Trigeminal neuralgia

Joanna M Zakrzewska professor of pain medicine in relation to oral medicine, Mark E Linskey professor of neurological surgery

Trigeminal neuralgia is a rare, episodic facial pain that is unilateral, electric shock-like, and provoked by light touch. At first, it is often mistaken as a tooth problem owing to its presentation in the two lower branches of the trigeminal nerve. Patients may undergo unnecessary—and sometimes irreversible—dental treatment before the condition is recognised. Initially, a small dose of an antiepileptic drug (such as carbamazepine) rather than any analgesic drug can provide excellent pain relief. However, up to 10% of patients will not respond to antiepileptic drugs, and in rare instances trigeminal neuralgia can be secondary to a brain tumour, multiple sclerosis, or vascular anomalies, which will be identified only on neuroimaging. If quality of life becomes impaired and symptoms are uncontrolled with drug treatment, patients should be referred to a neurosurgeon for consideration of surgical management. Studies in Europe have shown that trigeminal neuralgia results in considerable interference with activities of daily living that is comparable to other neuropathic pain conditions, and could lead to suicide. This review aims to highlight the key features of trigeminal neuralgia and familiarise readers with both the medical and surgical management of this condition, which remains based on limited evidence and expert opinion.

How common is trigeminal neuralgia?

Trigeminal neuralgia is rare, and hence it is difficult to obtain high quality epidemiological data. Data from the United States and validated in the 1990s provided a crude annual incidence of 5.7 per 100,000 women and 2.5 per 100,000 men. Peak incidence lies between age 50 and 60 years, with prevalence increasing with age. A general practice based survey in London of neurological diseases showed an incidence of 8 (95% confidence interval 4 to 13) per 10,000 people per year and a lifetime prevalence of 0.7 (0.4 to 1) per 100,000 people per year. Subsequent studies examining general practice databases reported an incidence of 27 per 100,000 person years in the United Kingdom, and this figure was also noted in Holland. However, when trained specialists checked the data in Holland, the number fell to 12.6 per 100,000 person years. A community based study in Germany using face to face interviews with trained neurologists reported a lifetime prevalence of 0.3%.

Who are most at risk of having trigeminal neuralgia?

Data from the US have found that women were more at risk than men of trigeminal neuralgia, but the association was not as strong if correction was made for women living longer than men. The strongest association of having trigeminal neuralgia is with multiple sclerosis, which has been seen in both epidemiological data and in data for multiple sclerosis. There could also be an association with hypertension and stroke, but this could be due to chance because the epidemiology is similar between hypertension and other degenerative diseases.

What is the underlying pathophysiology of trigeminal neuralgia?

Large surgical series from many different centres have confirmed that microvascular decompression of the trigeminal nerve root is the most effective and durable treatment for trigeminal neuralgia. Strong empirical evidence indicates that vascular compression of the trigeminal nerve root is associated with trigeminal neuralgia in about 95% of patients. However, the exact pathophysiology of how vascular compression leads to trigeminal neuralgia remains speculative. Popular hypotheses include a combination of central demyelination of the nerve root entry zone and reinforcing electrical excitability (the ignition hypothesis). Recent studies suggest that this demyelination then leads to an impairment of the nociceptive system. Those patients with more background pain seem to have a loss of central inhibition of the nociceptive system; even after successful surgery, some form of abnormality of somatosensory function remains. Other factors including predisposing biology on a genetic basis are likely to be important because although rare, familial clusters do exist. The remaining small subset of trigeminal neuralgia cases are associated with multiple sclerosis plaques or lacunar infarctions within the brain stem trigeminal system or cerebellopontine mass lesions. Demyelinating multiple sclerosis plaques have been reported involving brain stem trigeminal nuclei. However,
in a study of consecutive patients with multiple sclerosis, MRI showed that the only lesion localisation common to all patients was the intrapontine course of fibres in the fascicular trigeminal nerve root, lending further support to the role of demyelination at the central nerve root in trigeminal neuralgia.

How is trigeminal neuralgia diagnosed?

The box shows the key clinical features and red flags of trigeminal neuralgia. The diagnosis of trigeminal neuralgia and other episodic, unilateral neuralgiform pain is based nearly entirely on the history. However, the diagnostic criteria have not been validated by case-control studies and remain based on expert consensus, mainly from headache neurologists and epidemiological studies from the 1990s. Trigeminal neuralgia often starts suddenly with a memorable onset. The periods of remission tend to get shorter with time and the attacks of pain often get longer; 65% of patients newly diagnosed with trigeminal neuralgia will have a second episode within five years, and 77% within 10 years. Fifty per cent of patients will have remissions of at least six months’ duration. Patients can have as few as three or four attacks a day, but they could have as many as 70 per day. At times the attacks of pain come so quickly that it is impossible to determine whether there is a gap between each attack. There is often a refractory period when the pain cannot be triggered. Pain can occur at night in a third of patients. It is unusual to have trigeminal neuralgia in the first ophthalmic division of the trigeminal nerve only. Some patients continue to have a background pain of lower intensity for 50% of the time. This condition has variously been called atypical trigeminal neuralgia, type 2 or—in the new International Classification for Headache Disorders—trigeminal neuralgia with concomitant persistent facial pain. Some patients might also have autonomic features such as conjunctival injection, lacrimation, nasal congestion or rhinorrhea, eye lid oedema, ptosis, or facial sweating. In the presence of autonomic symptoms, it can be difficult to determine whether this is still trigeminal neuralgia or a variant known as short unilateral neuralgiform pain with autonomic symptoms (SUNA) or short unilateral neuralgiform pain with conjunctival injection and lacrimation (SUNCT). A retrospective study of patients who had undergone a microvascular decompression indicated that up to 67% reported one autonomic symptom and 14% had four or more, and that those with autonomic features were more likely to have a poorer response to surgery.

What investigations should be done?

Trigeminal neuralgia itself is a purely clinical diagnosis. However, investigations could be required especially if red flags are noted (box) and the indications for them are based on case reports. These investigations are targeted towards identifying other craniofacial pain syndromes within a differential diagnosis of trigeminal neuralgia, identifying non-vascular compressive causes of trigeminal neuralgia, and obtaining baseline laboratory test values to assist with toxicity monitoring before starting pharmacological treatment.

Patients’ self assessment tools could develop in time to the point when they allow for a sensitive and specific diagnosis of trigeminal neuralgia, but evidence so far is sparse. In small studies of patients with trigeminal neuralgia or atypical facial pain, the McGill Pain questionnaire (a general tool for use in all pain conditions) was able to predict the correct diagnosis in 90% of the patients. In another study, an extended version of the Brief Pain Inventory identified the difference in effect on daily living between 114 patients with classic trigeminal neuralgia and 42 patients with atypical trigeminal neuralgia. Both of these tools have yet to be externally validated in a larger series of patients with trigeminal neuralgia.

Imaging

The most useful investigation is an MRI scan of the brain with and without contrast, which is used to rule out other potential causes of pain if the diagnosis is not clear cut or if red flags are present. MRI is very sensitive in identifying the following features:

- Sinusitis
- Extracranial masses along the course of the trigeminal nerve
- Pathological enhancement of the trigeminal nerve that could indicate perineural spread of malignancy
- Cavernous sinus masses
- Demyelination plaques that might indicate multiple sclerosis

Summary points

- Trigeminal neuralgia is a severe, unilateral, episodic pain of the face that is provoked by light touch; it should be differentiated from dental causes of pain.
- Magnetic resonance imaging (MRI) can distinguish between patients having secondary trigeminal neuralgia related to tumours and that related to multiple sclerosis.
- The first line drug for treatment is either carbamazepine or oxcarbazepine, and doses should be slowly escalated. Neurosurgical options should be discussed at an early stage, but surgery may not be required until quality of life is compromised.
- Microvascular decompression is a major neurosurgical procedure that provides the longest period of pain relief and aims to preserve function of the nerve.
- Percutaneous, palliative destructive procedures and stereotactic radiosurgery can provide temporary relief, but at the risk of facial numbness, which increases with repetition of the procedure.

Sources and selection criteria

We used Medline and Embase and the search terms ‘trigeminal neuralgia’ and ‘tic douloureux.’ One author (JJ) has done Cochrane reviews on both medical and surgical outcomes for trigeminal neuralgia, and the search strategy is shown in those publications. We searched the Cochrane Neuromuscular Disease Group specialised register, Cochrane Library, Medline, and Embase using the search terms ‘trigeminal neuralgia/facial neuralgia/tic douloureux,’ ‘tic douloureux,’ ‘tic douloureuex,’ or ‘tic douloreux’ with no language exclusion. Clinical knowledge summaries and international guidelines for trigeminal neuralgia were published in 2008, and the search strategy can be found on www.aan.com. We also used our own extensive archives of references.
Diagnostic criteria for trigeminal neuralgia and red flags

<table>
<thead>
<tr>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain is unilateral in the distribution of the trigeminal nerve, bilateral in only 3% of patients, and rarely is the pain active on both sides at the same time.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Periodicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic and sudden onset of pain, lasting a few seconds to minutes and stopping suddenly, with many attacks a day. There is a refractory period between each attack. Pain might then go into remission for weeks or months; pain-free intervals gradually shorten between episodes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electric shock-like, sharp, shooting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very severe attacks, but attacks can get milder when patients are given drug treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Factors affecting pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be provoked by light touch to the face, eating, cold winds, or vibrations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Associated factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rarely associated with history of other chronic pain or migraine. Some forms have more continued aching background pain after main attack. Rarely associated with autonomic features</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Red flags</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory changes, deafness or other ear problems, difficulty achieving pain control, poor response to carbamazepine, history of any skin lesions or oral lesions that could lead to perineural spread, ophthalmic division only or bilateral as suggestive of benign or malignant lesions or multiple sclerosis, age of onset under 40 years, optic neuritis, family history of multiple sclerosis</td>
</tr>
</tbody>
</table>

• Intrinsic brain lesions in the thalamus or trigeminal brain stem pathways such as lacunar infarctions
• Cerebellopontine angle mass lesions such as tumour, epidermoid, dermoid, or arachnoid cyst, aneurysm, or arteriovenous malformation.

MRI is the most sensitive screening and diagnostic test available for detecting multiple sclerosis and has the highest positive predictive value. Although rare, brain tumours can be associated with trigeminal neuralgia. Posterior fossa tumours are the tumours most likely to be associated with typical trigeminal neuralgia pain characteristics, and are most commonly vestibular schwannomas, meningiomas, or epidermoid cysts. It is tempting to order an MRI scan to assess the trigeminal nerve for vascular compression, and in our experience, it is sometimes requested by patients once they have been diagnosed with trigeminal neuralgia and have done some research on the subject. MRI can detect vascular contact with the trigeminal nerve; however, this contact is best seen with specialised T2 and T1 volumetric acquisition techniques with fine slicing in all three planes (fig 1)).

These techniques are expensive and not usually included as standard MRI head protocol, and will be available only in specialist settings. In addition, because the vessels in question are normal blood vessels and vascular contact with cranial nerves is a normal variant found in many patients without trigeminal neuralgia, an image showing vascular contact could be read as “normal” by the radiologist reading the study. A multidisciplinary evidence based review of the published literature by the American Academy of Neurology and the European Federation of Neurological Societies concluded that MRI is currently too insensitive for detecting vascular compression of the trigeminal nerve to recommend routine use. Some small studies with more sophisticated technology have suggested improved correlations but these technologies are not available routinely at present. However, more sophisticated techniques have been used recently, as reported in small series, which have shown actual changes in the trigeminal nerve.

Biochemical investigations

Depending on the drugs chosen to treat trigeminal neuralgia, particularly among antiepileptic drugs, issues related to reductions in white blood cell count, elevation in liver transaminases, and hyponatraemia are well documented. Thus, depending on the treatment planned, a complete blood count at baseline with differential, serum electrolytes, and liver function tests are needed to monitor for potential drug toxicity over time. Regular blood test monitoring is not recommended unless there is a clinical indication. For patients taking enzyme inducing drugs, the National Institute for Health and Care Excellence (NICE) recommends a full blood count, measurements of electrolytes, liver enzymes, and vitamin D levels, and other tests of bone metabolism (for example, serum calcium and alkaline phosphatase) every two to five years.

What are the medical options for treatment?

All drugs currently used to treat trigeminal neuralgia were initially developed for other indications, principally for epilepsy. Only a handful of small randomised controlled trials have investigated drug treatments for trigeminal neuralgia, many of which are old and have methodological flaws. International guidelines, Cochrane systematic reviews, and Clinical Evidence have highlighted the key treatments (table 1)).

In the UK, the only drug licensed specifically for trigeminal neuralgia is carbamazepine, but drugs licensed for use in neuropathic pain are often used (trigeminal neuralgia is considered a neuropathic condition). However, updated NICE guidelines for management of neuropathic pain state that in primary care only carbamazepine should be used and if it fails patients should be referred for specialist care. The guidelines specifically exclude use of other neuropathic drugs for trigeminal neuralgia in primary care. All the drugs should be started at low doses and gradually escalated every three to seven days to determine the best pain control with lowest side effects. Careful monitoring is needed initially and if drug doses become high.
trigeminal neuralgia, the best surgical results in the short term (≤4 years) are achieved with microvascular decompression; the next best results come from the palliative destructive procedures, which have roughly equivalent results. A meta-analysis suggested that radiofrequency lesioning had a slight outcome advantage for patients with a higher incidence of treatment induced numbness. Although all surgical procedures for trigeminal neuralgia have roughly equal chances of achieving pain relief without the need for drug treatment, microvascular decompression has a recurrence rate of about 4% per year which plateaus to about 1-2% per year by year six; the palliative destructive procedures have a recurrence rate of about 50% after three to five years, increasing linearly thereafter.

Even in experienced hands, microvascular decompression does carry the risk of a patient having to undergo general anaesthesia, a risk (<3%) of hearing loss, as well as the risks (<1%) common to elective open cranial microsurgery. Percutaneous procedures (radiofrequency lesioning, glycerol rhizolysis, and balloon compression) all require brief periods of heavy sedation and are associated with autonomic responses of trigeminal-vagal nerve reflex, which may be important considerations for patients with significant cardiac disease. Large case series report that radiofrequency lesioning has the highest risk of facial numbness (often an intended consequence), and that balloon compression has a risk of temporary motor weakness in the trigeminal nerve. Stereotactic radiosurgery has the lowest risk of numbness, but does not take effect immediately, taking an average of four to six weeks for the onset of pain relief.

No randomised clinical trials have compared the outcomes of surgical procedures for trigeminal neuralgia. But in two prospective cohort trials, microvascular decompression provided better results for pain relief as well as a lower recurrence rate than the Gamma Knife.

### What to do in a crisis?

Patients who develop severe unremitting pain often attend emergency departments and are usually given opioids, although there have been no reported trials investigating this. However, opioids anecdotally have no effect on this pain, and they have not been recommended by NICE guidelines. Clinical experience shows that local anaesthesia injected into a trigger area can help pain relief. This technique was used in a randomised controlled trial of 25 patients with second division pain, those given an 8% spray of lidocaine as opposed to saline had a statistically significant decrease in pain for a mean of four hours.

There is one report of three patients responding to intravenous infusion of fosphenytoin, although this should be performed only under specialist supervision because hospital admission and cardiac monitoring are required. This procedure can help to break the cycle and should be followed up by an increase of oral drug treatments. Patients sometimes need to be admitted for rehydration and possible management of hyponatraemia if they have used high doses of antiepileptic drugs. Good oral hygiene needs to be maintained to prevent any additional dental pain, and a hygienist may be needed to provide more detailed instructions. Patients in a crisis should be kept calm because they can feel overwhelmed by the pain and its continuation, which can induce more attacks.
What other support is available for patients with trigeminal neuralgia?

In view of the rarity of trigeminal neuralgia, few general practitioners have experience of dealing with these patients, who can feel isolated and live in fear of developing a severe pain attack. Patient support groups have been shown to be helpful. Meeting other healthcare professionals and fellow patients can help decision making about treatment choices, which is difficult because of the paucity of high quality evidence.

Contributors: JMZ and ML conceived and designed the article, drafted the manuscript, and approved the final version of the manuscript to be published. JMZ is guarantor of the article.

Competing interests: We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: JMZ is partly funded by University College London and University College London Hospital Trust, which received a proportion of funding from the Department of Health (via the Biomedical Research Centre funding scheme from the National Institute for Health Research), and receives consultancy fees from Convergence pharmaceuticals; ML has no competing interests.

Provenance and peer review: Commissioned; externally peer reviewed.
Questions for future research

What is the natural history of trigeminal neuralgia and are there associated risk factors?
Is there a genetic basis?
Are there objective biomarkers to confirm the clinical diagnosis, and can they be used to predict prognosis?
What are the best care pathways to optimise quality of life and when should treatment change from medical to surgical management?
What novel trial designs should be used to evaluate new drugs and different surgical procedures?
How do we improve decision making for patients and ensure they give informed consent?

Tips for non-specialists

Rule out dental causes for the pain, but also remember that trigeminal neuralgia can present as toothache and result in unnecessary dental treatment
Careful history taking should detect signs of symptomatic trigeminal neuralgia; if there are red flags, imaging should be used
Carbamazepine or oxcarbazepine are highly effective but need to be titrated up slowly because they cause significant side effects to the central nervous system
Patients will have periods of remission, but it is important that they continue to have access to their drugs and learn to titrate the drugs themselves with the use of pain diaries
Untreated or poorly treated trigeminal neuralgia could result in weight loss and depression, and can lead to suicide; thus prompt referral to multidisciplinary teams with an interest in this condition (neurosurgeons, neurologists, pain specialist) is important
Refer patients with uncontrolled symptoms for consideration of surgical procedures
Opioids do not control this pain, and lidocaine injected into trigger points is much more effective in patients who develop severe unremitting pain

Additional educational resources

Resources for healthcare professionals

NICE clinical knowledge summaries (http://cks.nice.org.uk/trigeminal-neuralgia)—provides evidence based material on the diagnosis and management of trigeminal neuralgia in primary care guideline 173, November 2013. Free, no registration
E-learning 20 minute session on trigeminal neuralgia hosted by the Cardiff University Community Centre (www.paincommunitycentre.org/article/diagnosis-and-treatment-Trigeminal-neuralgia)—prepared under the e-learning for healthcare scheme, it is targeted at primary care doctors and dentists, has short video clips on diagnosis, and a section on management and multiple choice questions. Free, no registration
PIER trigeminal neuralgia module from the American College of Physicians (http://smartmedicine.acponline.org/content.aspx?gbosId=299)—comprehensive evidence based review of trigeminal neuralgia. Must be a member to access
Professional sections on website for trigeminal neuralgia support groups (see below)

Resources for patients

Trigeminal Neuralgia Association UK (www.tna.org.uk)—also includes information for professionals, listing higher quality published articles and many links to other organisations for patients and professionals. Some information is freely available but members have access to a forum and more details
Facial Pain Association (formerly the Trigeminal Neuralgia Association) (www.fpa-support.org/ and www.endthepain.org)—the association caters for people with trigeminal neuropathic pain. Registration needed for free access
Trigeminal Neuralgia Association Australia (www.tnaaustralia.org.au)—provides basic information on trigeminal neuralgia for free, but there is also a members’ area and regular e-newsletter that provides research updates and details on each support group
Trigeminal Neuralgia Association of Canada (www.tnac.org/)—provides basic information for free but also has a members’ area. This site provides clear pictures of surgical procedures (www.umanitoba.ca/cranial_nerves/trigeminal_neuralgia/manuscript/medications.html)

Weigel G, Casey KE. Striking back: the trigeminal neuralgia and face pain handbook. Trigeminal Neuralgia Association, 2003—written by a patient with input from a neurosurgeon, it provides comprehensive material on trigeminal neuralgia that is jargon free
Zakrzewska JM. Insights facts and stories behind trigeminal neuralgia. Trigeminal Neuralgia Association, 2006—written by a doctor for patients, it has contributions from over 100 patients and provides a comprehensive review from both patients’ and professionals’ perspectives
Brain and Spine Foundation (www.brainandspine.org.uk)—covers a wide range of neurological and neuurosurgical conditions, and includes free download of booklet on head and face pain that provides details of trigeminal neuralgia and other related facial pain conditions

Accepted: 9 January 2014

Cite this as: BMJ 2014;348:g474
© BMJ Publishing Group Ltd 2014
## Table

**Table 1** Most common drugs used for the medical management of trigeminal neuralgia*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Beware drug interactions; only drug licensed for trigeminal neuralgia in the UK</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Results in hyponatraemia at higher doses; equipotencies of carbamazepine and oxcarbazepine is about 1:1.5</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Useful in multiple sclerosis and when combined with carbamazepine</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Start treatment very slowly from 25 mg daily; can be used with carbamazepine or oxcarbazepine</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Only one small randomised controlled trial shows effectiveness</td>
</tr>
<tr>
<td>Pregablin</td>
<td>Long term cohort study shows effectiveness</td>
</tr>
</tbody>
</table>

*Only carbamazepine should be initiated in primary care.*
Figures

**Fig 1** MRI of the posterior fossa of the brain showing neurovascular compression. Sequential, 0.8 mm, fine cut axial images from a volumetric T2 MRI acquisition on a patient with right sided trigeminal neuralgia. Caudal (A) and rostral (B) axial images shown. Origin of the trigeminal nerve from the brainstem on both sides is indicated by small arrows positioned along the course of the nerve. Inferior and lateral compression of the right trigeminal nerve route by a flow void representing the superior cerebellar artery is indicated by large arrows positioned perpendicular to the nerve course. The trigeminal nerve root is not only contacted but also displaced medially in its cisternal course by the superior cerebellar artery (B).

**Fig 2** Compression of the trigeminal nerve in the posterior fossa and microvascular decompression. Intraoperative photographs taken during a microvascular decompression for left sided trigeminal neuralgia via a supralateral, cerebellar retrosigmoid approach. (A) Low power view showing severe proximal ventral trigeminal nerve compression of the trigeminal nerve (V) by the superior cerebellar artery (white arrow). (B) Higher power view showing the vascular interaction with the trigeminal nerve. (C) High power view of trigeminal nerve (V) after microvascular decompression, with superior cerebellar artery displaced rostrally (out of view) and held in position by shredded Teflon felt (white arrow). VII and VIII=cranial nerve VII and VIII complex.
Fig 3 Targeting the trigeminal nerve with stereotactic radiosurgery using the Gamma Knife. Fine cut, 1 mm, axial T2 targeting images of a rhizotomy to the left trigeminal nerve root in a patient with trigeminal neuralgia. (A) Overview of the pons and the posterior fossa anatomy. (B-C) Sequential high magnification views of the trigeminal nerve root in relation to the dose plan. Inner circle=95% isodose line (76 Gy for an 80 Gy maximum treatment dose); outer circle=20% isodose line (16 Gy for an 80 Gy maximum treatment dose). In this case, two sector blocks were used to custom sculpt the radiation fall-off so that the surface of the brain stem received a dose no greater than 16 Gy.