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Trigeminal Neuralgia: Comprehensive Treatment Strategies in a Multidisciplinary Approach – A Literature Review

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ABSTRACT

Introduction. Trigeminal neuralgia (TN) is a rare but debilitating craniofacial pain disorder characterized by sudden, severe, electric shock-like episodes affecting one or more branches of the trigeminal nerve. Despite its low prevalence, TN has a profound impact on quality of life. Accurate diagnosis and subtype classification are essential for guiding treatment. Advanced neuroimaging techniques help identify structural causes and guide therapy.

Purpose. This review offers a comprehensive, evidence-based summary of current treatment strategies for TN, including pharmacological, surgical, and supportive modalities. Special attention is given to recent advances and options for patients with refractory or complex cases.

Materials and Methods. This review is based on a structured analysis of peer-reviewed literature retrieved from PubMed, Google Scholar, and the Cochrane Library. Selection prioritized systematic reviews, randomized controlled trials, clinical guidelines, and high-quality cohort studies published between 2000 and 2024. Emphasis was placed on clinical relevance and methodological rigor.

Conclusion. Effective management of trigeminal neuralgia demands an individualized, stepwise approach. While carbamazepine and oxcarbazepine remain first-line treatments, a significant subset of patients requires surgical or adjunctive therapies. Microvascular decompression offers the best long-term outcomes in classical TN, whereas less invasive procedures and botulinum toxin injections may benefit selected patients. Neuromodulation techniques are emerging alternatives for drug-resistant cases. Multidisciplinary care is essential for accurate diagnosis and individualized treatment.

Keywords: trigeminal neuralgia, neuropathic pain, facial pain syndromes, pharmacological treatment

Content

1. Introduction

Trigeminal neuralgia (TN) is a disorder of severe unilateral facial pain, characterized by sudden, electric shock-like paroxysms occurring along the distribution of one or more branches of the trigeminal nerve [1, 2]. The attacks typically last from a few seconds to several minutes and are triggered by light stimuli such as chewing, speaking, or touching the face [2]. Although rare, with an incidence of 4–5 per 100,000 patients per year, it is more prevalent among women and people over 50 years of age [3, 4]. In most cases, trigeminal neuralgia is caused by focal vascular compression of the trigeminal nerve root near its entry into the pons, in the so-called root entry zone [5]. This region lies within central nervous system tissue and is particularly vulnerable to such compression by aberrant arterial or venous loops, a mechanism now thought to account for 80–90% of cases [5, 6]. Additional evidence of central sensitization and impaired brainstem pain modulation has been demonstrated using advanced imaging techniques [7]. Sodium channel dysregulation, particularly dysfunctional expression of Nav1.7, Nav1.3, and Nav1.8, may further contribute to abnormal trigeminal excitability [8]. In some patients, TN occurs secondary to other neurological

conditions. For example, multiple sclerosis (MS) may produce similar paroxysmal facial pain due to demyelinating lesions in the pons or root entry zone [1, 9]. Magnetic Resonance Imaging (MRI) studies suggest that in MS, lesions may precede the onset of TN by years [10]. Misdiagnosis is common: patients frequently undergo unnecessary dental procedures (including tooth extractions) before the correct diagnosis is established [1, 2]. This diagnostic delay, coupled with the condition's unpredictable onset and high pain intensity, can result in significant psychological distress and functional impairment.

2. Diagnostic Criteria

Trigeminal neuralgia (TN) is primarily diagnosed based on clinical presentation. Two major international frameworks standardize the diagnosis: the **International Classification of Headache Disorders, 3rd edition (ICHD-3)**, developed by the International Headache Society, and the **classification criteria of the International Association for the Study of Pain (IASP)**. According to the ICHD-3, TN is defined as recurrent, unilateral facial pain, localized to one or more divisions of the trigeminal nerve. The attacks typically begin abruptly, are of severe intensity, and are consistently triggered by innocuous stimuli such as light touch, chewing, speaking, or tooth brushing. [11]. The diagnostic criteria include:

A) Recurrent paroxysms of unilateral facial pain in the distribution of one or more trigeminal divisions, without radiation beyond the affected trigeminal divisions.
B) All the following:

    1. Duration from a fraction of a second to two minutes
    2. Severe intensity
    3. Pain described as electric shock-like, stabbing, or sharp.

C) Pain is triggered by innocuous stimuli.
D) Not better accounted for by another ICHD-3 diagnosis [11].

The IASP similarly classifies TN under chronic neuropathic orofacial pain, emphasizing its abrupt onset, short duration, consistent triggering by non-painful mechanical stimuli, and stereotyped paroxysmal character. However, according to the IASP classification, trigeminal neuralgia is considered a form of chronic neuropathic pain, characterized by recurrent episodes of facial pain persisting for more than three months, resulting from a lesion or disease of the somatosensory nervous system. [1, 12, 13]. Additional classification systems, including the **International**

Classification of Orofacial Pain (ICOP), further help delineate TN from other facial pain syndromes [14]. These systems stress the importance of ruling out alternative explanations. A subset of TN patients may exhibit cranial autonomic symptoms, including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid oedema, ptosis, or facial sweating. The presence of these features can complicate the clinical picture and raise diagnostic uncertainty. In such cases, the condition may resemble other headache syndromes within the trigeminal autonomic cephalalgias (TACs) group, particularly short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) or short-lasting unilateral neuralgiform headache with autonomic symptoms (SUNA). Accurate differentiation between TN and these syndromes is essential, as their pathophysiology and treatment strategies may differ [16, 2]. **High-resolution MRI is recommended to evaluate potential neurovascular compression, demyelinating plaques (as in multiple sclerosis), and space-occupying lesions such as tumors.** [15, 16]. In MS-related TN, demyelination near the trigeminal root entry zone is often visible, and in some cases, these lesions might precede symptom onset by several years [10]. Accurate classification is essential, as treatment decisions and prognosis vary significantly between TN subtypes.

Table 1. Subclassification of Trigeminal Neuralgia (ICHD-3 and IASP)

Subtype	Underlying Mechanism
Classical TN	Presumed vascular compression of the trigeminal nerve root, supported by MRI or intraoperative findings
Idiopathic TN	No evident structural lesion or systemic cause detected by imaging or clinical evaluation
Secondary TN	Secondary to an identifiable causative lesion (e.g., tumor, arteriovenous malformation, multiple sclerosis) confirmed by imaging or diagnostic tests

Note: The subclassification presented in this table is based on the diagnostic standards defined by ICHD-3 and IASP, and is consistent with current clinical evidence.

3. Treatment

The management of TN focuses on pain relief and improving quality of life. First-line pharmacologic treatment includes carbamazepine and oxcarbazepine, which remain the cornerstone of TN management [2,16]. Accordingly, practice guidelines endorse either carbamazepine or oxcarbazepine as first-line treatments for classical TN [17]. Nevertheless, a significant subset of

patients either do not achieve adequate relief with medications or cannot tolerate their side effects. In such medically refractory cases, surgical intervention is often considered [18,19]. Neurosurgical options – including microvascular decompression (MVD) and percutaneous ablative procedures, as well as stereotactic radiosurgery – can provide long-term pain relief when medications fail [20,21,22]. Emerging therapies such as botulinum toxin type A injections have shown efficacy in selected cases and are included in some treatment algorithms as adjunctive options. A stepwise, escalation-based approach is recommended: initial pharmacologic therapy is followed by second-line options or combination regimens if necessary. In refractory cases, intervention selection should be tailored to the TN subtype. Referral to a multidisciplinary facial pain team is advised to confirm diagnosis and guide advanced management [23].

4. Pharmacological Treatment

Carbamazepine (CBZ) and oxcarbazepine (OXC) are the recommended first-line pharmacologic agents for trigeminal neuralgia (TN). Clinical trials report pain remission rates of up to 80% during initial treatment [24, 16]. Typical starting doses range from 400–1200 mg/day for carbamazepine or 900–1800 mg/day for oxcarbazepine [18]. Periodic monitoring of liver enzymes is advisable during long-term CBZ therapy due to the risk of elevated aminotransferase levels. However, side effects such as dizziness, ataxia, and diplopia are common and may lead to treatment discontinuation in approximately one-quarter of patients [16]. OXC demonstrates similar efficacy to CBZ and may offer improved tolerability due to a more favorable interaction profile [15,16]. One important consideration is the risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients of Asian ancestry who carry the HLA-B*15:02 allele. The U.S. Food and Drug Administration recommends genetic screening for this allele prior to initiating carbamazepine in individuals from high-risk populations, including those of Han Chinese, Thai, Vietnamese, Indian, and other Southeast Asian descent. If the allele is present, alternative agents should be considered, unless the potential benefit outweighs the risk [25].

Lamotrigine acts by stabilizing the slow-inactivated state of type IIA neuronal sodium channels, thereby suppressing repetitive neuronal firing during sustained depolarization while sparing normal signal transmission. Through this mechanism, it inhibits the pathological release of glutamate, a neurotransmitter involved in central sensitization and other mechanisms underlying chronic pain [26]. Lamotrigine is sometimes used as an adjunctive option in patients with trigeminal neuralgia (TN) who cannot tolerate high doses of first-line therapies such as carbamazepine or oxcarbazepine. However, its efficacy as monotherapy in refractory TN is limited. In a crossover, head-to-head trial

comparing lamotrigine (400 mg/day) and carbamazepine (1,200 mg/day), lamotrigine achieved pain control in 62% of patients, compared to 90.5% with carbamazepine [18,27]. Furthermore, in a double-blind placebo-controlled trial involving patients with various types of neuropathic pain, lamotrigine failed to show superiority over placebo in any outcome measures; notably, only a small subgroup had TN [18,28]. These findings suggest that lamotrigine is not a reliable monotherapy in TN patients who are resistant to first-line agents. Overall, current evidence does not support lamotrigine as reliable monotherapy for TN, although it may offer adjunctive benefits in select patients, especially when first-line agents are limited by tolerability [26].

Phenytoin (PHT) was the first effective anticonvulsant used to treat trigeminal neuralgia and remains a rescue option in acute exacerbations of the disorder [29]. Its mechanism of action involves blocking voltage-gated sodium channels, which stabilizes neuronal membranes and inhibits aberrant trigeminal signaling along the trigeminal nerve, which contributes to pain relief [29]. This biophysical effect underlies its rapid efficacy when administered intravenously. Although fosphenytoin is preferred for better solubility and safety profile, PHT may still be used depending on local availability [29]. Recent retrospective studies have provided preliminary clinical evidence supporting the use of intravenous PHT in emergency settings for TN. In a retrospective cohort study involving 32 patients with trigeminal neuralgia presenting to the emergency department, nearly all experienced partial symptom relief, and approximately two-thirds achieved substantial or complete remission following intravenous phenytoin administration [30]. Importantly, this response was observed across all subtypes of TN, including classical, idiopathic, and secondary forms, suggesting broad utility in acute management [29]. Adverse effects were rare, with mild pruritus reported as the only adverse effect [30]. Nevertheless, the administration of PHT requires close medical supervision due to the risk of serious cardiac complications. It is generally recommended that infusions be performed in high-dependency units with continuous ECG monitoring [30].

Baclofen acts by stimulating $GABA_B$ receptors, thereby inhibiting both mono- and polysynaptic reflex transmission at the spinal level. Its chemical structure is analogous to gamma-aminobutyric acid (GABA), and it exerts antinociceptive effects by reducing pathological reflexes such as muscle contractions, spasms, and clonus while sparing neuromuscular transmission. Baclofen has shown superiority to placebo in reducing the number of painful paroxysms in classical trigeminal neuralgia (CTN) and is considered a level C treatment option (based on limited clinical evidence) alongside lamotrigine and pimozide [31,32,33]. It may also be used as an add-on therapy when carbamazepine

or oxcarbazepine cannot be up-titrated due to side effects. Its potential efficacy as monotherapy has been suggested, but the supporting evidence remains limited [32].

Gabapentin is a structural analogue of gamma-aminobutyric acid (GABA), but it does not act directly on GABA receptors. Instead, it binds to the α2δ subunit of voltage-gated calcium channels in the central nervous system, reducing excitatory neurotransmitter release and neuronal hyperexcitability. It is commonly used in various neuropathic pain syndromes. However, the current NICE guidelines for neuropathic pain management recommend gabapentin or pregabalin only for conditions other than trigeminal neuralgia, emphasizing that first-line treatment for TN remains carbamazepine or oxcarbazepine. This recommendation reflects the lack of high-quality evidence supporting gabapentin in the treatment of TN specifically. A Cochrane review concluded that gabapentin may reduce pain in certain chronic neuropathic conditions [34], although TN-specific data remain scarce. In clinical practice, gabapentin is sometimes used as an adjunctive agent in combination with carbamazepine or oxcarbazepine, especially when first-line agents cannot be titrated to effective doses due to adverse effects [15, 34].

Table 2. Summary of Pharmacological Treatment Options for Trigeminal Neuralgia

Drug	Mechanism of Action	Clinical Use
Carbamazepine	Sodium channel blocker	First-line; proven efficacy, but side effects common
Oxcarbazepine	Sodium channel blocker	First-line alternative; better tolerated than CBZ
Lamotrigine	Sodium channel blocker; glutamate inhibition	Second-line; useful in refractory and chronic TN
Phenytoin	Sodium channel blocker	Historical/backup option; narrow therapeutic range
Baclofen	GABA receptor agonist	Adjunct in refractory TN, esp. in MS-related cases
Gabapentin	α2δ calcium channel modulator	Second-/third-line; off-label in TN

Note: For detailed dosing, consult the Summary of Product Characteristics (SmPC) or relevant treatment guidelines.

5. Surgical Approaches

Surgical treatment is considered in patients with trigeminal neuralgia (TN) in whom pharmacological therapy fails to provide adequate pain relief or causes significant adverse effects [35]. The selection of a surgical approach is guided by several factors, including the patient's age, general health, and the clinical subtype of TN. Available interventions range from invasive microsurgical decompression to less invasive or non-invasive ablative techniques. Surgical techniques vary in mechanism of action, success rates, risk profiles, and durability of pain relief.

Microvascular decompression (MVD) is the preferred surgical option for classical TN with radiological evidence of neurovascular compression. This technique directly targets the presumed cause of classical TN-vascular compression of the trigeminal nerve root. MVD is a neurosurgical procedure that involves performing a small craniectomy to access the trigeminal nerve and decompress the nerve by relieving vascular contact. The offending vessel is gently mobilized and separated from the nerve using a semirigid Teflon® prosthesis, which is placed between the structures to prevent further contact and irritation [19]. MVD has demonstrated long-term effectiveness in the treatment of trigeminal neuralgia, with approximately 70% of patients remaining pain-free without medication ten years postoperatively. Most recurrences occurred within the first two years, and the annual recurrence rate dropped to below 1% by the ten-year mark. The procedure carries a low risk of serious complications, with major adverse events such as mortality and brainstem infarction occurring in less than 0.3% of cases [20]. Compared to ablative procedures, MVD results in fewer complications like facial numbness or dysesthesia and allows more patients to discontinue medications.

Percutaneous techniques are minimally invasive surgical options for trigeminal neuralgia that aim to create controlled injury to the trigeminal nerve to relieve pain. These include radiofrequency lesioning, glycerol rhizotomy, and balloon compression, which exert their effects through thermal (radiofrequency), chemical (glycerol), or mechanical (balloon) mechanisms [2]. All procedures are performed via the foramen ovale and are less invasive than MVD, with lower rates of perioperative morbidity and mortality [20]. However, they induce targeted lesions in the nerve, which can occasionally lead to complications such as anaesthesia dolorosa or keratitis [20]. Among percutaneous options, radiofrequency rhizotomy appears to offer the highest rates of initial and long-term pain relief, particularly when performed using a curved electrode and avoiding dense lesions [21]. Long-term data suggest, however, that recurrence is common: only 20–28% of patients remain

pain-free after 5–6 years following radiofrequency or glycerol rhizotomy [20]. Furthermore, sensory side effects are more frequent than with MVD. In one comparative study, facial numbness occurred in 75% of patients after radiofrequency rhizotomy, compared to 22% after MVD. Neuropathic facial pain was also more frequent in the rhizotomy group (37% vs. 13%) [20]. Despite these drawbacks, radiofrequency rhizotomy remains a preferred first-line surgical treatment for many patients due to its efficacy, lower morbidity compared to MVD, and cost-effectiveness [21]. Balloon compression may also be appropriate in select cases. The choice of procedure should be individualized, and neurosurgeons should be familiar with both percutaneous and posterior fossa techniques to tailor treatment to the patient's needs [21].

Gamma Knife Radiosurgery (GKRS) is a minimally invasive treatment option for trigeminal neuralgia (TN), particularly suitable for patients deemed unfit for open surgery due to advanced age, comorbidities, or personal preference [22]. The procedure involves delivering a high dose of focused radiation, typically between 70 and 90 Gy, to the trigeminal nerve root entry zone using stereotactic imaging guidance [22, 36]. Unlike conventional radiotherapy, GKRS delivers a highly focused dose with rapid fall-off, minimizing exposure to adjacent structures and lowering the theoretical risk of radiation-induced malignancies [22]. Initial pain relief is reported in approximately 60–80% of patients, with some series reporting up to 100% short-term success. However, long-term pain control is less predictable: recurrence rates average around 25%, and only 30–45% of patients remain pain-free without medication at 10 years post-treatment [36]. The analgesic effect of GKRS is typically delayed, with improvements appearing within one to two months after the procedure [36]. GKRS is generally well tolerated. The most common adverse effects include facial hypesthesia or paresthesia, reported in 12-50% of patients depending on the exact target and dose parameters [15,36]. Other complications such as dry eye, dysesthesia, deafferentation pain, or keratitis may occur, especially if the root entry zone is irradiated rather than the anterior retrogasserian portion of the nerve [36]. Nevertheless, due to its safety profile and patient convenience, GKRS has become an increasingly utilized option, especially in individuals who cannot undergo or wish to avoid more invasive interventions [22].

Table 3. Comparison of Surgical Treatment Options for Trigeminal Neuralgia.

Method	Invasiveness	Mechanism	Pain Relief Onset	Initial Success Rate
Microvascular Decompression	Invasive (craniotomy)	Relieves vascular compression of trigeminal nerve root	Immediate	80–90%
Radiofrequency Rhizotomy	Minimally invasive	Heat-induced lesion in trigeminal ganglion	Immediate	~90%
Glycerol Rhizotomy	Minimally invasive	Chemical neurolysis near trigeminal cistern	Delayed (days)	~70–90%
Balloon Compression	Minimally invasive	Mechanical compression of trigeminal ganglion	Immediate	~80–90%
Gamma Knife Radiosurgery	Non-invasive	Focused radiation to trigeminal nerve root entry zone	Delayed (1–2 months)	~60–80%

Note: Recurrence rates vary among surgical modalities, with higher rates generally observed in non-decompression techniques. Careful patient selection and imaging are critical for optimizing outcomes.

6. Other and Supportive Treatment Options

Although pharmacological and surgical approaches continue to represent the cornerstone of TN management, several adjunctive and supportive therapies have emerged to support patients with refractory TN or contraindications to standard therapies. These methods are particularly valuable in individuals with persistent symptoms, atypical presentations, or complicating factors such as medication intolerance.

Botulinum toxin type A (BTX-A) has emerged as a promising non-surgical option for patients with trigeminal neuralgia (TN) refractory to standard pharmacologic treatments. Multiple open-label studies and randomized controlled trials have demonstrated that BTX-A significantly reduces both the intensity and frequency of pain attacks in TN patients who have not responded adequately to first-line therapies [37,38]. Clinical improvement has been observed as early as a few days after injection, with the analgesic effect typically lasting several weeks to several months [38]. In a randomized, double-blind, placebo-controlled trial, 68.2% of patients receiving BTX-A (75 U)

reported clinically meaningful improvement, compared to only 15% in the placebo group [37]. Another trial comparing two doses (25 U and 75 U) found both to be significantly more effective than placebo in reducing pain on the visual analog scale, with no significant difference in efficacy between the two doses [38]. These findings indicate that lower doses may offer substantial benefit while reducing adverse effects. The mechanism by which BTX-A alleviates neuropathic pain is not yet fully understood. It is hypothesized that, beyond muscle relaxation, BTX-A reduces peripheral sensitization and central excitability by inhibiting the release of pain-related neuropeptides, including glutamate, substance P, and CGRP, from sensory nerve endings [38]. This action likely contributes to its effectiveness in conditions like TN, where hyperexcitability of the trigeminal system plays a central role. Injection sites vary depending on the distribution of pain but often include the subcutaneous tissues of the affected branches, the zygomatic arch, or masseter region [37,38]. Pain relief is frequently achieved without inducing significant motor impairment, although mild and transient facial weakness, asymmetry, or local swelling have been reported [37,38]. These side effects are typically short-lived and well-tolerated by patients. Given its efficacy, favorable safety profile, and minimal systemic effects, BTX-A is increasingly considered a valuable option for patients with refractory TN, particularly when systemic medications or invasive procedures are contraindicated [37,38]. As an off-label therapy, BTX-A should be administered by clinicians experienced in anatomy of trigeminal nerve and dosing.

Neuromodulation Techniques aim to modulate abnormal pain signaling and offer alternative options for patients with drug-resistant trigeminal neuralgia. The most widely accessible modality is Transcutaneous Electrical Nerve Stimulation (TENS), which applies low-intensity electrical currents through the skin. Based on the gate-control theory of pain, TENS may attenuate pain transmission by activating large-diameter afferent fibers. Although evidence remains limited, small prospective studies have reported meaningful pain relief in more than 80% of TN patients following 2–4 weeks of daily treatment [39]. Its non-invasive nature, low cost, and favorable safety profile make TENS an attractive adjunctive option. A more invasive technique is Peripheral Nerve Stimulation (PNS), where electrodes are surgically implanted near branches of the trigeminal nerve. Several case series have shown significant pain reduction in selected patients with refractory TN, with some reporting a >70% reduction in pain scores. However, findings across studies are inconsistent. In the largest retrospective series to date, more than half of patients failed the initial trial stimulation and did not proceed to permanent implantation [39]. While TENS and PNS offer potential for pain control in difficult TN cases, current evidence remains insufficient to support

formal clinical recommendations. Larger prospective studies are needed to confirm their long-term effectiveness and appropriate patient selection criteria.

7. Summary

This review presents a comprehensive overview of current treatment strategies for trigeminal neuralgia. First-line treatment relies on sodium channel–blocking anticonvulsants, which are effective in many cases but often limited by tolerability. For patients who do not respond adequately to medication, surgical interventions such as microvascular decompression, percutaneous techniques, and stereotactic radiosurgery offer additional treatment avenues tailored to clinical subtype and neuroimaging results. Adjunctive approaches, including botulinum toxin injections and neuromodulation techniques, may be considered in selected refractory cases. Optimal management requires a structured, patient-specific approach based on diagnosis, symptomatology and treatment response.

Disclosure

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