Neuropathic orofacial pain

Diagnosis and multimodal management

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Pain in the orofacial region and involving the trigeminal nerve includes burning mouth syndrome, atypical odontalgia, facial postherpetic neuralgia and trigeminal neuralgia. Treatment is multidisciplinary, including treatment with drugs and natural compounds and psychological and behavioural management. New therapies include neuromodulation, analgesic peptides and autologous stem cells.

The prevalence of chronic pain in the adult Australian population has been reported at 17.1% of males and 20% of females and the condition has the criteria to be classified as a disease entity.[1,2] Neuropathic pain is a frequently encountered chronic pain state and is defined by the International Association for the Study of Pain (IASP) as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'; it has a prevalence of 7 to 8% in the population.[3,4] In addition, there is an enormous economic burden from neuropathic pain, with US estimates of annual costs (direct medical, indirect and lost productivity) of US$27,000 per patient.[5]

Neuropathic pain conditions are classified as relating to injury or disease to nerves in either the peripheral or the central nervous systems (PNS, CNS). PNS neuropathic pain conditions include postsurgical neuropathic pain associated with mastectomy and amputation surgery, postherpetic neuralgia and painful diabetic neuropathy. CNS neuropathy includes post-stroke pain, spinal cord injury pain and multiple sclerosis pain.[6]
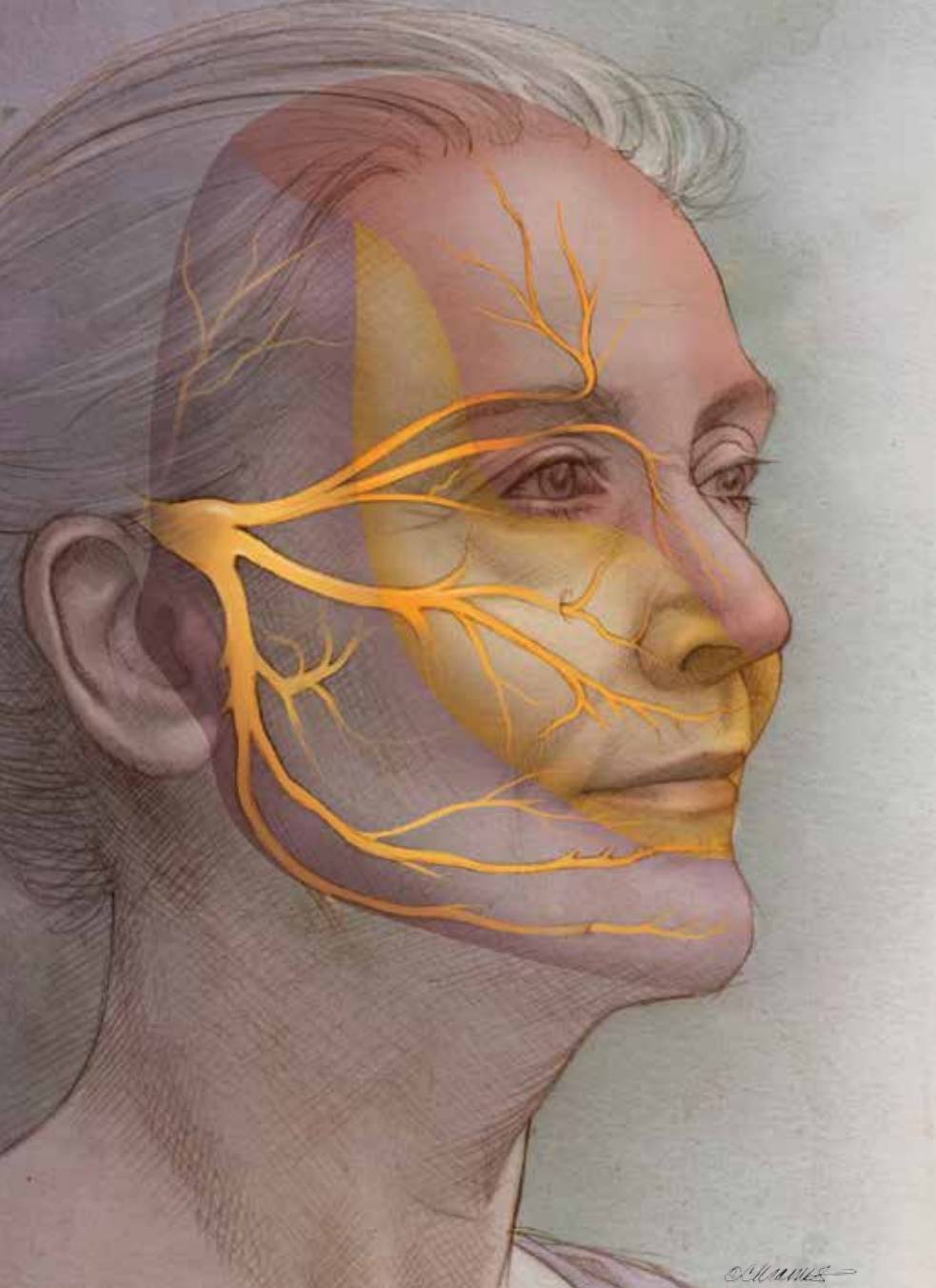
Pain experienced in the orofacial region and involving the sensory branches of the trigeminal nerve is currently termed 'neuropathic trigeminal pain' and 'neuropathic orofacial pain' (both names are used in the literature). It was initially identified as an intraoral pain in a series of patients reporting persistent pain following root canal therapy or tooth extraction, and was given the term phantom tooth pain.[7,8] Persistent pain of neuropathic origin has an incidence of 7% and pain intensity of 7/10 (visual analogue scale) after endodontic treatment, the pain intensity being disproportionate

to the minor nature of dental pulp extirpation.[9] Its pathophysiology is similar to that of phantom limb pain.

Examples of neuropathic orofacial pain are burning mouth syndrome (1.7% of the population), atypical odontalgia (phantom tooth pain), facial postherpetic neuralgia and trigeminal neuralgia ('typical' and 'atypical'). The term atypical facial pain has fallen from favour as it misrepresented the psychological parameters of chronic facial pain. Pain is a necessary phenomenon to prevent further tissue injury. However, for the patient it can be a personal, unpleasant and hurtful experience – 'my pain is cruel, punishing and dreadful', in contrast to the clinician's diagnostic perspective – 'but is it

KEY POINTS

- Neuropathic orofacial pain manifests as a disease entity.
- Typical pain qualities are aching, throbbing, burning and sharp.
- Secondary phenomena are sympathetically maintained pain and local muscle pain.
- Pharmacological treatments includes amitriptyline, duloxetine, gabapentin, pregabalin and carbamazepine.
- Psychological treatment is often required for associated depression and anxiety.
- Multidisciplinary treatment is the gold standard.

aching, throbbing, burning or sharp?'

Typical acute dental pain states such as dental caries, pulpitis (toothache), periapical infections and fractured teeth (which are types of nociceptive pain) are clinically and radiographically readily identifiable and resolve with standard treatment. However, acute nociceptive pain and classical inflammation may have a disordered molecular healing phase and progress to chronic pain. This is underpinned by neurogenic inflammation and a surrounding inflammatory 'soup' of algogenic (pain-eliciting) neuropeptides such as substance P and other neurokinins.[10] These peptides can be resistant to enzymatic cleavage, ultimately causing persistence of pain signals. This progression of nociceptive pain to chronicity is more likely to occur in situations of psychosocial stress.

The neuropathies and nociceptive pain states involving the trigeminal nerve are listed in Box 1.

Pathophysiology

Nociceptive pain serves a protective function, is transient and well localised, and the individual can differentiate between pain (C and A-δ fibres) and touch (A-β fibres). Acute inflammatory pain mediators are released following tissue injury; mediators involved are derived from the circulation and include bradykinin, histamine and prostaglandin E2. Resolution of pain typically occurs within four to 10 days of the injury.

Neuropathic pain follows injury or disease in the nervous system. Multiple potential cofactors include genetic predisposition, epigenetics, infection, trauma, surgery and psychosocial stress. At times chronic pain occurs without evidence of ongoing nociception or nerve injury; here the predominant mechanism relates to nervous system sensitisation.

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1. TRIGEMINAL NEUROPATHIES AND NOCICEPTIVE PAIN STATES IN THE OROFACIAL REGION

Neuropathic trigeminal pain states

- Atypical odontalgia (also known as phantom tooth pain)
- Burning mouth syndrome
- Facial postherpetic neuralgia
- Type 1 (classical) and type 2 (atypical) trigeminal neuralgia

Nociceptive trigeminal pain states

- Cervicogenic pain (cervical spine degeneration can cause mandibular pain as the dorsal [sensory] roots of C2 to C4 innervate the border of the mandible in addition to the mandibular division of the trigeminal nerve)
- Dental pain such as from caries, pulpitis, abscess or a cracked tooth
- Jaw/facial fracture and trauma
- Myofascial pain from bruxism involving the masticatory muscles (temporomandibular disorder)
- Neurological disorders, including headache syndromes
- Oral mucosal pain from aphthous ulcers, oral lichen planus and autoimmune disorders (pemphigoid, pemphigus, Stevens-Johnson syndrome, Behçet's disease)
- Pathology such as maxillary sinus disease, oropharyngeal cancer
- Psychiatric conditions of deliberate trauma such as Münchausen (or Münchausen by proxy)
- Referred pain to the chin and mandible (from myocardial infarction)
- Temporomandibular joint osteoarthritis and meniscal derangement

- Pain is usually constant, and moderate to severe in intensity
- Pain has specific qualities, including burning (C fibre activation) and sharp, shooting neuralgic pain sensation (A-δ activation). In addition, there can be aching and throbbing qualities
- Oral mucosal, facial and radiographic examination is normal but there is severe pain
- Precipitating factors may include facial plastic and maxillary sinus surgery, maxillofacial trauma, dental infection, viral infections, endodontics and dental treatment
- Local anaesthetic sodium channel blockade (lignocaine injection) is ineffective or only partial effective. Neuropathic pain can involve the loss of the magnesium block from the calcium channel, resulting in pain despite numbness from the local anaesthetic block
- Over-the-counter drugs such as paracetamol, codeine, tramadol and even morphine do not reduce pain
- Pain can spread from one oral quadrant to the ipsilateral and other contralateral quadrants of the mouth
- Secondary myofascial pain and sympathetically maintained pain (indicated by cheek swelling and redness) may be present
- Persistent pain can cause depression, anxiety and frustration. About 75% of patients with neuropathic pain of the trigeminal nerve have a moderate to severe psychiatric diagnosis, often due to unremitting pain

The pathophysiology of neuropathic pain and pain associated with nervous system sensitisation involves maladaptive primary, secondary and tertiary events. At the molecular level, there may be upregulation of stimulatory algogenic chemicals and peptides occurring within hours of the triggering event. Peripheral sensitisation alters the excitability of nociceptors and sympathetic fibres. Clinically this is observed as allodynia (pain elicted by an innocuous nonpainful stimulus) and hyperalgesia (increased response from a painful stimulus) – akin to sunburn.[11] Sodium ion channel reorganisation occurs in peripheral nerve injury with neuroma formation, with a resultant sodium channel translocation from the cell body to the neuroma. Shift in the voltage potential towards a negative potential results in hyperexcitability and ectopic discharges.[12] Moreover, calcium channel activation through loss of the ion channel block by extracellular magnesium and partially by zinc ions leads to inadequate pain relief from a local anaesthetic test (sodium channel blockade). Repeated surgery, erroneously to 'amputate' the pain, subsequently aggravates the nervous system response.

Glutamate, an excitatory amino acid, is the main neurotransmitter released at central terminals of primary nociceptive afferents after a noxious event. It acts on the N-methyl-D-aspartate (NMDA) receptor (a nonspecific cation channel involved in inflammation), with resultant phosphorylation of the receptor and an increase in receptor expression (i.e. passage of calcium and sodium ions into the cell and potassium ions out of the cell).[13] Conversely there is a loss of gamma-aminobutyric acid (GABA) receptors (receptors responding to GABA, the main inhibitory neurotransmitter, and involved in relieving pain) and reduced therapeutic benefit of GABA-ergic drugs (i.e. gabapentin and pregabalin). The nervous system is inherently 'plastic'. In some settings this can be adaptive, for example, via nerve growth factor (NGF) release to regulate and repair damaged neurons. However, in other settings, maladaptation can occur, with nerve 'sprouting', loss of central inhibition and hypersensitivity. Adjacent nonpainful nerve fibres at peripheral and central levels may subsequently be involved, causing a marked expansion of the pain field.

Another development in neuropathic pain may be abnormal (ongoing) sympathetic activity, termed sympathetically maintained (or mediated) pain (SMP). SMP is defined as pain that is maintained by sympathetic efferent innervation caused by emotional and psychological distress, or by circulating catecholamines. Coupling occurs via NGF-derived neuronal sprouting between sympathetic and somatosensory pathways at the peripheral and spinal cord levels. Following nerve damage or chronic inflammation, a subset of C-polymodal nociceptors has been shown to develop sensitivity to sympathetic stimulation and sprouting can occur within three to 20 days after surgery (rat model).[14] In addition, sustained or repeated nociception activates regional muscles, leading to secondary myofascial pain. Clinicians, in diagnosing neuropathy of the trigeminal nerve, must frequently treat multiple, concurrent components – for example, a primary neuropathic state with secondary myofascial, sympathetically mediated and psychological components.

For detailed reviews on neuropathic pain pathophysiology, see Costigan et al., 2009 and Cousins et al., 2009.[15,16]

Diagnosing the pain problem

The patient with orofacial pain must have a comprehensive workup to determine if the pain is acute (nociceptive) or chronic (neuropathic) or if both pain states are present (such as incidental acute dental pulpitis concurrent with a neuropathy in the same trigeminal nerve branch). This must include a complete dental examination, ENT investigations for sinus pathology and a CT to exclude intracranial pathosis. Myofascial pain and sympathetically maintained pain may be present secondary to trigeminal neuropathic pain. It should be remembered that trigeminal neuropathic pain in a younger person might be the first sign of multiple sclerosis. Features of the clinical presentation of neuropathic orofacial pain are listed in Box 2.

In the chronic pain state, the diagnosis of the multiple contributors to the experience of pain requires a detailed and documented approach. It is helpful to differentiate physiological pain from emotional hurt/suffering, the former requiring appropriate pharmacotherapy and the latter psychological therapy. This leads, in turn, to the development of a multimodal management plan.

Pain questionnaires

Use of a pain questionnaire is valuable to record baseline information and subsequent changes during the treatment phase. A 0 to 10 visual analogue or numerical rating scale can be used by patients to indicate their pain intensity changes during treatment, but is uninformative as to the nature of pain. The Brief Pain Inventory is a useful short questionnaire that includes measures of pain intensity and pain interference.

Multiple questionnaires are available to help in the diagnosis of neuropathic pain, including the short-form McGill Pain Questionnaire and the Leeds assessment of neuropathic pain and signs (LANSS) Pain Scale.[17,18] These global scales designed to help diagnose neuropathic pain use word descriptors such as constant, aching, burning, throbbing and sharp that are suggestive of neuropathic symptoms. Additionally, the Depression Anxiety Stress Scales (DASS) and the Kessler 10 measure (for psychological distress) have been developed, with the DASS having normative values for the Australian population.[19]

Tests

Pharmacological tests conducted by an anaesthetist or pain specialist can include a patient-blinded, saline control lignocaine IV infusion to test for neuropathic pain (local anaesthetic sodium channel blockade) and phentolamine infusion to test for sympathetically maintained pain (sympathetic blockade).[20] Such testing has not, as yet, been shown to correlate with treatment outcome, and a pragmatic trial of antidepressants and/or anticonvulsants is a valid alternative strategy.

Quantitative sensory testing provides a standard set of validated neurosensory measures to determine the presence of neuropathy.[21]

Another form of noninvasive testing is facial thermography. The technique is highly selective in thermal accuracy (100%), with results showing the affected (painful) side of the face to be hotter than the nonpainful side (range 0.4 to 3.1ºC, mean=1.1 ± 0.8).[22]

Figures 1a and b. Peptide substance P 1–7 (SP1–7) therapy. a (left). Secondary sympathetically maintained pain in a woman with trigeminal neuropathic pain. Note the cheek swelling and redness from sustained sympathetic nervous system activation. b (right). Treatment with SP1–7 reduced swelling, redness and pain intensity. Previous trials of several antineuropathic medications of antidepressants and anticonvulsants were ineffective. SP1–7 was delivered as an oral mucosal spray (dose 50 µg twice daily) with a reduction in pain intensity from 8/10 to 5/10. (Patient permission obtained.)

Developing technology such as magnetic resonance spectroscopy has revealed that patients with trigeminal neuropathy have a significant reduction in the N-acetylaspartate to creatine ratio, a biochemical marker of neural viability, in the region of the thalamus that also displays grey matter volume loss.[23]

Managing neuropathic orofacial pain

Neuropathic pain is generally not curable and so management is directed at reducing the effects of the pain including psychological distress, loss of self-esteem, financial issues due to lost work or inability to work and relationship difficulties. The understanding and management of neuropathic pain is by nature best done within a multidisciplinary team with an understanding of the above effects.
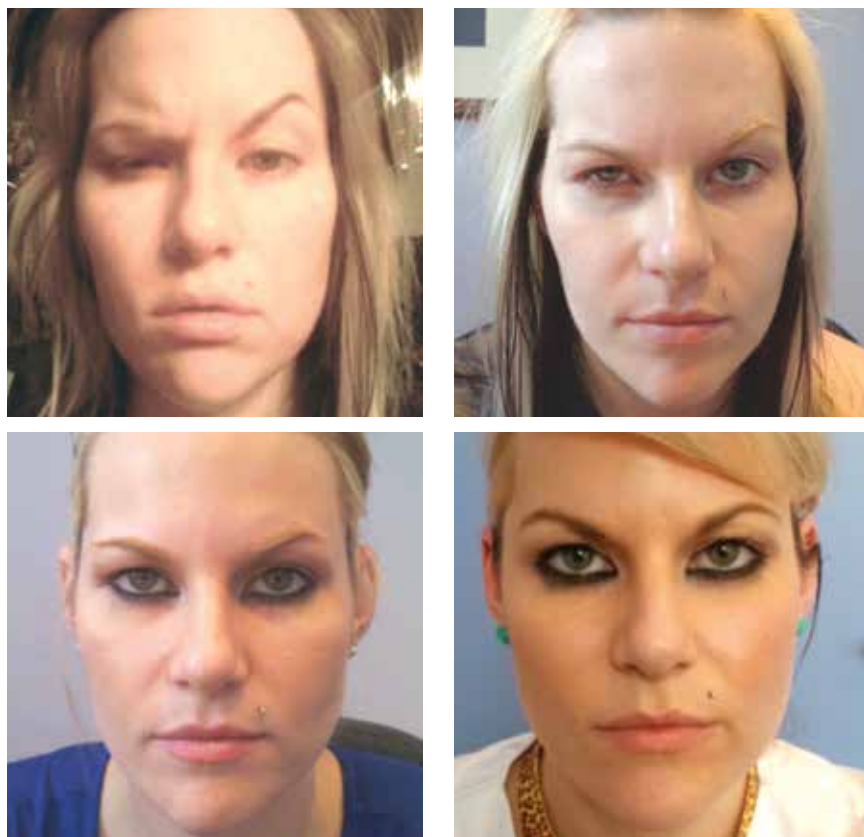
Pharmacological treatments

Neuropathic pain is usually refractory to simple analgesics but any associated nociceptive pain will respond to these medications.

The evidence supporting pharmacotherapy for neuropathic pain is not strong, with numbers needed to treat for 50% reduction in neuropathic pain in the range of four to 10 (i.e. only one patient with pain reduction of 50% or more for every four to 10 patients treated) for tricyclic antidepressants, serotonin and noradrenaline reuptake inhibitors, gabapentin, pregabalin and opioids. An excellent resource of the current evidence base for the pharmacological treatment of neuropathic pain can be found at the Hunter Integrated Pain Service website (see the document in the Health professional resource section titled 'Reconsidering drug therapy for neuropathic pain, CRPS and fibromyalgia'; www.hnehealth.nsw.gov.au/Pain/Pages/Health-professional-resources.aspx).

The treatment for oral and general neuropathic pain is identical, with first-line agents generally being antidepressants,

Figures 2a to d. Autologous stem cell therapy.[41] A 27-year-old woman presented with SUNCT headache of six years' duration, pain intensity 8–10/10. She was having three to five attacks daily of sharp, shooting neuralgic pain that was refractory to anticonvulsants. Previous treatment of multiple botulinum toxin injections had rendered significant facial atrophy. a (top left). Before treatment. b (top right). One month after stem cell treatment (autologous cells administered to branches of the trigeminal nerve). The pain intensity had reduced to 5/10 and there were signs of facial regeneration. c (bottom left). Four months after stem cell treatment. The patient was free of pain for 6.5/7 days and the pain intensity was 2/10 on the remaining half-day. There was excellent recovery of facial atrophy. d (bottom right). Eighteen months after stem cell treatment. Long-term pain reduction and cosmetic improvement were excellent. (Patient permission obtained.)

anticonvulsants and 5% lignocaine patches, and second-line agents being opioids (including tramadol).

Tricyclic antidepressants (amitriptyline, nortriptyline, dothiepin) have an analgesic dose as low as 25 mg nocte for neuropathic pain (off-label use). At this level a substantial number of patients are able to tolerate the dose with minimal side effects of dry mouth, drowsiness and weight gain. In addition, there may be an improvement in sleep pattern supporting pain rehabilitation.[24,25]

Anticonvulsants are particularly indicated for sharp, shooting neuralgic pain qualities. These include gabapentin, pregabalin, carbamazepine and sodium valproate (and also oxcarbazepine, although this is used mainly by specialist neurologists). Pregabalin and gabapentin are TGA indicated for neuropathic pain, carbamazepine is TGA indicated for trigeminal neuralgia, and sodium valproate and oxcarbazepine are used off label for neuropathic pain.[26]

SNRIs such as duloxetine and venlafaxine are used off label for neuropathic pain; 5% lignocaine patches are TGA indicated for postherpetic neuralgia. There are varying levels of evidence on the benefit of morphine for neuropathy. Further information on medication and dosages to treat neuropathic pain can be found at www.racgp.org.au/afp/2013/march neuropathic-pain-update.[27]

Mexiletine, a nonselective sodium channel blocker used for cardiac arrhythmias, could in theory be useful if there is a positive response to a lignocaine infusion; however, it is not available in Australia.

Occasionally with severe breakthrough pain, the patient may need to be hospitalised under the care of a pain clinic team for close supervision of use of IV opioids, antineuropathics and NMDA antagonists (ketamine).[28] Stellate ganglion blocks with bupivacaine or guanethidine can be considered to help break the pain cycle if there is a positive response to a phentolamine infusion test.[29]

Natural compounds

Pain related to the oral mucosa can be distressing as it can restrict normal daily functions of eating and talking. Oral neuropathy, particularly if identified early, can be successfully treated with topical capsaicin cream (0.025% and 0.075% capsaicin concentration; TGA indicated for the treatment of postherpetic neuralgia).[20] The cream is applied for five to 10 minutes twice daily for eight weeks to the painful oral mucosa. The capsaicin can cause an initial burning sensation in the first few days; this can be reduced by pretreating the mucosa with topical anaesthetic mouthwash (lignocaine 1%).

There is some evidence for using topical ginger (containing gingerol) as an antineuropathic.[30] If the patient finds it difficult to isolate capsaicin or gingerol from the tongue, a dental stent or mouth guard can be constructed by a dentist.

In addition to the topical natural compounds, there is some evidence for palmitoylethanolamide, an active compound from egg yolk and peanut oil, being effective in the treatment of neuropathic pain.[31]

Psychological and behavioural management

Psychological treatments are crucial for many patients with orofacial pain, a 'damaged face equals damaged self'. Psychological morbidity (anxiety and depression) is strongly correlated with orofacial pain – for example, the onset of burning mouth syndrome correlates with significant life events and not oral trauma.[32] Psychiatric diagnoses (moderate to severe) have been reported in 72% of patients with chronic orofacial pain.[33]

The influence of psychological factors should not be underestimated. The presence of negative thoughts of distress and anxiety increased pain intensity fourfold in patients with acute postoperative orofacial pain.[34]

There is a need for further research to address the role of psychological and behavioural therapies in treating orofacial pain. Physical activity and the maintenance of social roles are important aspects of multimodal therapy. One recent study has shown that cognitive behavioural therapy can be very helpful in pain rehabilitation.[35]

GPs who are co-ordinating the overall therapeutic approach can adopt simple practical strategies that may include:
- explaining pain mechanisms
- planned physical activity
- addressing psychological distress, e.g. with relaxation or mindfulness
- supporting restoration of social roles.

The use of active self-management strategies may make it possible to wean patients off medications over time.

Therapies in development
Peptides

There is evidence from animal studies on the use of novel endogenous compounds. These may provide greater therapeutic efficacy than traditional pharmaceutical antineuropathic agents. Potent antineuropathic peptides recently identified include the opioid peptides endomorphin-1 and -2.[36] The fragment of substance P known as SP1–7 is pain relieving and comprises seven of the 11 amino acids of the algogenic parent substance P (Figures 1a and b).[37] Other novel compounds are fatty acid antineuropathics

such as maresin and resolvins.[38,39] A likely advantage of these compounds when available for human use is the possible reduction of side effects and drug interactions compared with current pharmaceuticals.

Neuromodulation

Neuromodulation of the trigeminal nerve is another area of contemporary research for patients with intractable craniofacial pain.[40] Modalities include direct electrical stimulation (spinal cord stimulation) and transcranial magnetic stimulation to alter electrical signals, and devices to deliver chemicals and readjust the neurochemistry of the CNS.

Stem cell therapy

Preliminary studies of autologous stem cell therapy have shown it to be safe and effective for treating neuropathic pain in animals and humans. Results of the human study showed a reduction in pain intensity (mean reduction of 43%) in 78% of patients at six months from a single administration of stem cells at the trigeminal pain site.[41] Furthermore, the stem cells in this Australian-based study demonstrated a dramatic regenerative potential to treat both facial atrophy and SUNCT (short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing; a cluster headache variant), as shown in Figures 2a to d.

Conclusion

Chronic neuropathic pain is a complex chronic disease state caused by an interplay of multiple potential factors including genetic predisposition, epigenetic factors, infection, trauma, surgery and psychosocial stress. The pathophysiology involves maladaptive primary, secondary and tertiary events. At the molecular level there is upregulation in stimulatory algogenic chemicals and peptides. This leads to altered cell receptor expression with an increase in NMDA receptors and a loss of GABA receptors. There is sodium ion channel reorganisation and loss of the magnesium block of the calcium channel. Sustained or repetitive nociception activates

regional muscles, leading to secondary myofascial pain. Moreover, neuronal connections to the sympathetic ganglia results in sympathetically maintained pain.

A patient with orofacial pain must be investigated comprehensively to identify whether the pain is neuropathic or nociceptive, as treatment is different for each form of pain.

Treatment of neuropathic pain must be multidisciplinary to provide appropriate medication for complex multidimensional chronic pain. The utilisation of first-line systemic antineuropathics includes drugs such as amitriptyline, gabapentin, pregabalin and duloxetine. Capsaicin is a useful topical antineuropathic agent, and new and developing therapies are neuromodulation, analgesic peptides and autologous stem cells.

Identification and treatment of the common comorbidities of anxiety and depression is imperative in patients with neuropathic pain. Regaining physical activity and employment leads to an improved quality of life and successful pain management.　　　　MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

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