International Journal of Trend in Scientific Research and Development (IJTSRD)
Volume 9 Issue 4, Jul-Aug 2025 Available Online: www.ijtsrd.com e-ISSN: 2456 – 6470

Trigeminal Neuralgia: Diagnostic Challenges and Evolving Therapeutic Strategies

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ABSTRACT

Trigeminal Neuralgia (TN) presents a unique clinical challenge due to its unpredictable course, diagnostic complexity, and variable response to treatment. Understanding its underlying mechanisms has advanced significantly over time, opening the door for both improved diagnostic techniques and creative treatment approaches. This study offers a thorough synthesis of the most recent data on TN, with an emphasis on the combination of cutting-edge imaging techniques, developing pharmaceutical therapies, and new non-invasive therapies. This article attempts to close the gap between conventional management and innovative approaches by examining the complex nature of TN, from its genetic and electrophysiological foundations to clinical decision-making. The limits of existing therapy paradigms and the potential for patient-specific, tailored care are specifically discussed. We emphasize the value of a multidisciplinary approach in maximizing results for people with this incapacitating pain disease by using this holistic viewpoint.

KEYWORDS: *Trigeminal neuralgia, electrophysiological testing, neurovascular compression, diffusion tensor imaging, neuromodulation*

How to cite this paper: Khamani Pedaprolu | Narender Boggula | L Satyanarayana | Mandepudi Lakshmi Chandini "Trigeminal Neuralgia: Diagnostic Challenges and Evolving Therapeutic Strategies" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-9 | Issue-4, August 2025, pp.43-49, URL: www.ijtsrd.com/papers/ijtsrd97198.pdf

IJTSRD97198

INTRODUCTION

Trigeminal neuralgia (TN) is a facial pain disorder characterized by paroxysmal, sudden, recurrent, unilateral shock-like pain localised to the somatosensory distribution of the trigeminal nerve. These painful episodes are often triggered by innocuous stimuli like light touch, chewing, swallowing, talking, and brushing teeth, leading to profound impairment of day-to-day activities. About 80-90% of Trigeminal neuralgia arises due to neurovascular compression at root entry zone of the trigeminal nerve, secondary causes include central nervous system lesions such as meningioma, acoustic neuroma, epidermoid cyst, arteriovenous malformation, or saccular aneurysm, as well as systemic conditions like multiple sclerosis (MS), Diabetes mellitus, herpes simplex virus (HSV). A minor portion of cases remains idiopathic [1].

Trigeminal neuralgia is a rare craniofacial pain disorder with reported incidence of approximately 29.5 per 100,000 person-years in a population-based study from Central Sweden. Similarly, an electronic health record study in Korea reported an overall incidence rate of 4.7 per 100,000 person-years and showed TN incidence increases steadily with age and is highest in individuals over 60 years of age. A hospital-based study conducted in North India tertiary dental care reported that the prevalence of TN among patients with orofacial pain is approximately 0.03-0.3%with a higher involvement of the mandibular (V3) division, followed by the maxillary (V2) division. these studies also state that TN predominantly affects the female population more than the male population, with a female-to-male ratio ranging from 15:1 to 17:1. The lifetime incidence of TN I is estimated to range between 0.16%-0.3%. According to The International Classification of Headache Disorders, 3rd edition (ICHD-3), trigeminal neuralgia is classified into three types: a) Classical trigeminal neuralgia, b) Secondary trigeminal neuralgia, c) Idiopathic trigeminal neuralgia [1-3].

Trigeminal neuralgia, whether classical, secondary, or idiopathic, often results from vascular or tumor compression at the root entry zone of the trigeminal nerve. The root entry zone is highly vulnerable to compression due to its transition from peripheral Schwann cell myelination to central oligodendroglia myelination. This results in inflammation leading to myelin erosion and disintegration. Surgical biopsies confirm evidence of , demyelination, and remyelination of the injured nerve and direct contact between demyelinated axons in compressed area. These demyelinated afferents become hyperexcitable, generating ectopic impulses that cause spontaneous pain. Ephaptic transmission between Aβ and Aδ demyelinated fibres may cause touch evoked pain.

A key contributor to neuroinflammatory process is transient receptor potential ankyrin type-1 (TRPA1) ion channels. By oxidative and inflammatory stress signals, TRPA1 channels and satellite glial cells get activated and release pro-inflammatory mediators such as cytokines and neuropeptides which promote peripheral sensitization ultimately heightening trigeminal ganglion excitability, and intensifying pain signalling. Prolonged peripheral input and TRPA1 activity result in central sensitization, contributing to chronic pain. In idiopathic TN, possible pathologies include Mutations or altered expression in sodium channels such as Nav1.3 and Nav1.7 and non-multiple sclerosis brainstem lesions [3-5].

In this review, we discussed about the advancements in diagnostic technologies, pharmacological innovation, surgical interventions, integrating innovations and emerging non-pharmacological interventions. In the conclusion possible challenges and future prospectives will be summarised.

Diagnosis of TN

Clinical features of TN are essential for accurate diagnosis and understanding how it affects patients' quality of life. According to ICHD-3, TN is diagnosed based on specific criteria:

A. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond,1 and fulfilling criteria B and C

B. Pain has all the following characteristics:
- Pain lasting from a fraction of a second to two minutes.
- Severe intensity.
- Electric shock-like, shooting, stabbing, or sharp pain.

C. triggered by innocuous stimuli within the affected trigeminal distribution

D. The symptoms can't be explained better by another diagnosis under ICHD-3.

Although the ICHD-3 criteria provide a well-defined framework for diagnosing TN, it remains challenging to diagnose in clinical settings, due to overlapping symptoms with other facial pain disorders. Hence, Differential diagnosis is essential to distinguish TN from similar conditions before initiating treatment several disorders can mimic the characteristic paroxysmal pain of TN and should be carefully excluded. Differential diagnosis in trigeminal neuralgia includes;

- **Glossopharyngeal neuralgia -** differs from TN as it causes stabbing pain in the tongue, pharynx, or ear triggered by swallowing, coughing, or sneezing.
- **Painful posttraumatic trigeminal neuropathy -** causes TN like pain following trauma, with sensory gain and loss in affected nerve.
- **Persistent idiopathic facial pain -** characterized by constant, dull, ching pain**.**
- **Painful trigeminal neuropathy attributed to acute herpes zoster** - includes sensory alterations, tingling, and searing, stabbing pain following a herpes rash.
- **Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (SUNA), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or paroxysmal hemicrania** - symptoms include autonomic symptoms, frequently side-shifting, and brief, acute orbital or temporal pain.
- **Cluster headache -** characterized by autonomic symptoms, restlessness, and persistent orbital or temporal pain that frequently alternates between sides.
- **Primary stabbing headache -** features Temporary, stabbing scalp pain without autonomic symptom.
- **Cracked tooth -** chewing hard foods causes intense, evoked pain when a tooth is cracked.
- **Caries or pulpitis -** Prolonged discomfort brought on by hot, cold, or sweet stimuli is a symptom of dental caries or pulpitis.
- **Secondary TN (due to multiple sclerosis or tumours**) - While secondary TN (caused by tumours or MS) can resemble primary TN, it is more frequently bilateral, manifests earlier, and involves neurological impairments.

As a result, the development of advanced imaging and neurophysiological methods has become crucial to enhance diagnostic accuracy and detect underlying secondary causes [6,7].

Diagnostic technologies

High-resolution MRI techniques (3D-FIESTA-c and 3D-TOF-MRA): MRI technologies play an important role in the non-invasive diagnosis and preoperative evaluation of TN by significantly delivering high-definition visualization of craniofacial neurovascular anatomy with image resolution and soft tissue contrast. Advanced steady-state imaging techniques such as 3D-FIESTA-c (Fast Imaging Employing Steady-State Acquisition-Constructive Interference in Steady State) help detect neurovascular compression (NVC) by showing difference between CSF from nerves, vessels, and dura mater. Vascular imaging such as 3D-TOF-MRA (Time-of-Flight Magnetic Resonance Angiography) it complements 3D-FIESTA-c by detecting fast-moving small blood vessels to enhance detection accuracy of arterial compression.

MRVE imaging technology (Magnetic Resonance Virtual Endoscopy): MRVE helps by differentiating small arteries and veins, especially when standard MRI sequences fail. MRI also helps in detecting secondary causes like tumours, Cysts and Demyelinating lesions (in multiple sclerosis) these are essential for excluding other possible or coexisting conditions. diagnosing TN becomes easier when MRI results are combined with symptoms and patient details. This helps guide personalised treatment plans and point to possible directions for further study.

Diffusion tensor imaging (DTI): The functional MRI method is called Diffusion Tensor Imaging enables detection of microstructural changes (such as demyelination, neuroinflammation, or axonal injury) in trigeminal nerves affected by trigeminal neuralgia. Within DTI, Fractional Anisotropy (FA) serves as a key quantitative metric that evaluates the directionality of water diffusion in tissues, especially in white matter tracts like nerves. A significant reduction in fractional anisotropy (FA) values was observed on the painful side, suggesting structural damage compared to the unaffected side. While Conventional MRI fails to detect these microstructural anomalies, DTI demonstrates superior sensitivity making it a valuable diagnostic tool for identifying subclinical nerve damage in TN.

Inflammatory biomarkers: Key cytokines -SCGF-β, IL-4, and IL-16 are identified to be significantly involved in TN. SCGF-β enhances the proliferation and differentiation of immune cells that produce pro-inflammatory cytokines, thereby increasing neuroinflammation in the trigeminal nerve, and IL-4 promotes Th2 cell differentiation shifting the immune response towards inflammation and potential tissue damage, thus contributing to trigeminal neuralgia pathology, while IL-16 acts as a chemoattractant for CD4+ T cells, potentially drawing regulatory immune cells that help suppress excessive inflammation and protect against nerve damage. In TN, the acute-phase protein C-reactive protein (CRP) demonstrated a protective function by assisting in the removal of inflammatory debris, stimulating the complement system, and lowering chronic neuroinflammation. Although correlations were noted, the exact biological processes by which CRP, IL-4, IL-16, and SCGF-β affect TN are still unknown and need more experimental proof.

Electrophysiological testing: Electrophysiological tests help in distinguishing classical TN from symptomatic cases caused by lesions like tumours or multiple sclerosis. These tests evaluate the trigeminal nerve pathways' integrity and conduction, especially the sensory Fibers. Blink Reflex Test assesses the facial (efferent) and trigeminal (afferent) nerve pathways in order to identify anomalies in nerve conduction. whereas Inhibitory Masseter Reflex detects disturbances in the trigeminal motor pathway by measuring the inhibitory reflexes in the jaw-closing muscles. The functional correlation between structural anomalies and electrophysiological data is a useful addition to MRI. These tests help determine whether pain in patients with overlapping or ambiguous symptoms is indeed neuropathic or originates from another source. These tests also help clinicians determine the severity and extent of nerve involvement, which is critical for surgical or interventional decisions.

Quantitative sensory testing: In TN patients, QST identifies sensory abnormalities that are often overlooked during routine neurological exams. QST is a trustworthy method for evaluating sensory disturbances in TN because it offers objective, measurable sensory data. It captures the entire range of sensory abnormalities by identifying hypoesthesia (reduced sensation) and hyperalgesia (increased pain response). QST suggests deeper pathophysiological involvement, broadening the diagnostic perspective of TN beyond a purely peripheral nerve disorder. By identifying bilateral sensory anomalies, it shows that changes are taking place on both sides of the body. Systemic sensory changes, especially in areas like the hands, suggest widespread engagement of the sensory system. According to the QST data, TN affects more than just the peripheral trigeminal nerve, demonstrating the central nervous system's flexibility.

It helps identify central sensitization pathways by linking malfunctioning sensory processing to the perception of persistent pain in TN. Through the integration of peripheral and central diagnostic findings, QST facilitates more accurate classification and offers a more comprehensive understanding of TN pathophysiology [8-12].

Current and emerging therapeutic strategies in management of trigeminal neuralgia

Management of TN begins with a detailed collection of history focusing on onset (trauma, herpes), pain characteristics (intensity, quality, duration, and location), and associated neurological or autonomic symptoms. A focused neurological exam should assess trigeminal sensory function and look for signs suggestive of multiple sclerosis or cerebellopontine angle tumours. Essential investigations include ECG, blood tests (electrolytes, liver and kidney function), and MRI of the brain and brainstem are needed to rule out secondary causes. In order to differentiate between primary and secondary TN, the diagnosis must satisfy predetermined criteria. Consideration should be given to differential diagnoses, including dental or other facial pain syndromes. The first line therapy (Sodium channel blockers such as carbamazepine or oxcarbazepine) is given with cautious tapering and gradual titration. Alternative medications (Lamotrigine, baclofen, pregabalin, or gabapentin) can be added when there is insufficient response. if medication fails, surgical options (microvascular decompression or ablative procedures) may be considered. Long-term follow-up is essential to monitor complications and requires multidisciplinary coordination among neurology, neurosurgery, and neuroradiology specialists.

Phenytoin was first prescribed medication for the treatment of trigeminal neuralgia in 1942, and is currently administered intravenously in refractory TN cases. Later, carbamazepine, launched clinically in 1959, demonstrated superior efficacy and rapidly became the first-line therapy for TN. Three trials that were placebo-controlled, the largest of which involved 77 patients, supported this. Since the early 1960s, carbamazepine has remained the gold standard in TN management [13-115].

First-line treatment

The first-line antiepileptic medications used to treat TN include carbamazepine (CBZ) and oxcarbazepine (OXC). Carbamazepine work by frequency-dependently blocking voltage-gated sodium channels, which prevents neurons from firing quickly and repeatedly, this mechanism makes them very effective in people with episodic (paroxysmal) pain. However, there is a significant chance of major adverse effects from CBZ, such as liver failure, aplastic anemia, and hyponatremia, which makes routine monitoring of liver function tests, CBC, and serum sodium necessary. Hormonal alterations include decreased levels of testosterone and thyroxine and increased levels of sex hormone-binding globulin may also result from it. Nausea, ataxia, and drowsiness are typical adverse effects.

In contrast to carbamazepine, which targets L-type channels, oxcarbazepine and its active metabolite (MHD) block voltage-gated sodium channels to treat trigeminal neuralgia. MHD specifically blocks N/P- and R-type calcium channels. Because it selectively induces enzymes and has fewer medication interactions than carbamazepine, it is better tolerated, however hyponatremia happens more often. In patients with the HLA-B*1502 allele, it carries the same risk of SJS/TEN as carbamazepine. Hence, these medications frequently cause tachyphylaxis, which is a decreasing responsiveness to a drug with time, requiring greater doses that raise the possibility of side effects [16,17].

Second-line treatment

Despite having limited evidence bases and usually being used in combination regimens, second-line medications can be useful alternatives in cases when first-line treatments are unsuccessful or poorly tolerated. Second-line agents include lamotrigine, gabapentin, pimozide, pregabalin, baclofen , phenytoin and fosphenytoin, clonazepam, valproate.

Lamotrigine (LTG) stabilizes the membrane and prevents excitatory neurotransmitter release by acting on voltage-sensitive sodium channels. The two most dangerous adverse effects of lamotrigine are Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which are uncommon but potentially fatal skin reactions. Although they might appear at any point throughout treatment, these usually happen when therapy first begins. Skin rash, headache, and dizziness are some frequently reported side effects that are frequently dose-dependent. Because there is a chance that a rash could develop into SJS or TEN, it should be stopped right away.

Pregabalin and gabapentin work by inhibiting the voltage-gated calcium channel's α2δ auxiliary subunit, which lessens neuronal hyperexcitability. Gabapentin considered less effective than oxcarbazepine but, it considerably lowers the number of pain days when used with ropivacaine blocks. Sedation, light-headedness, cognitive clouding (sometimes known as "foggy thinking"), and in rare cases, peripheral edema or weight gain are among the adverse effects. When administered as an adjuvant medication, pregabalin exhibits fewer adverse effects

and is particularly beneficial in cases where carbamazepine is not working. Sedation, light-headedness, and lower limb edema are typical side effects; thrombocytopenia is seen seldom.

Baclofen inhibits the release of excitatory neurotransmitters by acting as an agonist on the $GABA_B$ receptor to inhibit mono- and polysynaptic neuronal transmission. Phenytoin and fosphenytoin reduces the rate of repeated firing by blocking voltage-dependent membrane sodium channels that enhance action potentials. It has demonstrated notable effectiveness in lowering the number of daily spasms and the severity of pain in TN patients. When combined with either phenytoin or carbamazepine, baclofen proved to be more effective than when administered alone.

Pimozide, an antipsychotic that inhibits serotonin and dopamine receptors, has demonstrated a significant level of effectiveness in lowering TN pain. Its use in TN is restricted and infrequent, despite its potential efficacy, because of its substantial adverse effect profile, which includes extrapyramidal symptoms, neuroleptic malignant syndrome, and cognitive deficits.

Levetiracetam, an anticonvulsant that inhibits presynaptic calcium channels and binds to SV2A, may lessen neuronal excitability in TN. Although it's not frequently used as a monotherapy, it has promise as an adjuvant, particularly in patients that are refractory. When clonazepam, a strong and long-acting benzodiazepine that functions as a positive allosteric modulator of $GABA_A$ receptors, was tested on TN patients who were not responding to carbamazepine, 40% of them experienced total pain relief. Significant adverse effects include ataxia, drowsiness, memory loss, and an elevated risk of dementia with prolonged use. In certain people, paradoxical behaviours like anger and aggressive conduct might also happen. The anticonvulsant valproate, which increases GABA levels and blocks voltage-gated sodium channels, has demonstrated a moderate level of effectiveness in treating TN. Valproate does, however, include black box warnings for teratogenicity, pancreatitis, and hepatotoxicity. While thrombocytopenia, increased liver enzymes, and hyperammonemia are more serious adverse effects, common side effects include weight gain, hair loss, and nausea.

Misoprostol, a prostaglandin E1 analogue, has shown more than 50% reduction in pain frequency and intensity in the majority of patients with multiple sclerosis-related TN particularly those who are not responding to conventional treatments. Adverse effects were mostly mild, but one patient stopped due to severe menorrhea. Its efficacy is likely linked to the decrease in inflammation caused by multiple sclerosis [3,18-20].

Emerging therapeutic medications

Although the best course of treatment for TN has not yet been determined, new medicines and repurposed older medications are being investigated to improve outcomes. New products that are currently being used are: Dextromethorphan, a non-competitive NMDA receptor antagonist with antitussive and anticonvulsant effects works through the regulation of glutamatergic neurotransmission, which contributes to the sensitization of central pain, making its potential use in managing trigeminal neuralgia.

The benzodiazepine lorazepam acts as an antiepileptic by increasing GABAergic inhibition. Because of its anxiolytic and muscle relaxant qualities, lorazepam may also have supplementary advantages. Because of the unpredictable and intense nature of pain attacks, TN patients frequently suffer from increased anxiety. Lorazepam may help reduce this anxiety, which could in turn lessen the overall perception of pain. Its muscle-relaxing properties may also aid in easing the face muscular tension brought on by TN bouts. Long-term use includes concerns of tolerance, dependency, and withdrawal symptoms, and there is little evidence to support its direct analgesic efficacy in TN. Thus, although lorazepam is generally not advised as a regular treatment for TN, it can be taken into consideration as a short-term adjuvant in certain circumstances.

Ketamine was first created as a dissociative anesthetic, but it has since shown promise in treating chronic pain, including TN. Its primary mechanism of analgesia is non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors, which are essential for central sensitization and the modulation of neuropathic pain. Ketamine impacts excitatory neurotransmitters like glutamate and inhibitory neurotransmitters like GABA via altering NMDA receptor function, which promotes neuroplasticity and dendritic regeneration.

A pure neurotoxin made by *Clostridium botulinum*, botulinum toxin type A (BoNT-A), has shown promise as an alternate treatment for trigeminal neuralgia, especially in cases when traditional treatments like carbamazepine or oxcarbazepine have failed. Although chronic migraine is the only FDA-approved pain indication for it, there is mounting evidence that it can also be used off-label to treat neuropathic pain syndromes, such as TN. BoNT-A is thought to provide an analgesic effect in TN by: preventing peripheral sensitization by lowering the release of neurotransmitters linked to pain (such as

glutamate and substance P), reducing hyperexcitability in the trigeminal pain pathway by altering central sensitization.

According to clinical research, administering 25-100 units submucosally or intradermally to trigger points along the trigeminal nerve will considerably lower Penn Facial Pain Scale scores, paroxysm frequency, and pain severity. Usually, the analgesic effect lasts three to six months. Although they have been reported, mild side effects such temporary facial weakness or asymmetry are usually easily tolerated. BoNT-A is particularly beneficial for those who: cannot handle antiepileptic medications or do not react to them.do not qualify for invasive treatments such as microvascular decompression. BoNT-A is an all-around safe, minimally invasive, and successful adjunct or substitute for treating TN; nonetheless, additional high-caliber randomized trials are required to standardize dosage and validate long-term effectiveness.

Other new drugs include amitriptyline (Elavil, Amytril), eslicarbazepine lidocaine, ropivacaine, proparacaine, cannabinoids, tocainide, desvenlafaxine venlafaxine, lacosamide, topiramate, retigabine, calcitonin gene related peptide antagonists, monoclonal antibodies, lasmiditan, minocycline, N-methyl-d-aspartate receptor antagonists, tizanidine, voltage-gated ion channel blockers, vixotrigine, topical capsaicin cream, intranasal lidocaine, sumatriptan, and amitriptyline.

Surgical interventions

Surgical procedures could be taken into consideration for trigeminal neuralgia patients who are not responding to medication treatment. These consist of Microvascular Decompression (MVD), percutaneous balloon compression, Radiofrequency thermocoagulation, chemo-denervation, glycerol rhizotomy, gamma knife radiosurgery and peripheral nerve blocks [21-26].

Advances in nonpharmacological therapy

Developments in Nonpharmacological Treatment In addition to traditional RFA, novel techniques that use short-term, reinforced RF doses-known as pulsed RF and other attenuated laser therapy-are becoming more and more popular these days. The new therapeutic modalities are Pulsed radiofrequency (PRF), Ozone injection around Gasserian ganglion (OIAGG), Cryotherapy, Neuromodulation, Low level laser therapy (LLLT), Carbon dioxide laser, Neural prolotherapy, Nerve combing, Complimentary medicine include standard acupuncture, electroacupuncture, and spinal regulation therapies, sound therapy; low-intensity and low-frequency acoustic ultrasound patch; and vitamin B, C, and biofeedback [27-29].

CONCLUSION

In summary, trigeminal neuralgia is a complex disorder that can significantly impact a person's day-to day functioning. Other medications are now available for those who do not respond well to carbamazepine or cannot handle it, even though it is still the primary medication used to treat it. Accurately diagnosing the illness has become simpler thanks to new imaging techniques, particularly when it comes to distinguishing between classical and secondary kinds. Long lasting relief can be obtained by operations such as microvascular decompression for patients who do not improve with medication. Furthermore, less invasive, more recent therapies including injections of botulinum toxin and pulsed radiofrequency are showing promise. In the future, additional study will be required to improve the diagnosis and treatment of the ailment as well as track the effectiveness of novel medications. In order to properly treat trigeminal neuralgia, physicians from various specializations must collaborate to provide patients with the best care available.

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