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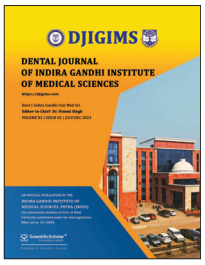

Review Article

A Narrative Review on Pharmacological Therapy of Trigeminal Neuralgia with Recent Advances

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ABSTRACT

Trigeminal neuralgia (TN), a profoundly debilitating condition, is characterized by recurrent bouts of facial pain that are intense, brief, and electric shock-like. New diagnostic criteria that subclassify TN according to the presence of trigeminal neurovascular conflict or an underlying neurological disorder should be put into place to accurately characterize patients and support the decision-making process for medicinal and surgical interventions. High-resolution trigeminal sequencing and MR imaging should be part of the diagnostic workup. Oxcarbazepine and carbamazepine are the first-choice drugs. Lamotrigine, gabapentin, pregabalin, baclofen, and botulinum toxin type A can all be used alone or in combination as supplemental treatments.

Keywords: Pharmacological therapy, paroxysmal short-lasting pain, Recent advances, Trigeminal neuralgia

INTRODUCTION

Recurrent, unilateral, short-lived (less than 1 second to 2 minutes), excruciating pain episodes that resemble electric shocks and have abrupt start and termination are the hallmarks of trigeminal neuralgia (TN). It is a very crippling illness that affects everyday human activities like eating, drinking, talking, and touching one's face, which lowers one's quality of life. Increased anxiety and sadness are linked to a higher risk of suicide, according to epidemiological studies.[1] This emphasizes how crucial early diagnosis, research, and therapy are. The pain usually goes away entirely in between attacks. Usually, it doesn't happen while the person is sleeping. Bilateral involvement, simultaneous involvement of other nerves, or rapid spreading to other divisions all point to a secondary condition like multiple sclerosis (MS) or an enlarging cranial tumor.[2]

Among the divisions of trigeminal nerve, the mandibular branch is most commonly impacted. The mandibular branch is most commonly impacted.[3]

DIAGNOSTIC CRITERIA AND CLASSIFICATION

The International Classification of Headache Disorders, third edition (ICHD-3) criteria for TN require recurrent paroxysms of unilateral facial pain limited to the trigeminal distribution, lasting between a fraction of a second and two minutes, severe in intensity with an electric shock-like shooting, stabbing, or sharp quality, and triggered by harmless stimuli.[4] According to prospective trigeminal MR imaging investigations, classical TN is linked to neurovascular compression and morphological abnormalities (distortion, indentation, and atrophy) on the

symptomatic side, although the same changes are uncommon on the asymptomatic side.[5] About 15% of instances are of the secondary kind, which is caused by a neurological condition that can be identified as the source of TN (apart from trigeminal neurovascular compression). Examples of these conditions include MS, arteriovenous malformation, and cerebellopontine angle tumor. The symptoms of TN are present in about 2% of individuals with MS.[6] About 10% of cases are of the idiopathic form, which is identified when there is no discernible etiology for TN.

CLINICAL FEATURES

The key characteristics of the TN phenotype are described in the ICHD-3 diagnostic criteria.

1. Temporomandibular joint dysfunction, persistent idiopathic facial pain, and, infrequently, migraines with facial pain are examples of idiopathic cases with continuous or prolonged bilateral trigeminal pain if examinations are normal. Laterality and pain location: 60% of the injured face is on the right side, while 60% is on the left.[7] Bilateral simultaneous or side-alternating trigeminal paroxysmal pains are rare and should be cautiously ruled out as a sign of a neurological or non-neurological condition affecting the skull.[8]
2. **Zones and triggers** - One of the defining clinical features of TN attacks is their susceptibility to innocuous mechanical stimulation of the face and intraoral mucosa ipsilateral to the side of discomfort. Triggered attacks, which are reported by 91% to 99% of patients, are frequently thought to be pathognomonic of TN.[9,10] Patients typically report both provoked and spontaneous attacks, with spontaneous attacks accounting for 68% to 98% of instances. When triggerable attacks are completely absent, a thorough evaluation should be conducted to rule out other possible diagnoses, such as trigeminal autonomic cephalalgia or craniofacial disease. In contrast to painful and hot stimuli, which appear to be ineffectual at evoking pain in TN, mild tactile stimulation is the most effective trigger.[11] Light contact, chatting, chewing, cleaning teeth, washing or drying, drinking, and shaving are examples of common triggers.[12]
3. **Refractory Phase** - Most TN patients typically experience a refractory phase, which is a period of seconds or minutes after a triggered attack during which no more episodes can be triggered. In contrast, there is typically no refractory time following exposure to a trigger in SUNHA, a trigeminal autonomic cephalalgia.[13]
4. Examples of TN-related cranial autonomic symptoms include several case reports. Due to this, it could be challenging to differentiate TN from trigeminal autonomic cephalalgias, which are identified by strong autonomic brain symptoms. face autonomic symptoms, including lacrimation (31%), rhinorrhea (9%), hypersalivation (7%), and facial swelling/flushing (5%), were evident in 98 out of the 229 patients (43%) that Rasmussen reported experiencing discomfort.[14] A recent study found that during attacks, ipsilateral cranial autonomic symptoms occurred in 48 out of 158 patients (31%).[15] These symptoms were reported more frequently in both series by patients with ocular division trigeminal pain (V1).

On the other hand, Sjaastad *et al*. thoroughly examined the phenotypic of 19 patients with V1 TN and found that while rhinorrhea (11%), conjunctival injection (16%), and lacrimation (42%), all of the patients had minor cranial autonomic symptoms.[16]

THEORIES DESCRIBED FOR TRIGEMINAL NEURALGIA

1. Trigeminal Convergence Projection Theory

The spinal trigeminal nucleus is where the constant nociceptive impulses from the head and neck converge. A form of persistent neuropathic pain is caused by the excitation of second-order neurons by neurotransmitters produced from the nucleus.[17]

2. Bioresonance Hypothesis

This novel theory suggests that the trigeminal nerve experiences resonance when the vibration frequency of a structure close to it approaches its natural frequency. This may result in pain and irregular transmission.[18]

3. Ignition Hypothesis

Trigeminal afferent neurons in the root entry zone (REZ) are hyperexcitable and exhibit coordinated discharge activity when they are injured.[19]

MANAGEMENT

The preferred medication for TN is carbamazepine, an anticonvulsant. Oxcarbazepine follows as the second preferred medication.[20] When comparing these two medications, oxcarbazepine has higher tolerability but fairly similar efficacy. Additional medications may be used, including sodium valproate, baclofen, lamotrigine, clonazepam, topiramate, phenytoin, gabapentin, and pregabalin. When patients cannot handle greater dosages of carbamazepine, polytherapy can be helpful.[21] Opioids shouldn't be prescribed because they are thought to be ineffective against TN. To control emotional status, a multidisciplinary strategy utilizing

antidepressants and antianxiety medications such duloxetine and amitriptyline is required. Because acupuncture has an analgesic impact on both idiopathic TN and the secondary myofascial pain that is associated with it, it may be a viable therapeutic choice for idiopathic TN.[22]

Pain can also be effectively reduced by peripheral nerve blocks that use a local anesthetic in combination with glycerol or pure alcohol.[23] For a few months or perhaps years, a patient may experience no symptoms if nerve blocks are performed correctly.[24] Additionally, it lowers the quantity and dosage of medications. Injections of botulinum toxin type A (BTX-A) have been suggested in small studies to treat persons with TN who are no longer able to manage their discomfort with medication.[25] Following therapy with BTX-A, a recent meta-analysis verified modest efficacy and demonstrated a pooled reduction of pain by −3.009 points on a 0 to 10 verbal rating scale (95% CI), $p < 0.001$.[26] Before this treatment is widely used for this ailment, further research must be done.

Surgery is typically only advised after medication has failed to work or when the adverse effects of the medication are unbearable. When TN is unresponsive to medicinal treatment, especially in young people, microvascular decompression is the preferred surgical procedure.[27] Gamma knife radiosurgery, percutaneous balloon compression, glycerol rhizotomy, and radiofrequency thermocoagulation are typically recommended for patients with substantial medical comorbidities. In cases of negative vascular investigations during surgery and big intraneural veins, partial sensory root sectioning is recommended.[28] Vascular decompression can be accomplished solely with endoscopic technology or in conjunction with a microscope.[29]

1. Carbamazepine and oxcarbazepine

The first-line treatments for TN, carbamazepine and oxcarbazepine, provide over 90% of patients with significant acute pain relief, albeit this may not last over time. The negative effects of these medications outweigh their benefits, and up to 40% of patients experience withdrawal.[30] Elderly patients with comorbidities may experience issues due to the metabolic interactions of carbamazepine with other drugs. Although it is more likely to result in excessive central nervous system depression or dose-related hyponatremia, oxcarbazepine has fewer adverse effects and a lower risk of medication interactions than carbamazepine. Women are far less tolerant of both of these medications, which is a gender-related factor.

Since each person reacts differently to the two medications, if one is ineffective, the other may be attempted. When switching from carbamazepine to oxcarbazepine, 200 mg of the former is equivalent to 300 mg of the latter. It's crucial to understand that patients should only take the modified-release (retard) form of carbamazepine once they have stabilized. Both medications work well in liquid form for people who have severe pain that makes swallowing difficult. Although these medications are good at controlling paroxysmal pain, they typically have little effect on the concurrent, ongoing pain. These agents should not be used in cases of allergic reactions or cardiac conduction issues.[31]

There is a notable degree of cross-reactivity among the aromatic antiseizure medications carbamazepine, oxcarbazepine, phenytoin, and phenobarbital. A doctor assessing the efficacy and adverse effects can titrate or lower prescription dosages for most patients.[32] It is frequently not necessary to regularly check the serum medication concentrations of carbamazepine and oxcarbazepine. Nonetheless, we advise regular monitoring of kidney, liver, and calcium function testing. Even though cholestatic liver function test results and hyponatremia are rarely clinically problematic, patients should be regularly monitored to ensure they don't worsen with time. Older women already have a higher prevalence of osteoporosis, which requires careful monitoring over time.[30]

2. Lamotrigine

According to a small, randomized, cross-over experiment, lamotrigine is beneficial as an adjuvant therapy.[33] Lamotrigine can be used as an adjuvant medication to boost efficacy or in patients who are unable to tolerate carbamazepine and oxcarbazepine. Generally speaking, it has fewer adverse effects than oxcarbazepine and carbamazepine. Since the incidence of lamotrigine-induced rash is known to be dose and titration-dependent, the former should be increased gradually. Approximately 10% of lamotrigine users experience mild adverse skin responses. However, rare instances of life-threatening illnesses like Stevens-Johnson syndrome can happen. Since a slow-dose titration technique was implemented, the incidence of severe rashes has decreased to between 0.1% and 0.01%.[34]

Lamotrigine is not suitable for treating severe TN exacerbations in patients who require immediate pain relief due to the requirement for this slow-dose titration.[35]

3. Gabapentin and pregabalin

There are 16 Chinese-language randomized controlled trials that compare gabapentin to carbamazepine. However, because the inclusion criteria, goals, and dosage are either unclear or very variable, it is challenging to make any significant inferences. Pregabalin does not have such trials, although a long-term study indicates that it might be useful.[36]

4. Baclofen

Particularly for those with multiple sclerosis who may be taking the medication for spasticity, baclofen can aid with TN.[37]

5. Botulinum toxin type A

The effectiveness of BTX-A in TN has been demonstrated by recent randomized controlled trials. The gingival mucosa was occasionally exposed to subcutaneous injections of BTX-A. Depending on the trial, the dose can range from 25 to 100 units administered after the pain distribution, spaced 1 cm apart, frequently for a total of 10–20 injection sites. Most trial results were assessed after three months. In every trial, BTX-A consistently outperformed a placebo by a large margin. Respondents to BTX-A varied from 68% to 86%, whereas those who received a placebo ranged from 15% to 32%. Temporary facial weakness and oedema were among the mild to moderate adverse effects.

RECENT ADVANCES IN PHARMACOLOGICAL THERAPY

A few new pharmaceuticals that work by lowering the electrical activity of the already stimulated nerve have recently been developed.

1. Vixotrigine: Vixotrigine is a new sodium channel blocker that suppresses seizures or unpleasant stimuli by preferentially targeting higher frequencies. In an open-label research, patients with TN who received 150 mg of vixotrigine three times a day experienced effective pain alleviation during the last week of treatment as compared to a placebo.[38] The medication was taken for 21 days. In comparison to a placebo, there was a 60% drop in the frequency of paroxysms and a 55% decrease in the intensity of pain. This new medication had a 33% treatment failure rate, and no significant side effects were observed. The outcomes of a multicentric prospective phase III randomized controlled study that is now in progress will provide more information on this medication.[39]
2. Eslicarbazepine: This drug, a third-generation antiepileptic that is currently approved as an additional therapy for focal seizures, targets voltage-gated sodium channels and is classified as a dibenzepine. In a recent open-label intervention, eslicarbazepine was administered to TN patients at a dose of 200–1200 mg/day, and while 71% of patients experienced side effects, 88.9% of patients reported good pain relief.[40]
3. Sumatriptan is an agonist that blocks 5-hydroxytyptamine receptors (1A/B/C). The medication prevents demyelination and vasodilation close to the irritated trigeminal nerve root. The medication is available as an injectable, nasal spray, or tablet form. The effects of oral administration of 50 mg twice daily and subcutaneous injection of 3 mg of sumatriptan were examined in two randomized controlled studies. Baseline pain scores dropped fifteen minutes after the sumatriptan injection.[41,42]
4. Intranasal carbon dioxide (CO_2): It has long been believed that CO_2 modulates pain in hyperactive neurons, and recent studies have shown that CO_2 is a nociceptive modulator of afferent active trigeminal neurons.[43] In a controlled, randomized, parallel-group study, the effects of intranasal CO_2 on transient receptor potential cation channel subfamily V member 1 (TRPV1)-mediated experimental trigeminal pain in healthy volunteers were investigated. This was based on the idea that CO_2 lowers mucosal pH, which in turn starts the nociceptive action of primary trigeminal afferent neurons.
   Since changes in pain ratings were therapeutically irrelevant, the clinical value of intranasal CO_2 insufflation at flow rates of 1 L/min appeared to be limited, despite the fact that only a mild modulatory impact was observed. As a result, a second phase 2 placebo-controlled study was conducted in which TN patients received CO_2 and a placebo for one minute. Three doses of CO_2 and a placebo were given to each patient, and it was discovered that CO_2 improved Visual analogue scale (VAS) scores.[44]
5. Calcium channel blockers (CCBs): A sodium channel blocker alone is typically insufficient to control pain in patients whose ongoing pain is caused by other pathophysiological causes; additional medications are typically required. Trigeminal neuralgia in patients not alleviated by sodium channel blocker monotherapy has been treated with CCBs and antidepressants.[45]
6. Miscellaneous drugs: Despite the existence of other medications, including topical capsaicin, lignocaine, misoprostol, and intranasal lignocaine, their widespread use is still not advised. Misoprostol, a prostaglandin E1 analogue, was found to be an effective treatment for TN; a small number of studies reported success in treating a total of 27 patients with TN related to multiple sclerosis;[46] however, there is insufficient data to confirm or refute the use of this medication in TN.[47]

DISCUSSION

Each of the 44 patients responded favourably to various carbamazepine dosages, according to H.S. Loh *et al.* Notably, there were four patients receiving antidepressants (amitryptyline, doxepin, and dothiepin), two patients using mild tranquilizers (diazepam), and one patient receiving acupuncture treatment. Twelve cases of transcutaneous

electric nerve stimulation, six of cryosurgery, two of soft laser therapy, and two of peripheral neurectomy were among the other modalities used to further reduce the pain. Neurologists were consulted for additional assessment and treatment in just two cases.[48] Alan J. Drinnan claims that sometimes, pain that originates in one division will spread to the next division, a phenomenon known as "double zone pain," but this usually isn't seen until the problem has been present for a number of years.[49] Treatment for trigeminal neuralgia, a severe facial discomfort, is quite challenging. For TN, medication is the first line of treatment, and patients who have not received medication should not immediately have surgery.[50]

CONCLUSION

Improved mechanistic understanding of pathophysiology has led to a revision of the conventional criteria of TN in recent years. A correct diagnosis among the many differential diagnoses is the first step in the management and therapy of TN pain. This is followed by a suitable trial of one of the many efficient pharmacologic treatments that are currently on the market. Trigeminal nerve radiosurgery or percutaneous and open microvascular surgical decompression are frequently saved for patients whose symptoms persist after a period of nonsurgical treatment. Even with the amount of research on this subject that is already available, more study is still required to fully understand the pathogenesis and treatment of TN.

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