

# Trigeminal Neuralgia

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## Introductory article

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**Trigeminal neuralgia (TN) is characterized by paroxysmal excruciating unilateral facial pain. Knowledge of the proper diagnosis and management of trigeminal neuralgia is essential to successfully treat these patients. There are several clinical features that are typical of TN, but there may be red flags that should suggest alternative diagnoses. There is convincing evidence that TN develops from focal demyelination at the trigeminal root entry zone with subsequent ephaptic transmission (crosstalk) between axons. Vascular compression of the nerve root causes the demyelination in most patients. Medical management of this condition, with anticonvulsants and other drugs, aims to dampen the abnormal electrical signals and thereby ameliorate the symptoms. Refractory cases may require surgical intervention, such as microvascular decompression of the trigeminal root. Gamma knife therapy is emerging as an alternative treatment for patients with medically refractive TN, particularly the elderly patient with co-morbid conditions.**

## Clinical Features

Trigeminal neuralgia (TN), or tic douloureux, may be an extremely disabling illness, capable of causing such suffering that it is sometimes referred to as the 'suicide disease'. The incidence of TN is estimated to be approximately 4.5 cases per 100 000. It is increasingly common with advancing age and nearly twice as common in women than men.

ELS subject area: Neuroscience

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The symptoms of TN are quite distinct. There is electric, lancinating pain on one side of the face, with an abrupt onset and termination, lasting a few seconds. It can be so intense that the patient often winces in a tic-like fashion (Table 1). Cutaneous stimuli may 'trigger' an attack, leaving some patients unable to chew, drink, shave or brush their teeth. Some patients will have a brief refractory period following an attack, during which subsequent cutaneous stimuli will not trigger an episode. For this reason, patients may intentionally provoke an attack to induce a brief 'holiday' during which they can accomplish a necessary task, such as brushing the teeth. Less often, noncutaneous stimuli, such as a bright light or loud noise, will elicit an attack. There is often diurnal variation in the pain attacks, with frequent morning exacerbations. Potential explanations for this clustering include 'wearing-off' of medications or concentrated periods of facial stimulation accompanying morning activities. Pain attacks are characteristically absent during sleep. Symptoms often occur in bouts lasting weeks to months, and initially there are periods of spontaneous remission. Between attacks, there is often anxiety regarding the subsequent attack. Other than subjective hypoesthesia, however, there are no other symptoms in the intervening periods. **See also:** [Pain and Analgesia](#)

**Table 1** Clinical criteria for the diagnosis of trigeminal neuralgia

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Paroxysmal attacks of unilateral facial pain, within one or more divisions of the trigeminal nerve, lasting < 1 s to 2 min
At least one of the following characteristics of pain
Intense, sharp, superficial or stabbing quality
Precipitation by trigger zones or certain activities
Lack of symptoms between attacks
Characteristic, stereotyped pattern of attacks within individual patients
No objective neurological deficit
No other identified causes of facial pain

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TN commonly afflicts the second or third divisions of CN V, or less commonly the combinations of V1/V2, V2/V3 or all 3 divisions. Solitary involvement of the first division occurs in less than 5% of cases. V1 and V3 involvement with sparing of V2 would be distinctly unusual and the diagnosis of TN should be in question. **See also:** Brainstem

As the disease progresses, the pain-free intervals between attacks often grow shorter and may eventually disappear. The efficacy of medications which control the disease may wane. With increasing disease duration, more divisions of the trigeminal nerve are likely to become affected. Eventually, a minority of patients may develop persistent pain between typical paroxysms, regarded as 'atypical' TN.

Patient burden from this condition is significant. In one cross-sectional study of treated patients, pain was still rated as severe by 15% and moderate by an additional 50%. Furthermore, pain significantly interferes with general activity, mood, work and social relationships. During prolonged attacks, pain can be severe enough to lead to inadequate nutrition, hydration or dental care. Careful attention to the proper, appropriately aggressive management of this condition is therefore imperative.

## Differential Diagnosis

There is an extensive differential diagnosis for facial pain, and several elements from the history and examination are critical to confirming the correct diagnosis of TN. These entities can often be distinguished by the quality of pain described; the location of pain (with respect to distributions of trigeminal divisions); stereotypic patterns of pain; the duration of pain (ranging from brief and paroxysmal to persistent, with attention to distinguish the summation of multiple overlapping attacks); the frequency of attacks (with attention to diurnal or seasonal patterns); the onset of symptoms; identified triggers and associated autonomic features.

Processes to consider, in the appropriate circumstances, are: dental abnormalities (including dental caries, root abscesses and broken teeth); temporomandibular joint pain; eye pain (including glaucoma, orbital cellulitis and trauma); facial trauma and bony fractures; tumour of the facial bones or infiltrating the trigeminal nerve; giant cell arteritis; Tolosa–Hunt syndrome (idiopathic inflammation in or around the cavernous sinus); trigeminal autonomic cephalgias (such as cluster headache and paroxysmal hemicrania) and other primary headache syndromes (including migraine and tension-type headache).

Post-herpetic neuralgia should be distinguished by a history of herpetic rash, although a small number of zoster patients may not have a detectable rash. The pain of herpes zoster tends to be burning in quality and more constant (although if there are superimposed paroxysms, it may mimic TN). Finally, herpes zoster usually involves the ophthalmic division of the trigeminal nerve which is uncommonly involved in isolation in typical TN.

Glossopharyngeal neuralgia is much less common than TN, and is characterized by longer paroxysms of pain that are triggered by swallowing or yawning, without a lancinating or electrical quality. Systemic autoimmune disorders, such as lupus, typically cause an aching, steady pain with erythema in the midportion of face. Atypical facial pain is a syndrome of steady, aching, throbbing pain, occasionally with a paroxysmal component, that shows a strong female predominance. It can be distinguished from TN by its extension beyond the trigeminal distributions, its bilateral involvement, a lack of cutaneous trigger zones and an association with fibromyalgia and preceding depression.

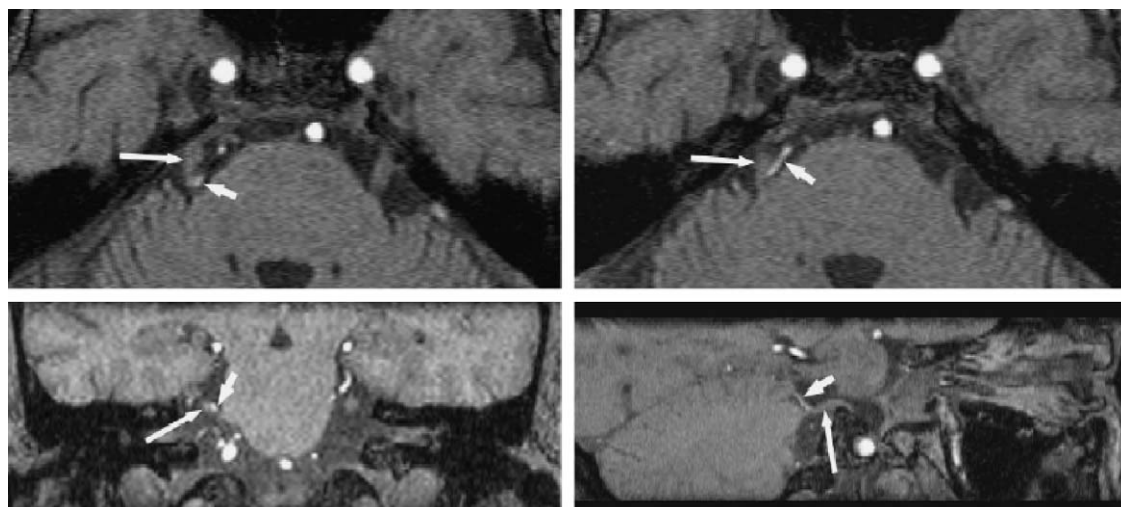
Finally, structural pathology may cause a secondary form of TN. These processes include tumours or cysts of the cerebellopontine angle, such as acoustic neuroma, and brainstem pathology, such as demyelination or stroke.

## Pathogenesis

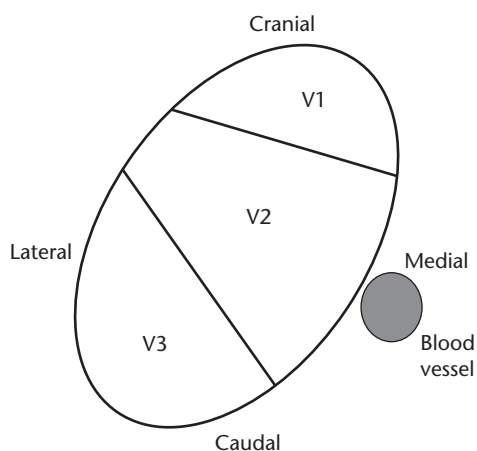
The leading theory of pathogenesis in TN implicates demyelination of trigeminal sensory fibres within the proximal nerve root. In most cases of TN (80–90%), an overlying blood vessel causes compression of the nerve at the root entry zone. The offending vessel is most commonly the superior cerebellar artery (75%) or the anterior inferior cerebellar artery (10%) (**Figure 1**). In addition, a vein can contribute to the compression (70% of cases) and sometimes is the only compressing vessel (10% of cases). Because of the distribution of fibres within the nerve root, medial compression tends to cause V2 symptoms, lateral or caudal compression may cause V3 symptoms and cranial compression will cause V1 symptoms (**Figure 2**).

Pathologic studies have examined the trigeminal root entry zone, where there is a transition between central myelin and peripheral myelin roughly 1.0–2.5 mm from the pons. Histological examination of specimens taken during vascular decompression reveals focal demyelination in the immediate vicinity of the vascular indentation. The pathological arrangement of demyelinated axons in direct apposition permits the ectopic generation of spontaneous nerve impulses and abnormal nonsynaptic ephaptic transmission to adjacent fibres (**Figure 3**). Pulsatile mechanical displacements caused by a compressing vessel may also give rise to aberrant impulses within the demyelinated axons. Furthermore, because fibres subserving light touch and pain are closest in proximity within the root entry zone, this theory provides a ready explanation for the common phenomenon of paroxysmal pain provoked by cutaneous stimuli.

TN is a well-recognized manifestation, and can even be the presenting symptom, of primary demyelinating diseases such as multiple sclerosis (MS). In this case, the pathophysiology likely differs, and is due to a *central* demyelinating lesion within the proximal part of the nerve root (**Figure 4** and **Figure 5**). TN that occurs in patients with MS can be difficult to manage; although a minority of these patients may still benefit from surgical intervention,



**Figure 1** Compression of the medial aspect of the trigeminal root entry zone (long arrow) by the superior cerebellar artery (short arrow), identified by magnetic resonance angiography (MRA); axial, coronal and sagittal views. Reproduced with permission from Yoshino N, Akimoto H, Yamada I, *et al.* (2003) Trigeminal neuralgia: evaluation of neuralgic manifestation and site of neurovascular compression with 3D CISS MR imaging and MR angiography. *Radiology* 228: 539–545. Copyright© Radiological Society of America.



**Figure 2** Anatomic distribution of fibres to V1, V2 and V3 in the trigeminal root entry zone, and typical medial compression by an offending blood vessel. Reproduced with permission from Yoshino N, Akimoto H, Yamada I, *et al.* (2003) Trigeminal neuralgia: evaluation of neuralgic manifestation and site of neurovascular compression with 3D CISS MR imaging and MR angiography. *Radiology* 228: 539–545. Copyright© Radiological Society of America.

microvascular decompression is ineffective for most of these patients. **See also:** [Multiple Sclerosis](#)

## Diagnostic Work-up

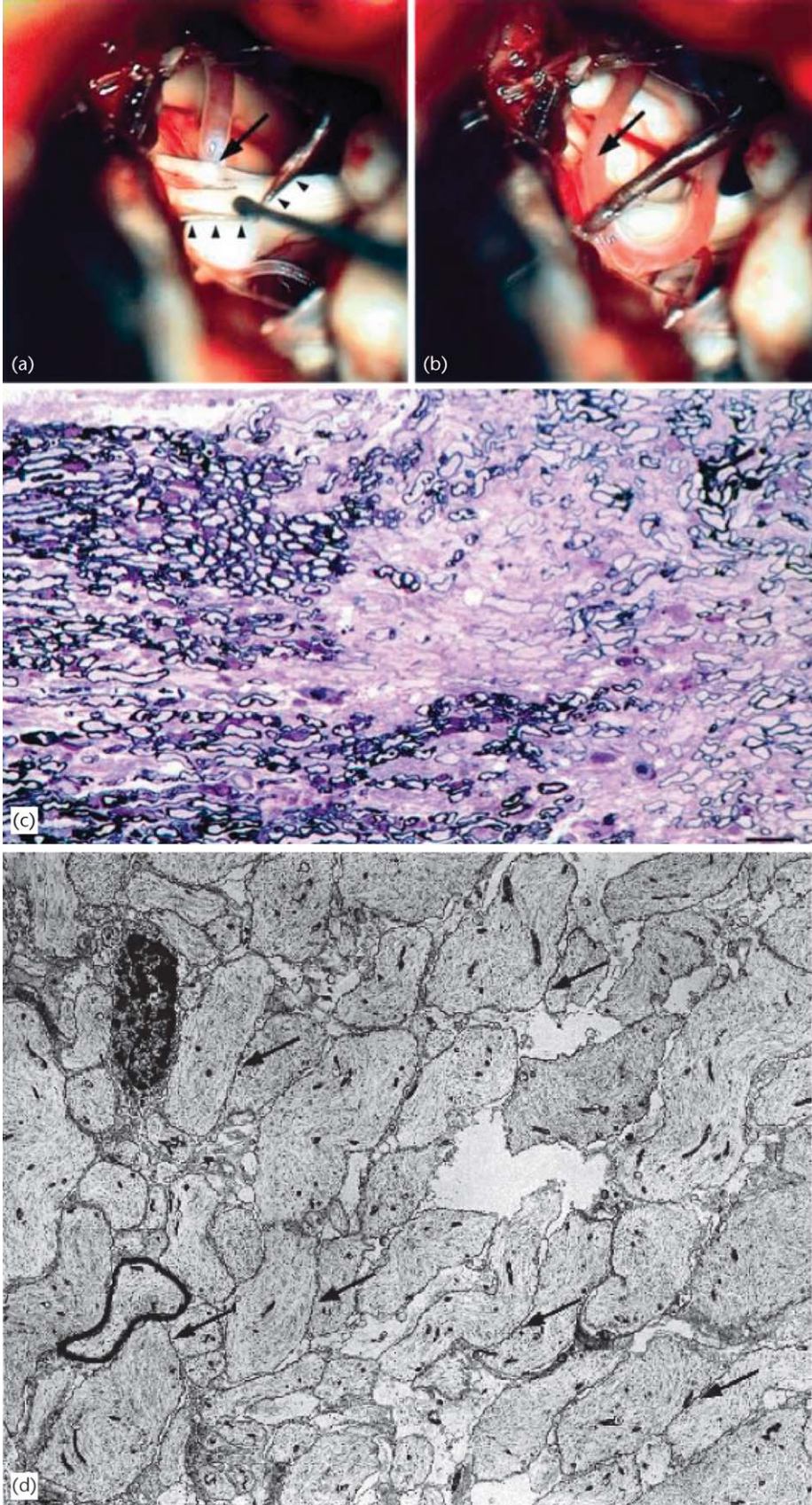
Patients with new-onset TN should typically undergo neuroimaging, preferably by MRI, to exclude a tumour, demyelination, stroke or other lesion. Advanced MRI (magnetic resonance imaging) and MR angiography,

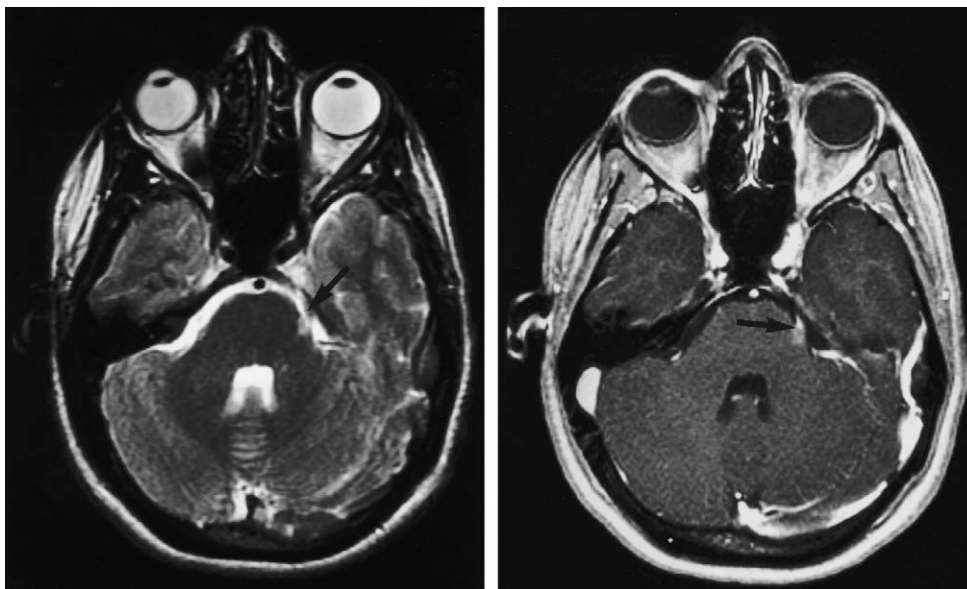
which attempts to visualize the trigeminal nerve and possible compressing vessels, may be helpful in evaluating refractory patients for possible microvascular decompression. However, the resolution of many of these imaging studies remains limited. Furthermore, although it may be possible to demonstrate a close anatomic relationship between the trigeminal root entry zone and a nearby vessel, it can be very challenging for the neuroradiologist to determine if this proximity is pathological.

## Medical Treatment

Prompt relief of the severe pain associated with this disorder is essential. Over the short term, nonsteroidal anti-inflammatory agents, narcotics or a short course of oral corticosteroids may provide symptomatic relief. However, in almost all circumstances, daily prophylactic therapy should be strongly considered (**Table 2**).

Carbamazepine is a first-line treatment for TN and is effective in nearly 90% of cases. To specifically alleviate painful morning exacerbations, the extended-release formulation can be useful at nighttime. Serum drug levels are rarely useful in effective medication titration, which can be done based on symptomatic control alone. The efficacy of carbamazepine is balanced by the common occurrence of adverse side effects, including drowsiness, dizziness, ataxia, constipation and rash. In addition, the drug causes bone marrow and liver dysfunction, and it affects the metabolism of other drugs. Therefore, carbamazepine dose titration should occur slowly to minimize the occurrence of untoward side effects which limit its tolerability. Compared to its use in patients with epilepsy, lower doses are often effective. However, because carbamazepine induces the hepatic enzymes which metabolize the drug, its efficacy





**Figure 4** Axial MRI from a patient with multiple sclerosis and trigeminal neuralgia. Left, high signal abnormality along left trigeminal nerve course (arrow). Right, the nerve enhances after gadolinium injection (arrow). Reproduced from Prasad S and Galetta S (2009) Trigeminal neuralgia: historical perspectives and current concepts. *Neurologist* 15: 87–94, with permission from Elsevier.

may wane after a period of stability at a given dose, and higher doses may become necessary.

Gabapentin is also commonly used to treat TN and is effective in approximately 40% of cases. The dose necessary to control pain typically ranges from 700 to 1250 mg daily, but doses up to 2700 mg daily may be safely tolerated. Gabapentin has a relatively low incidence of side effects. In addition, gabapentin is unique among the anticonvulsant drugs in that it is neither metabolized nor bound to serum protein; this is of particular significance in the elderly patient, in whom altered drug pharmacokinetics may narrow the therapeutic window of many medications. For these reasons, despite the lack of definitive randomized, controlled trial data, gabapentin has become a mainstay of treatment in TN.

Other anticonvulsants also have a role in the treatment of TN. Oxcarbazepine is a compound related to carbamazepine, but with less complex pharmacokinetics and a substantially lower incidence of adverse side effects. Phenytoin may be effective in 50% of cases. In some refractory cases, carbamazepine and phenytoin in combination can have a synergistic effect and achieve symptom control. Lamotrigine may have moderate benefit as an add-on therapy to carbamazepine or phenytoin. However, it requires very careful dose escalation, given the incidence of possible life-threatening rash. Pregabalin has proven effective in other painful neuropathies, and may be useful in treating TN as well.

Numerous alternative medications are also occasionally used. Baclofen is a centrally acting GABA (gamma-aminobutyric acid) agonist that probably provides small, but significant benefit. Tricyclic antidepressant compounds such as amitriptyline and nortriptyline may be used alone or in combination with an anticonvulsant. There may be a role for botulinum-A toxin injection for refractory patients.

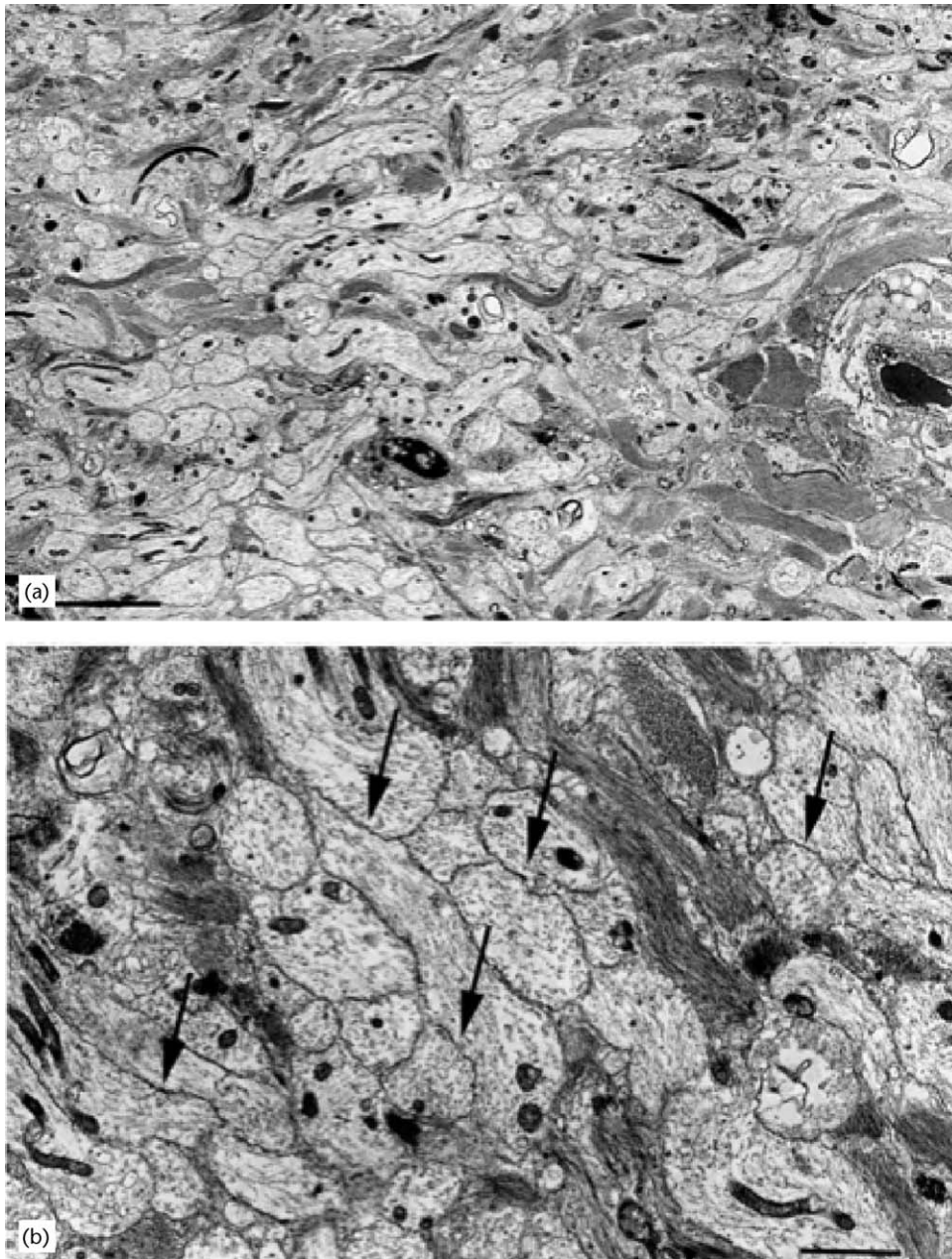
Because spontaneous remissions are characteristic of the natural history of TN, it can be appropriate to consider weaning medications in an asymptomatic patient. Typically, if a patient is completely pain-free for six weeks, a very slow taper may be initiated. Recurrence of symptoms may necessitate the dose to be increased again. Because it is common for some patients to have considerable anxiety about pain recurrence, a medication wean is not always acceptable.

## Surgical Treatment

In patients with medically intractable pain or intolerable medication side effects, invasive therapeutic approaches are often necessary, and can provide excellent success.

During a microvascular decompression procedure, an operating microscope is used to move the offending vascular loop(s) and secure the trigeminal nerve with

**Figure 3** Trigeminal neuralgia due to vascular compression of the nerve root. (a) Posterolateral surgical approach, and retraction of a vein (arrowheads) reveals an area of indentation (arrow) on the trigeminal nerve by an anteriorly placed artery. (b) The offending artery has been mobilized and repositioned behind the nerve root. (c) Pathologic specimen, of toluidine blue-stained semithin sections from the region of nerve root compression, demonstrates demyelination within the proximal nerve root in the immediate vicinity of the vascular indentation. (d) Electron microscopy confirms large numbers of demyelinated nerve fibres, several in direct apposition (some indicated by arrows). Reproduced from Love S and Coakham HB (2001) Trigeminal neuralgia: pathology and pathogenesis. *Brain* 124: 2347–2360, with permission from Oxford University Press.



**Figure 5** Trigeminal neuralgia due to multiple sclerosis. (a) Electron micrograph illustrating a focus of chronic nerve root demyelination in a patient with multiple sclerosis (scale bar=10  $\mu\text{m}$ ). (b) Higher magnification shows areas of apposition (some indicated by arrows) between several nerve axons (scale bar=2  $\mu\text{m}$ ). Reproduced from Love S and Coakham HB (2001) Trigeminal neuralgia: pathology and pathogenesis. *Brain* 124: 2347–2360, with permission from Oxford University Press.

a synthetic sponge prosthesis. This technique allows decompression without any disruption to the nerve itself. Several long-term studies have demonstrated the enduring efficacy of this procedure. Immediate postoperative relief is complete in approximately 80% of patients and partial in 15%. At 1 year, 75% of patients continue to have excellent results, and at 10 years this number is approximately 65%.

The exact mechanisms by which microvascular decompression alleviates TN are not fully understood.

Decompression often produces rapid improvement, probably due to immediate reversal of the underlying distortion and compression of demyelinated axons, reducing the occurrence of spontaneously generated impulses and their ephaptic spread. Less clear is the extent to which normal remyelination occurs over the long-term, reversing the pathological axonal arrangement.

Alternatives to microvascular decompression are usually considered for elderly patients and those with significant

**Table 2** Pharmacological management of trigeminal neuralgia

First-line agent	
Carbamazepine (Tegretol <sup>®</sup> ) <sup>a</sup>	Start 150 mg daily, increase by 100 mg every 3 days as needed to a total daily dose of 800–1600 mg, divided in 3 doses
Second-line agents	
Oxcarbazepine (Trileptal <sup>®</sup> ) <sup>b</sup>	Start 300 mg daily, increase by 300 mg every 3 days as needed to a total daily dose of 1200–1800 mg, divided in 2 doses
Gabapentin (Neurontin <sup>®</sup> ) <sup>c</sup>	Start 300 mg thrice daily, increase as needed to a total daily dose of 3600 mg, divided in 3 doses. Also commonly used as first-line therapy
Phenytoin (Dilantin <sup>®</sup> ) <sup>d</sup>	Start 300 mg daily, increase as needed, divided in 2 or 3 doses
Third-line agents (add-on therapy or monotherapy)	
Lamotrigine (Lamictal <sup>®</sup> ) <sup>e</sup>	Start 25 mg daily, increase by 25 mg every 7 days as needed to a total daily dose of 200–400 mg, divided in 2 doses
Baclofen (Lioresal <sup>®</sup> ) <sup>f</sup>	Start 15 mg daily, increase by 5 mg every 3 days as needed to a total daily dose of 60–80 mg, divided in 3 doses

<sup>a</sup>Tegretol (Novartis, New Jersey, USA).

<sup>b</sup>Trileptal (Novartis, New Jersey, USA).

<sup>c</sup>Neurontin (Pfizer, New York, USA).

<sup>d</sup>Dilantin (Pfizer, New York, USA).

<sup>e</sup>Lamictal (GlaxoSmithKline, London, UK).

<sup>f</sup>Lioresal (Novartis, New Jersey, USA).

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co-morbidities. Less-invasive procedures include radio-frequency thermocoagulation, retrogasserian glycerol injections and trigeminal ganglion balloon compression. All of these procedures permanently lesion the trigeminal ganglion, and have a high risk of producing severe facial numbness, dysesthesia and corneal keratitis. Thermo-coagulation may offer greater pain relief, at the cost of more frequent permanent dysesthesia, than glycerol injections. However, glycerol injections are often effective for several years, and the procedure can be repeated when symptoms recur.

Stereotactic gamma knife radiosurgery is an alternative noninvasive, nondestructive therapy which treats

the trigeminal root entry zone with a targeted beam of gamma radiation. Initial pain relief may occur in a vast majority of patients (more than 90%), typically within 1 month. The procedure has an especially low-risk profile, making it particularly suitable for elderly patients or those with co-morbid disease. In addition, there seems to be a very low rate of trigeminal dysfunction as a side effect.

Finally, repetitive transcranial magnetic stimulation (rTMS) of the contralateral motor cortex is a novel therapy under investigation for the treatment of several pain disorders, including TN. Although it is not used often in clinical practice, it is showing promising results in trials that demonstrate its efficacy in dampening pain, possibly by altering thalamo-cortical circuits. Further study is needed to delineate the optimal treatment regimen and the long-term tolerability of the procedure. **See also:** Brain Imaging; Observing Ongoing Neural Activity

## Conclusions

TN is among the most painful conditions described. Recent advances have led to a better understanding of the pathophysiologic substrate underpinning this condition. A majority of cases are due to vascular compression near the trigeminal root entry zone leading to focal demyelination and ephaptic axonal conduction. Anticonvulsants are among the most effective medications that provide relief to these patients. Refractory patients may benefit from a number of procedures, including microvascular decompression and gamma knife therapy. The selection of a surgical therapy often depends on patient preference, age and co-morbidities.

## Acknowledgment

Portions of this article are adapted with permission from Prasad S and Galetta S (2009) Trigeminal neuralgia: historical perspectives and current concepts. *Neurologist* **15**: 87–94.

## Further Reading

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