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.**

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.

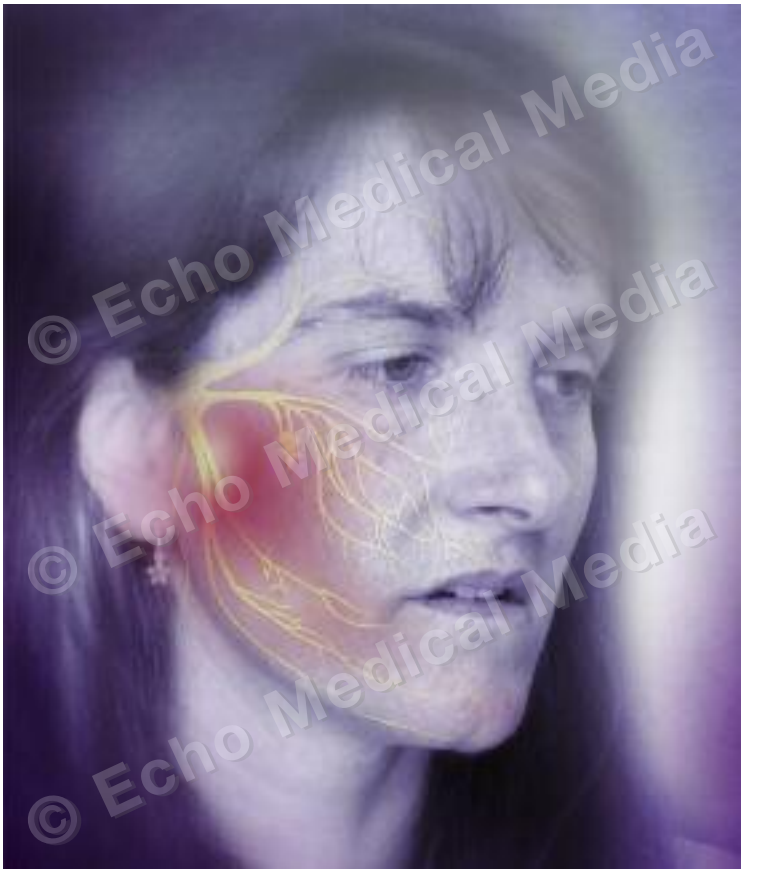
At the initial consultation, adequate time should be given to explain the variability of patient responses to medications. Then, at the follow-up appointment, there is the need to establish carefully the ratio of therapeutic benefit to side effect profile of the trialled drug.

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.

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.

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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.

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.

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 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 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 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 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 pain) 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

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.

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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COMPETING INTERESTS: None