



## Review Article

## Management of Trigeminal Neuralgia

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## ABSTRACT

Trigeminal Neuralgia (TN) is orofacial pain restricted to one or more divisions of the trigeminal nerve. Attacks of intense, electric shock-like facial pain can occur without warning or be triggered by touching specific areas of the face by movements, brushing, laughing or following emotional stimuli. The exact cause of trigeminal neuralgia is not fully elucidated, a blood vessel is often found compressing the nerve. TN dramatically reduces the quality of life of affected individuals not only due to pain attacks but also to other disease-associated comorbidities, such as anxiety and depression. The Therapy used is often conservative with variable results

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## 1. Introduction

Trigeminal neuralgia (TN), is rare nerve disorder, known as *tic douloureux*, is a painful disorder of a nerve in the face called the trigeminal nerve or fifth cranial nerve. There are two trigeminal nerves, one on each side of the face. These nerves are responsible for detecting touch, pain, temperature and pressure sensations in areas of the face between the jaw and forehead. TN may have a significant impact upon quality of life due to the associated depression and anxiety. TN may have a significant impact upon quality of life due to the associated depression and anxiety. Severe attacks may cause an inability to speak or eat.<sup>1</sup>

The estimated annual incidence of TN is 12.6/100,000 persons/year and its incidence increases with age. TN was more prevalent (52.4%) in rural population than urban population (47.6%). Although the peak onset of TN occurs between 50 and 70 years, it can also occur in children.<sup>2</sup> The diagnosis of TN is usually based on the characteristic clinical picture. The key feature is a sudden and severe lancinating pain, usually unilateral, precipitated by touching facial zones. This pain occurs

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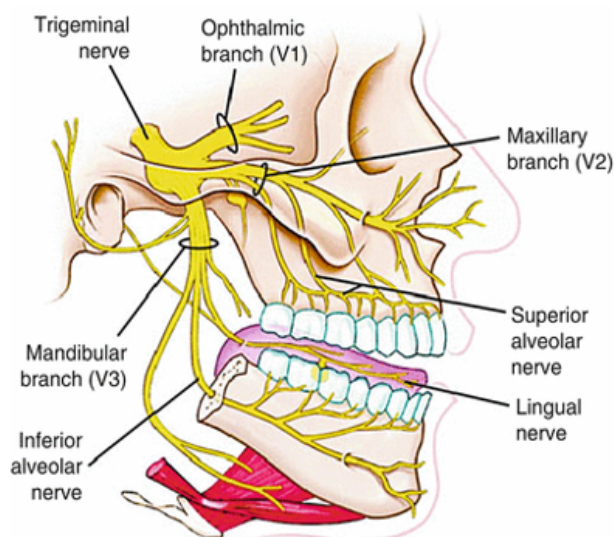
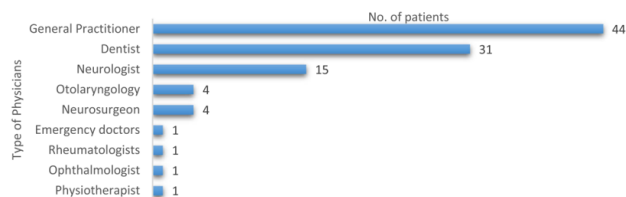
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Fig. 1: Course and divisions of Trigeminal nerve

in paroxysms, within the trigeminal nerve distribution; typically involving the maxillary nerve (V2) or mandibular nerve (V3) distribution and lasts for a fraction of a second

to 2 minutes.<sup>3</sup> Histamine level increases significantly ( $P < 0.05$ ) in acute TN. The degranulating mast cells release biologically active substances, such as histamine, serotonin and others, into the intercellular space. Hence, histamine release and accumulation in the trigeminal nerve during a local allergic reaction plays an important role in the pathogenesis of neuralgia.<sup>4</sup> The primary pathological factor in trigeminal neuralgia is demyelination of sensory axons due to sustained (static) or pulsatile micro vascular compression of the trigeminal root. The etiological factors are certain benign and vascular anomalies may compress the trigeminal nerve root, granulomatous and non-granulomatous infections involving the fifth cranial nerve, Cavities found in the alveolar and jaw bones, multiple sclerosis, post traumatic neuralgia, arteriovenous malformations, aneurysms and vascular compression may also result in trigeminal neuralgia. aneurysms of the internal carotid artery, Post herpetic neuralgia and anomaly of superior cerebellar artery.<sup>5</sup> Individually the cases of TN are seen by general practitioners and dentists in more significant numbers. TN is frequently misdiagnosed with toothache, so there is need to educate the medical practitioners and public to avoid un-necessary tooth extractions.



**Fig. 2:** Diagnosis of symptoms of TN by medical faculty

## 1.1. Managing Trigeminal Neuralgia

### 1.1.1. Medical Treatment

**Table 1:** Therapeutic options in Trigeminal Neuralgia

First line	Carbamazepine (600-1200 mg/day) or oxcarbazepine (600-1800 mg/day)
Second line	Add-on or switch to lamotrigine (400 mg/day) Baclofen (40-80 mg/day) Pimozide 2 to 12mg/day)
Surgery	Percutaneous Procedures on the Gasserian ganglion Percutaneous glycerol rhizolysis Radiofrequency thermocoagulation Balloon compression Gamma knife radiosurgery Microvascular decompression

### 1.1.2. First line Therapy

**Carbamazepine (CBZ) and oxcarbazepine (OXC)** are the first-choice medical treatment in TN. They have the same mechanism of action, the blockade of voltage gated sodium channel in a frequency dependent manner, resulting

in the stabilization of hyperexcited neural membranes and in the inhibition of repetitive firing. The initial dosage of Carbamazepine is 200-400mg daily until freedom from pain is achieved (normally at 200mg 3-4 times daily). In the majority of patients a dosage of 200mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600mg daily may be needed. Oxcarbazepine is an acceptable alternative to carbamazepine, which may have provided pain relief but has caused unacceptable adverse effects. Better tolerability can also be considered an advantage over carbamazepine. Oxcarbazepine can be started at 150 mg twice daily. The dose can be increased as tolerated in 300 mg increments every third day until pain relief occurs. Maintenance doses range between 300-600 mg twice daily. OXC should be preferred over CBZ because of its proven efficacy and excellent side effect profile in children, adolescents,<sup>6</sup> The first double-blind, crossover trial to evaluate the efficacy of oxcarbazepine (900–2100 mg/ day) versus carbamazepine (400–1200 mg/ day) reported a comparable analgesic effect between the two treatments, leading to the conclusion that oxcarbazepine offers an alternative to carbamazepine in the treatment of TN. **Advantages of Oxcarbazepine Over Carbamazepine** in Neuropathic Pain are: No monitoring of hematologic parameters required, Fewer drug-drug interaction and Improved tolerability Carbamazepine possesses side effects like dizziness, ataxia, drowsiness and reduction of alertness occurs and these effects seem to be increased with stable doses on doses.<sup>7</sup>

Efficacy and safety of eslicarbazepine in TN patients was first assessed in 2018. The results of this open-label study suggested that eslicarbazepine is an effective, safe, and well-tolerated treatment for TN. A small dose of eslicarbazepine (400 mg daily) provided excellent control of the TN and the incidence of hyponatremia of less than 1%.. Other advantages of eslicarbazepine include better safety profile, a reduced potential to act on cytochrome P450 enzymes and a longer elimination half-life of 20 to 24 h, which allows single daily dosing.<sup>8</sup>

### 1.1.3. Second-line therapy

Second-line treatment is based on very little evidence. Three drugs are included in this class - lamotrigine, baclofen, and pimozide. Each drug has been studied in few trials.

### 1.1.4. Lamotrigine

Has a bimodal mechanism of action, it inhibits release of the excitatory neurotransmitter glutamate, most likely by inhibiting voltage-sensitive sodium channels, and is antagonistic at neuroexcitatory N-methyl-d-aspartate receptors. It can also act at calcium channels. The initial dose of lamotrigine is 25 mg twice daily, and can be increased gradually to a maintenance dose of 200-400 mg/d in 2 divided doses. The dosage required for adequate pain

relief varied widely from 100-400 mg/d.<sup>9</sup>

### 1.1.5. Baclofen

Baclofen is a  $\gamma$ -aminobutyric acid (GABA) agonist approved for the treatment of spasticity and commonly used in the management of many types of neuropathic pain. The initial dose of Baclofen is 10 mg/d for 3 days, which can be increased to 10-20/d every 3 days if needed. The maximum tolerated dose is 60-80 mg/d, administered 3-4 times per day. Baclofen has significantly exhibited analgesic efficacy, all groups, as a whole, were improved by 68.61 %. These results substantiate that baclofen is useful in the treatment of trigeminal neuralgia and other painful conditions.<sup>10,11</sup>

**Pimozide** has potential for serious side effects, such as tardive dyskinesia, this drug should be reserved for patients who failed other medical approaches. Pimozide is a highly selective blocker of dopamine D<sub>2</sub> receptors in the limbic system, the corpus striatum and the pituitary. It also blocks the alpha-1-adrenoceptors and serotonergic receptors, although to a lesser extent. Pimozide treatment produced greater reduction in trigeminal neuralgia symptoms than carbamazepine treatment in resistant cases Pimozide can prolong the cardiac QT interval, but not necessarily in an abnormal range<sup>10,11</sup>

### 1.1.6. Third-line therapy

The newer AEDs tested within the past few years are gabapentin, pregabalin, topiramate, and levetiracetam

### 1.1.7. Gabapentin

Is often used to treat neuropathic pain; however, a substantial proportion of patients find this drug is partially effective. Gabapentin was effective in relieving or reducing paroxysmal pain. Onset of pain relief in most cases occurred within 1 to 3 weeks. The range of effective stable daily dosing varied greatly among patients, from 100 to 2,400 mg divided 3 times a day, with a mean of 930 mg. Unlike carbamazepine and some other antiepileptic drugs that may suppress ectopic electrogenesis by blocking Na channels, 8 gabapentin does not block Na channels. Gabapentin has been shown to interact with the 2subunit of voltage-dependent Ca<sub>2</sub> channels and to increase the concentration and possibly also the rate of synthesis of gamma -aminobutyric acid (GABA) within the brain. Gabapentin has also been shown to be effective in combination with carbamazepine or lamotrigine in idiopathic trigeminal neuralgia. Gabapentin is considered mostly under category of third line drug.<sup>12,13</sup>

### 1.1.8. Pregabalin

Appears to have similar efficacy to that of amitriptyline and gabapentin for neuropathic pain. Pregabalin (PGB) targets the alfa2-delta subunit of voltage gated calcium channels and exerts its pharmacological effect by reducing the release

of excitatory neurotransmitters from synaptic terminals. Pregabalin (150-600 mg/d) was proved to be effective in reducing TN pain by more than 50-74% of patients,<sup>14</sup>

### 1.1.9. Topiramate

The exact mechanism of action of is unknown. However, its pain-modulating effect might be related to its property of blockage of the voltage-gated sodium channel and an augmentation of GABA activity by binding to a non benzodiazepine site on the GABA<sub>A</sub> receptor. Topiramate (100-400 mg/d) was found effective in 75% of patients.

### 1.1.10. Botulinum toxin A

The BTX-A's mechanism of analgesic effect is still unclear, but it is postulated it causes local release of anti-nociceptive neuropeptides such as substance P, glutamate, and calcitonin-gene related peptide, inhibiting central and possibly peripheral sensitization, or mucosal injection of BTX-A effective for adult TN patients, significant benefit over placebo. Response was achieved in approximately 70-100%

**Lacosamide** in patients with refractory TN, a majority of the patients responded at least initially, despite multiple previous medication trials and surgical procedures in some. LCS was well tolerated and should be considered as a treatment option in chronic TN.

## 1.2. Mode of action

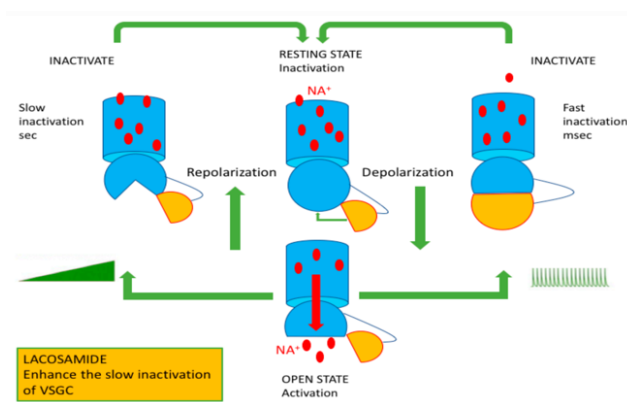


Fig. 3: Lacosamide mode

Enhancing slow inactivation of VGSC peripheral (Nav 1.7 and Nav 1.3) and central (Nav1.7), Stabilization of hyper excitable neuronal membranes and Inhibition of neuronal firing [17 a,b]

### 1.3. Levetiracetam

It is thought to target highvoltage, N-type calcium channels as well as the synaptic vesicle protein 2A (SV2A); by this, it impedes impulse conduction across synapses. Its

evidence in TN is less. 67% of those users who reviewed Levetiracetam reported a positive effect, while 17% reported a negative effect. There was a significant tendency towards improvement in pain severity compared with baseline with higher doses of 4,000 mg/day. (Dose range 1000 to 4000mg/d).<sup>15</sup>

#### 1.4. Vixotrigine

Is a voltage- and use-dependent sodium channel blocker. The 150 mg TID dose regimen was selected based on results from the Phase II study in patients with TN. The results of phase II multicentre trial were satisfactory. In Phase III trials, patients will receive vixotrigine 150 mg orally three times daily in the dose-optimization and open-label periods. The primary endpoint of studies is the proportion of participants classified as responders at Week 12 of the double-blind period. Secondary endpoints include safety measures, quality of life and pharmacokinetics.<sup>16</sup>

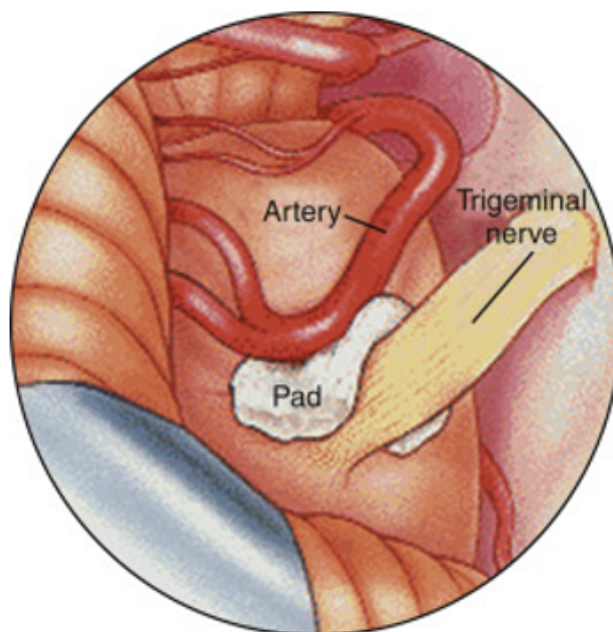
#### 1.5. Stem cell transplantation

Is a new approach for repairing damaged nervous system-induced neuropathic pain syndromes rather than simply providing palliation. Stem cells offer a totipotent cellular source for replacing injured or lost neural cells. They also represent a delivery modality for trophic factors for the injured nerve. Lesions in TN can be repaired through the injection of fat containing Adipose-Derived Stem Cells (ADSC), though this is under evaluation. MSCs (mesenchymal stem cells) have been reported to exert an anti-inflammatory effect through cytokine release that may combat the pathological inflammation involved in neuropathic pain, and have been shown to play an important role in nerve healing and regeneration. That the use of adipose-derived MSCs in an animal model of hind paw neuropathic pain resulted in a decrease in the pro-inflammatory cytokine interleukin (IL)-1 $\beta$  in the lesioned nerve.<sup>17,18</sup>

#### 1.6. Surgical manoeuvres

Surgical therapy should be considered if medical treatment fails or cannot be tolerated. Prior to considering surgery, all trigeminal neuralgia patients should have a MRI, with close attention paid to the posterior fossa. Regular surgical procedure for TN is neurectomy. It has been reported to be successful in 88.2% patients. Balloon compression is another method used to treat TN, for which initial pain relief has been reported in 93% patients. Surgical procedures may be percutaneous or open. Percutaneous techniques include glycerol injection, balloon compression, radiofrequency rhizotomy, and gamma knife stereotactic radiosurgery. The gamma knife utilises 85 Gy dose for TN providing a more durable pain relief. Open techniques include partial trigeminal rhizotomy and microvascular

decompression (MVD).as shown in Figure 4.



**Fig. 4:** Microvascular decompression (MVD).

The offending vessel is most often the superior cerebellar artery (75%) or the anterior inferior cerebellar artery (10%). In addition, a vein may contribute to the compression (68%), and sometimes it is the only compressing vessel (12%). MVD was found to be a safe and effective procedure to relieve typical TN in patients of all ages. MVD surgery is associated with an approximately 80% chance of pain freedom among carefully selected patients. The effect lasts for more than 10-20 years with a recurrence rate of 10%. The surgical procedures can cause stroke and meningitis.<sup>19-21</sup>

## 2. Conclusion

Trigeminal neuralgia remains challenge to neurologists. Idiopathic TN occurs without apparent cause. Classical TN is caused by vascular compression of the trigeminal nerve root. Secondary TN is the consequence of a major neurologic disease, e.g., a tumor of the cerebellopontine angle or multiple sclerosis. Trigeminal neuralgia cannot always be cured, there are many options available to alleviate the debilitating pain. Normally, anticonvulsive medications are the first treatment choice. First-line therapy is CBZ (600-1200 mg/day) or OXC (600-1800 mg/day), switching to or adding-on lamotrigine (200-400 mg/day), pregabalin (150-600 mg/day), gabapentin (1800-4200 mg/day) or topiramate (100-400 mg/day) may also be considered. If the combination therapy fails, a switch to baclofen (40-80 mg/day) can be tried. Surgery can be an effective option for those who become unresponsive to

medications Complementary techniques like acupuncture, nutritional therapy, and meditation may also help with some symptoms. Combination of multidisciplinary therapies do provide sustainable relief.

### 3. Conflict of Interest

None.

### 4. Source of Funding

None.

### References

- Guido CP, Santarlasci V, Gallo O, Mediatì RD, Cristofaro G. Trigeminal neuralgia complicating a syndromic craniosynostosis treated with acupuncture: a case report. *Int J Complement Altern Med*. 2020;13(5):193–5. doi:10.15406/ijcam.2020.13.00515.
- Chaurasia A, Katheriya G, Khan N, Iqbal J. Prevalence of trigeminal neuralgia in Indian population visiting a higher dental care center in North India. *Natl J Maxillofac Surg*. 2019;10(2):195–9. doi:10.4103/njms.njms\_64\_18.
- Raimundo R, Rego I, Veiga A. Image Diagnosis: An Uncommon Cause of Painful Trigeminal Neuropathy. *Perm J*. 2020;24(19):106.
- Sabalys G, Juodzbaly G, Wang HL. Aetiology and Pathogenesis of Trigeminal Neuralgia: a Comprehensive Review. *J Oral Maxillofac Res*. 2012;3(4):1. doi:10.5037/jomr.2012.3402.
- Kaur B. Trigeminal neuralgia and its management. *Int Dent J Stud Res*. 2016;4(2).
- Al-Quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia. The pharmacological and surgical options. *Neurosci*. 2015;20:107–14. doi:10.17712/nsj.2015.2.20140501.
- Carrazana E, Mikoshiba I. Rationale and Evidence for the Use of Oxcarbazepine in Neuropathic Pain. *J Pain Symptom Manag*. 2003;25(5):S31–5. doi:10.1016/s0885-3924(03)00067-8.
- Sanchez-Larsen A, Sopolana D, Diaz-Maroto I, Perona-Moratalla AB, Gracia-Gil J, García-Muñozguren S, et al. Assessment of efficacy and safety of eslicarbazepine acetate for the treatment of trigeminal neuralgia. *Eur J Pain*. 2018;22(6):1080–7. doi:10.1002/ejp.1192.
- Shaikh S. Lamotrigine for trigeminal neuralgia: Efficacy and safety in comparison with carbamazepine. *J Chinese Med Assoc*. 2011;74(6):243–9.
- Oomens MAEM, Forouzanfar T. Pharmaceutical Management of Trigeminal Neuralgia in the Elderly. *Drugs Aging*. 2015;32(9):717–26. doi:10.1007/s40266-015-0293-6.
- Green MW, Selman JE. The Medical Management of Trigeminal Neuralgia. *Headache: J Head Face Pain*. 1991;31(9):588–92. doi:10.1111/j.1526-4610.1991.hed3109588.x.
- Ta PP, Dinh HQ, Nguyen K, Lin S, Ong YL, Ariyawardana A, et al. Efficacy of gabapentin in the treatment of trigeminal neuralgia: A systematic review of randomized controlled trials. *Invest Clin Dent*. 2019;10(4).
- Cheshire WP. Defining the role for gabapentin in the treatment of trigeminal neuralgia: A retrospective study. *J Pain*. 2002;3(2):137–42. doi:10.1054/jpai.2002.122944.
- Hamasaki T. Pregabalin as a salvage preoperative treatment for refractory trigeminal neuralgia. *J Clin Neurosci*. 2017;.
- Jorns TP, Johnston A, Zakrzewska JM. Pilot study to evaluate the efficacy and tolerability of levetiracetam (Keppra®) in treatment of patients with trigeminal neuralgia. *Eur J Neurol*. 2009;16(6):740–4. doi:10.1111/j.1468-1331.2009.02585.x.
- Kotecha M, Cheshire WP, Finnigan H, Giblin K, Naik H, Palmer J, et al. Design of Phase 3 Studies Evaluating Vixotrigine for Treatment of Trigeminal Neuralgia. *J Pain Res*. 2020;13:1601–9. doi:10.2147/jpr.s247182.
- Collet C, Haen P, Laversanne S, Brignol L, Thiéry G. Trigeminal neuralgia: A new therapy? *Med Hypotheses*. 2013;81:1088–9. doi:10.1016/j.mehy.2013.10.010.
- Vickers ER, Karsten E, Lilischkis R, Flood J. A preliminary report on stem cell therapy for neuropathic pain in humans. *J Pain Res*. 2014;7:255–63. doi:10.2147/jpr.s63361.
- Krafft RM. Trigeminal Neuralgia. *Am Fam Physician*. 2008;77(9):1291–6.
- Sivakanthan JJS, Gompel PV, Alikhani H, Loveren V. Surgical Management of Trigeminal Neuralgia: Use and Cost-Effectiveness From an Analysis of the Medicare Claims Database. *Neurosurg*. 2014;75(3):220–6.
- Cohen. Microvascular Decompression for Trigeminal Neuralgia. *Neurol Atlas*. 2020;.

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