

Medical Treatment of Trigeminal Neuralgia

A review of the treatment of any condition must first define the diagnosis. This is by no means easy for trigeminal neuralgia (TN). Clinicians will agree that TN is a neuropathic pain syndrome characterised by brief severe lancinating pain in the trigeminal distribution of the face. These recurrent paroxysms of pain are often triggered off by direct and indirect stimuli that may be specific for individual patients. The IHS (International Headache Society) criteria for diagnosing TN is a useful definition of this condition (see Table 1).¹ However, the diagnosis is purely clinical, relying on pain descriptors and normal physical examination. Classical TN consists of painful paroxysms with little or no pain in-between each attack. Those with background pain and atypical presentation are variously known as atypical TN, TN with interparoxysmal pain (TNIP), painful trigeminal neuropathy or pretrigeminal neuralgia. Some of these conditions may merge with the syndrome of atypical facial pain.

Many patients with 'idiopathic' or primary forms of TN are found to have a loop of artery or, rarely, vein in contact with the dorsal root entry zone of the relevant trigeminal nerve. The success of microvascular decompression (MVD) in alleviating TN supports the assertion that these neurovascular contacts play a role in the pathogenesis of TN (see article by Hugh Coakham, ACNR 2007;7(2):17-18). There are also secondary forms of TN that may appear classical initially but where a plaque of demyelination, tumour or vascular malformation impinges on the trigeminal nerve. These secondary or symptomatic forms of TN may develop into 'atypical' TN with more obvious abnormal physical findings with time.

Differentiating between classical and atypical TN is important as the former is more likely to respond to MVD. This is also the case for medical treatment. Most drugs mentioned below appear to be less effective for atypical forms of TN. Making the correct diagnosis is important although response to treatment can sometimes differentiate between classical and atypical forms of TN (see Figure 1).

Assessing efficacy

Performing studies to assess therapy for TN is difficult because the condition is relatively rare and the diagnosis is dependent on clinical assessment. Spontaneous remission of TN is common and may bias both placebo and treatment effects. In addition, the pain of TN is so severe that it is difficult to justify using placebo without rescue medications. Furthermore, many medications for TN have long half lives and both therapeutic and side-effects may take time to become evident. For all these reasons, very few placebo controlled studies have been carried out for the medical treatment of TN.

Where studies are done, the main primary end points measured were pain frequency and severity. These measurements are now recognised to inadequately reflect the complex effects of chronic pain. A group of experts have formulated the IMMPACT guidelines so that future treatment efficacy should include the multi-dimensional aspects of pain.² The six suggested parameters to be measured in trials are: pain (severity, character, frequency, use of rescue medications), physical functioning, emotional functioning, patient global impression, adverse effects and patient disposition.

Comparing treatment effect is also difficult. Most chronic pain studies use the NNT (Number Needed to Treat) concept first proposed by Cook and Sackett in 1995. The NNT is calculated as the inverse of absolute risk reduction for any treatment. McQuay and colleagues have chosen pain relief of 50% or more as their end point.³

The formula for calculating NNT is:

$$\frac{1}{(N_{\text{active}}/\text{Total}_{\text{active}}) - (N_{\text{placebo}}/\text{Total}_{\text{placebo}})}$$

N_{active}	Number of patients on active treatment achieving a defined end point
$\text{Total}_{\text{active}}$	Total number of patients on active treatment
N_{placebo}	Number of patients on placebo achieving the same defined end point
$\text{Total}_{\text{placebo}}$	Total number of patients on placebo treatment

The raw data for calculating NNT is derived from randomised placebo controlled trials and is a useful way for estimating active intervention for pain relief. However, NNTs are not directly comparable between two different trials because specific patient populations studied cannot be generalised to all patient groups. The numbers of patients studied is also crucial. The larger the number of subjects studied, the narrower the standard deviation of any NNT calculation. In spite of its imperfections, NNT measurements remain a useful concept in the comparison of different therapeutic agents for pain alleviation.

Individual drugs

Carbamazepine (CBZ)

CBZ remains the gold standard for treatment of TN. These data were derived from three placebo controlled crossover studies involving 151 patients.⁴⁻⁶ The daily dose of CBZ prescribed was between 400mg-2.4g. Combining data from these studies derived a NNT of 2.6 (2.2-3.3). These three studies were reported between 1966-1969 and have never been repeated. The crossover periods were variable and in the largest study, each patient spent two periods of two weeks each on placebo and CBZ. There were also variable periods of follow-up ranging from 46 months to none. The outcomes measured included pain severity, paroxysms, triggers or pain relief. Although imperfect, this is the best published data for any medication for alleviating TN.

The side-effects of CBZ are well known to clinicians who use it for treating epilepsy. Many adverse effects are dose dependent (dizziness, sedation, diplopia, ataxia, confusion) while some are genetically linked (skin rash, Stevens-Johnson syndrome). For example, the risk of developing a cutaneous eruption with CBZ is reported to be linked to the HLA-B*1502 gene in people of Oriental descent.⁷ Slow titration of carbamazepine will minimise many of its adverse effects. This is obviously not ideal for patients with TN. The starting dose is usually 100mg twice a day with increments of 100mg daily every third day until satisfactory pain relief is achieved. Checking plasma levels can be helpful and the relatively short half life means that



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Table 1: IHS Diagnostic criteria of Trigeminal Neuralgia

- A. Paroxysmal attacks of pain lasting from a fraction of a second to two minutes, affecting one or more divisions of the trigeminal nerve and fulfilling criteria B and C
- B. Pain has at least one of the following characteristics:
 1. intense, sharp, superficial or stabbing
 2. precipitated from trigger areas or by trigger factors
- C. Attacks are stereotyped in the individual patient
- D. There is no clinically evident neurological deficit
- E. Not attributed to another disorder.

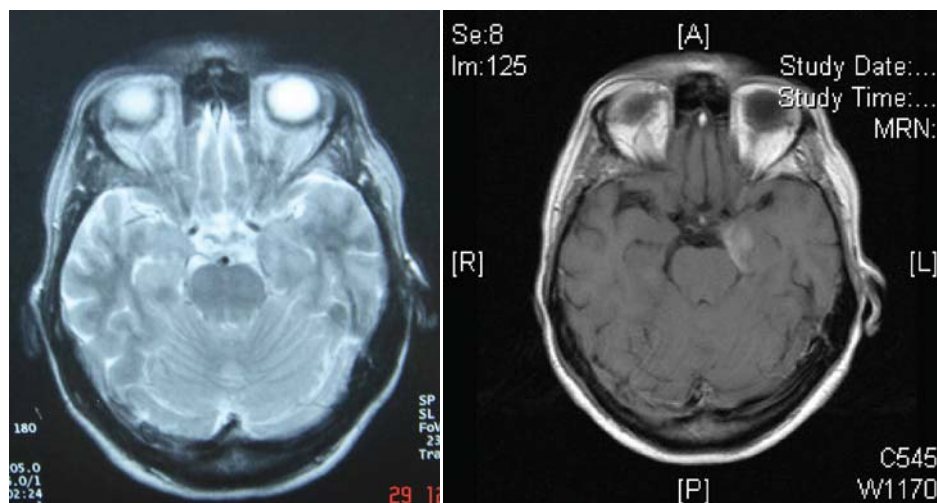


Figure 1: Atypical Trigeminal Neuralgia

This 57-year-old woman developed sharp shooting left sided facial pain with over 20 attacks an hour, each lasting for less than one minute. She experienced residual pain in-between attacks. Physical examination was normal apart from reduced sensation to light touch and pinprick over the mandibular and maxillary division of the trigeminal nerve on the left. She was diagnosed with trigeminal neuralgia initially but did not respond to carbamazepine. This diagnosis was revised to atypical TN and she subsequently achieved complete pain relief with gabapentin. An unenhanced MRI scan done at a different hospital was reported as normal. She was seen in the Neurology clinic two years later when she developed twitching of the face. A repeat MRI scan showed this lesion in the left middle fossa consistent with a meningioma. She has undergone treatment with radiosurgery.

a steady state can be reached within three days of dose alterations. In the United States, the FDA classify CBZ in the category of a 'black box warning' drug because of its rare side-effect of causing bone marrow suppression.

Oxcarbazepine (OXC)

OXC is the 10-keto analogue of CBZ and was developed in an attempt to reduce side-effects. It has been extensively used for treating epilepsy in Scandinavia. A number of case series have reported that it may be effective for TN. The best evidence comes from three randomised double-blind multi-centred studies that compared the use of CBZ (400-1.200mg/day) versus OXC (900-2.100mg/day). A meta-analysis of these studies reported that both drugs are equally efficacious with non-significant differences in frequency of attacks or evoked pain between the two patient groups.⁸ Statistically significant number of patients reported better tolerability of OXC over CBZ. This has also been reported when OXC was used to treat epilepsy. The results of these studies would argue for OXC to be used as the drug of choice for treating TN. The starting dose of OXC is 150mg twice a day and the daily dose can be increased by 300mg every three days up to a maximum of 2.4g. The serum sodium level should be monitored as OXC appear to have more of a tendency to cause hyponatraemia compared to CBZ.

Lamotrigine (LAM)

Lamotrigine is another anti-epileptic drug reported to be effective for alleviating TN. In a double blind, crossover study of 14 patients, LAM was compared to placebo as an add-on medication to either CBZ or phenytoin.⁹ Total pain score, global evaluation of efficacy and use of rescue medications showed superior results in the LAM treated group compared to those on placebo. The medication is well tolerated with no patient on active treatment withdraw-

ing from the study. Other case series have reported that LAM is effective for both idiopathic TN and that secondary to multiple sclerosis. Slow dose escalation is recommended with LAM as it has a tendency to cause severe skin reactions including a Stevens-Johnson reaction at its most extreme. For this reason, LAM is often used as an add-on with patients unresponsive or intolerant of OXC or CBZ.

Other anti-epileptic drugs

Gabapentin has a broad license in the UK as treatment for peripheral neuropathic pain. It is extensively used for alleviating post-herpetic neuralgia and painful diabetic neuropathy and is also used for treating many undiagnosed facial pains syndromes. No placebo controlled study of this medication for TN has been reported. Case studies and anecdotal reports indicate that it is effective. The advantage of this drug is that serious side-effects are rare and it is generally well tolerated. The dose can also be rapidly escalated by 300mg daily to a maximum total dose of 1.8 to 2.4g a day.

Similarly, pregabalin has been extensively studied for treating PHN and DPN and now has a licence for treating central neuropathic pain as well. However, no placebo controlled study of this medication for TN has been reported. Whether it has any advantages over gabapentin for TN is as yet unclear.

Clonazepam was reported in a number of case series for alleviating TN. Daily doses of 2-8mg has been used but sedation is a prominent side-effect. There have not been any placebo controlled studies of this medication and it can be used for short term pain relief in patients not controlled with other medications.

A number of case series have reported that topiramate is effective for treating TN, but a small placebo controlled crossover study of only three patients has found that it is no better than placebo. The use of this medication cannot be recommended.

Phenytoin and fosphenytoin are reported in case series to be effective for TN. The advantage of these two drugs is that fosphenytoin and to a certain extent phenytoin can be administered rapidly via loading doses. However, long term use of phenytoin for treating epilepsy is on the decline due to its numerous side-effects. There are drugs with better adverse effect profiles and more evidence for efficacy than phenytoin for TN.

Sodium valproate 1.2-2g daily has also been reported to be effective for reducing the attack frequency of TN. The advantage is that valproate can be administered intravenously and achieve therapeutic serum levels quickly. However, there have not been any placebo controlled studies and long term use of this medication, particularly among the elderly, has been reported to cause extrapyramidal side-effects.

Non-antiepileptic drugs

Of the non-epileptic drugs, the best evidence is that for baclofen for alleviating TN.¹⁰ One small placebo controlled crossover study of ten patients reported that baclofen 50-80mg daily is effective with a NNT of 1.4 (1-2.6). Baclofen has a short half life and needs to be administered three to four times a day. Most of its side-effects, like sedation, nausea, dizziness, confusion are dose dependent. Starting with 10mg three times a day, increments of 10mg daily every three days up to a maximum of 90mg daily may be used.

Pimozide and tocainide have also been reported to be effective for TN. Both of these drugs can cause cardiac arrhythmias and cannot be recommended for treating TN.

Pharmacotherapy for rapid pain control

As previously described, TN pain is very severe and distressing for the patients. Medical management using anti-epileptic drugs takes time to work because of slow dose escalation necessary to avoid side-effects. Acute treatment usually consists of local anaesthetic blocks or other even more invasive procedures. One much more promising and surprising medication that may be useful for rapid alleviation of TN is subcutaneous sumatriptan. In a double blind placebo controlled crossover study of 24 patients, 3mg subcutaneously was reported to provide pain relief for up to eight hours.¹¹ Complete pain relief was reported by 12/24 patients on sumatriptan as opposed to none of those on placebo. A follow-on study randomised 15 patients to oral sumatriptan 50mg twice a day for one week after initial pain relief with the subcutaneous preparation.¹² Once again, sustained pain relief was reported in all patients except for two who were unable to tolerate the oral sumatriptan. In four patients who relapsed while undergoing oral treatment, a repeat injection brought about pain relief of an even greater magnitude than the first injection. Sumatriptan is a medication licensed for treating migraine and has been shown to have a wide margin of safety. It should be avoided in patients with uncontrolled hypertension and severe heart disease.

This reported efficacy of sumatriptan

Table 2: Summary of starting dose and dose escalation of medications commonly used for treating TN

Drug	Starting dose	Dose Escalation	Usual Daily Dose (Maximum)
Carbamazepine	100mg twice a day	100mg every 3 days	400-1,200mg (1.6g)
Oxcarbazepine	150mg twice a day	300mg every 3 days	600-1,800mg (2.4g)
Lamotrigine*	25mg twice a day	25mg every 3 days	100-200mg (400mg)
Gabapentin	100mg three times daily	300mg daily	1.8-2.4g (2.4g)
Baclofen*	10mg three times a day	10mg every 3 days	30-90mg (90mg)

* The starting dose and dose escalation for both lamotrigine and baclofen is faster than that recommended by the British National Formulary (BNF). The reason is because TN is such a severe pain syndrome that rapid control is necessary. If patients are unable to tolerate this rapid dose escalation, a much slower regime as recommended by the BNF can be used.

implies that there may be an inflammatory element in the pathophysiology of TN. Sumatriptans is an agonist at 5HT_{1B/1D} receptors co-localised in the caudal nucleus of the trigeminal nerve and trigeminal afferent terminals innervating intracranial blood vessels. Agonists at these receptors reduce neurogenic inflammation by inhibiting trigemino-vascular activation, leading to the reversal of vascular dilatation and blocking the release of substance P and CGRP (Calcitonin Gene Related Protein) from afferent nerve terminals. It is unclear whether this is the mechanism of action for sumatriptan in TN. Sumatriptan has been reported to alleviate pain-fulfilling criteria for tension type headaches and even subarachnoid haemorrhage. However, another anti-inflammatory agent, the prostaglandin inhibitor misoprostol, has also been reported to alleviate TN pain secondary to multiple sclerosis. Further studies are necessary to determine whether all triptans and other compounds that block intracranial neurogenic inflammation have similar efficacy for TN.

Intranasal lignocaine was also reported to be effective for alleviating maxillary division TN in a placebo controlled crossover study.¹³ Twenty five patients were randomised to 2mls of 8% lignocaine or saline. The idea was to anaesthetise the sensory and parasympathetic fibres of the maxillary division of the trigeminal nerve as it passes through the sphenopalatine fossa. Ten out of the twenty patients who were administered lignocaine reported complete alleviation of their TN. In total, 23/25 of those on active treatment reported pain relief compared to 1/25 of the patients administered saline. Stinging of the nose was common in those given active treatment, which may have unblinded the study. There was only a single cycle of treatment and it is unknown whether

repeated courses will achieve the same effect. It is also unknown whether this will work in patients with TN of the ophthalmic and mandibular divisions. In spite of these limitations, intranasal lignocaine is a simple procedure with few anticipated side-effects that deserves to be assessed in larger studies.

There have been four case series of a total 16 patients reporting the benefit of botulinum toxin injections in the face for alleviating TN. Unfortunately, the diagnoses in some of these patients were not well clarified. The sites and dosage of injections vary and there is a risk of botulinum toxin causing muscle weakness when injected into the face. A properly conducted placebo controlled study is necessary to test this therapeutic option. Until then this treatment cannot be recommended for alleviating TN.

Summary

TN is a neuropathic pain syndrome characterised by severe paroxysmal facial pain. There are no pathognomonic features or tests to confirm the diagnosis and a careful clinical assessment is vital. Carbamazepine or oxcarbazepine remain the treatments of first choice for alleviating TN. Patients who are resistant or intolerant of these two medications should have a trial with gabapentin or lamotrigine. There is some evidence that baclofen and clonazepam can also help. For rapid pain control, a trial with sumatriptan is worth considering provided there are no contraindications. Surgery and microvascular decompression in particular give the best chance of long term cure but only in selected patients. Medical therapy is commonly used to control symptoms until the patients have a chance to assess their treatment options. Well designed placebo controlled studies are necessary to evaluate newer medications for alleviating TN, either alone or in combination.

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