antidepressants, anxiolytics, antineuropathic medication and psychological interventions such as cognitive behavioural therapy.

More than 50% of populations in western societies now use integrative/complementary therapies, and an increasing number of patients are asking their doctors for advice on the use of these therapies. The most frequently used modalities are herbal medicine, acupuncture and psychological techniques, each having differing levels of evidence for pain relief.

There is accumulating scientific data on the mode of action and efficacy of complementary therapies, particularly well-established therapies such as acupuncture and traditional herbal medicines. Discussion with the patient about the use of herbal

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medicine is required because of the uncontrolled over-the-counter purchase of herbs by patients and possible drug-herb interactions. In addition, patients need to be advised that herbal medicines should not be a substitute for prescription anticonvulsants particularly because herbs lack the therapeutic potency to prevent high-intensity neuralgic pain. However, several herbs can be useful in treating associated symptoms such as poor sleep patterns and mild to moderate depression and anxiety.

Herbal medicines that could be considered to be supportive (with a low level of empirical evidence) for neuralgic pain include:

- St John's wort – historically used to treat neuralgic pain. It is a mild to moderate antidepressant and mild anxiolytic, with mild antiviral properties. It has potential interactions with antidepressants and may cause serotonin syndrome
- Bacopa (brahmi) – a mild anticonvulsant, anxiolytic and sedative. It may reduce amnesic effects of benzodiazepines (animal model data only)[11]
- passionflower – improves sleep patterns, reduces myofascial pain and acts as a mild anxiolytic. It has no known drug interactions
- globe artichoke – a hepatoprotective herb if using sodium valproate. It has no known drug interactions but contact dermatitis from the fresh plant is possible.

Vitamin and mineral supplements used for pain relief include high potency vitamin B_{12} 1 mg (usually purchased as 1000 µg tablets) and magnesium supplements. Acupuncture has been shown to increase levels of several potent endogenous opioid peptides (endomorphin-1, beta-endorphin, encephalin) in plasma and brain tissue.[12]

A number of studies suggest acupuncture can be a safe and effective alternative to surgery in some cases of trigeminal neuralgia.

Psychological strategies used in pain management include cognitive behavioural therapy (modifying attitudes, beliefs and expectations), relaxation and biofeedback, and hypnosis. Cognitive behavioural therapy plays an important role in pain management and has an extensive evidence base for its use in numerous chronic pain states. Psychological techniques focus on reducing anxiety and stress, rebutting

Table 2. Comparison of data from patients with classic or atypical trigeminal neuralgia*

Variable	Trigeminal neuralgia (episodic pain)	Atypical trigeminal neuralgia (constant pain)
Demographics		
Number of participants	28 (9 men, 19 women)	12 (4 men, 8 women)
Age range (mean [SD])	13 to 89 (59.4 [18.2]) years	47 to 77 (62.7 [10]) years
Duration of pain (mean [SD])	3 months to 30 years (5.2 [9.9] years)	1 to 20 (8.5 [8.1]) years
Pain intensity range (0 = no pain, 10 = worst pain imaginable) (mean [SD])	1 to 10 (5.8 [2.7])	4 to 10 (6.9 [3.5])
Psychological morbidity (Depression Anxiety Stress Scale)		
Depression score (0 to 9 = normal)	3	7 (p=0.02 [t test])
Anxiety score (0 to 7 = normal, 8 to 9 = mild anxiety, 10 to 14 = moderate anxiety)	4	10 (p=0.02)
Stress score (1 to 14 = normal)	5	8 (p=0.01)
Pain quality according to the McGill Pain Questionnaire (short form), given as percentage of patients (number)		
Throbbing	43 (12)	67 (8)
Shooting	86 (24)	100 (12)
Stabbing	86 (24)	83 (10)
Sharp	79 (22)	92 (11)
Cramping	18 (5)	8 (1)
Gnawing	4 (1)	42 (5)
Hot/burning	32 (9)	67 (8)
Aching	46 (13)	75 (9)
Heavy	21 (6)	42 (5)
Tender	32 (9)	42 (5)
Splitting	21 (6)	50 (6)
Tiring	46 (13)	92 (11)
Sickening	18 (5)	42 (5)
Fearful	36 (10)	58 (7)
Punishing, cruel	43 (12)	92 (11)

* Forty-eight patients with trigeminal neuralgia were identified from an analysis of 504 consecutive chronic orofacial patients referred to the Pain Management Research Institute, University of Sydney at Royal North Shore Hospital, NSW. Unpublished data.
ABBREVIATION: SD = standard deviation.

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unhelpful beliefs, strengthening the patient's coping abilities and improving sleep patterns. These help in turning the passive helpless patient into an active participant in pain management.

Clinical comparison of classic and atypical trigeminal neuralgia

An analysis of 504 consecutive patients with chronic orofacial pain referred to the authors' institution (Pain Management Research Institute, University of Sydney at Royal North Shore Hospital) identified 48 patients with neuralgia. Ethics committee approval was obtained for analysis of data and individual consent obtained from each subject. Of 40 patients who completed a pain questionnaire, 28 patients had trigeminal neuralgia (episodic) and 12 patients had atypical trigeminal neuralgia (persistent pain). Demographic and pain data collected included sex, age, duration of pain and pain intensity (0 to 10 numerical rating scale). In addition, psychological morbidity was measured by the validated depression, anxiety and stress scale (short-form DASS) that has established normal levels for the Australian population.[13]

Results showed no significant differences between the groups of patients with trigeminal neuralgia and atypical trigeminal neuralgia in regard to demographic factors but patients with atypical trigeminal neuralgia had significantly more psychological effects (Table 2). Both groups reported a high incidence (79 to 100%) of the typical sharp, shooting, stabbing pain but a greater proportion of patients with atypical trigeminal neuralgia reported throbbing, burning and aching (neuropathic) pain qualities.

When questioned on the chronological history of pain episodes, 39 of 40 patients reported pain that initially commenced as classic trigeminal neuralgia of 'brief episodes of pain'. At the time of referral to the pain clinic only two of 39 patients claimed pain still occurred in 'brief episodes', while 25 then reported 'pain episodes of longer duration' (trigeminal neuralgia). The remaining 12 subjects reported 'constant pain' (atypical trigeminal neuralgia). The authors' interpretation of the results suggest trigeminal neuralgia is not a 'static' condition and that over time there is a progression towards an atypical trigeminal neuralgia/neuropathic pain state.

Conclusion

Trigeminal neuralgia and atypical trigeminal neuralgia are high-intensity pain states that require early diagnosis. Patients with orofacial pain invariably consult medical and/or dental practitioners according to the first site of pain. Pain seeming to originate in teeth can result in the dentist performing unnecessary and repetitive ablative procedures of multiple root canal therapies and tooth extractions. On the other hand, extraoral facial pain can lead doctors to conduct extensive neurological and ear, nose and throat investigations.

Taking a careful history of the location, quality and duration of the pain is the key principle in determining trigeminal neuralgia and atypical trigeminal neuralgia. Successful trials of medication using anticonvulsants for trigeminal neuralgia and amitriptyline (or other tricyclic antidepressants) for atypical trigeminal neuralgia at therapeutic dosages are diagnostic. Prior to the use of anticonvulsants, neuralgic pain from trigeminal neuralgia was described as 'the worst pain imaginable' leading to an extraordinarily high rate of suicide. Delays in diagnosis and medical treatment invariably lead to increased pathophysiology and psychological morbidity.

Patient trigeminal neuralgia and facial neuropathic pain support groups exist and are very helpful. The following websites are patient-orientated national organisations with medical advisory boards and feature continual updates on medical treatments and outcomes:

- Facial Neuropathic Pain and Trigeminal Neuralgia Association of North America: www.fpa-support.org
- Trigeminal Neuralgia Association (Australia): www.tnaaustralia.org.au MT

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