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Recent advances in diagnosis and treatment of trigeminal neuralgia. A systematic review.

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Abstract

Trigeminal neuralgia (TN), the most prevalent of the facial neuralgias, is a disabling illness marked by acute pain. Extreme neuropathic pain, like an electric shock that is localized to one or more branches of the trigeminal nerve, can have severe consequences, including suicidal tendencies. impact on a person's life and is frequently met first by dentists and general practitioners. The purpose of this systematic review is to analyze existing and newer treatment methodologies to manage this painful condition. The databases used included PubMed, web of science and Scopus.

Keywords- Trigeminal neuralgia. Facial pain. Chronic pain. Neuropathic pain. Anti-convulsant. Microvascular decompression.

Introduction

Trigeminal neuralgia (TN), or tic douloureux, is a chronic but uncommon syndrome characterized by recurrent bouts of lancinating facial pain occurring in the dermatome of the trigeminal nerve (1) TN is caused by a lesion or injury to a nerve, making it a neuropathic condition. Type 1 (TN1) is the "classic" or "typical" type of the condition, and it causes acute burning face pain that comes and goes at random intervals, with each episode lasting up to two minutes. Pain might sometimes begin in waves that last for several hours (2, 3). The "atypical" form of TN (TN2) is described as persistent, resembling burning and stabbing, but less severe than TN1 (4). Clinical diagnosis of TN requires the detection of episodes that occur in discrete bursts, or paroxysms, with clear beginnings and endings. Patients with TN1 frequently report feeling "stuck in agony" without any apparent triggers. Cases with detectable trigeminal nerve vascular compression due to a tumor, multiple sclerosis, or an arteriovenous malformation are

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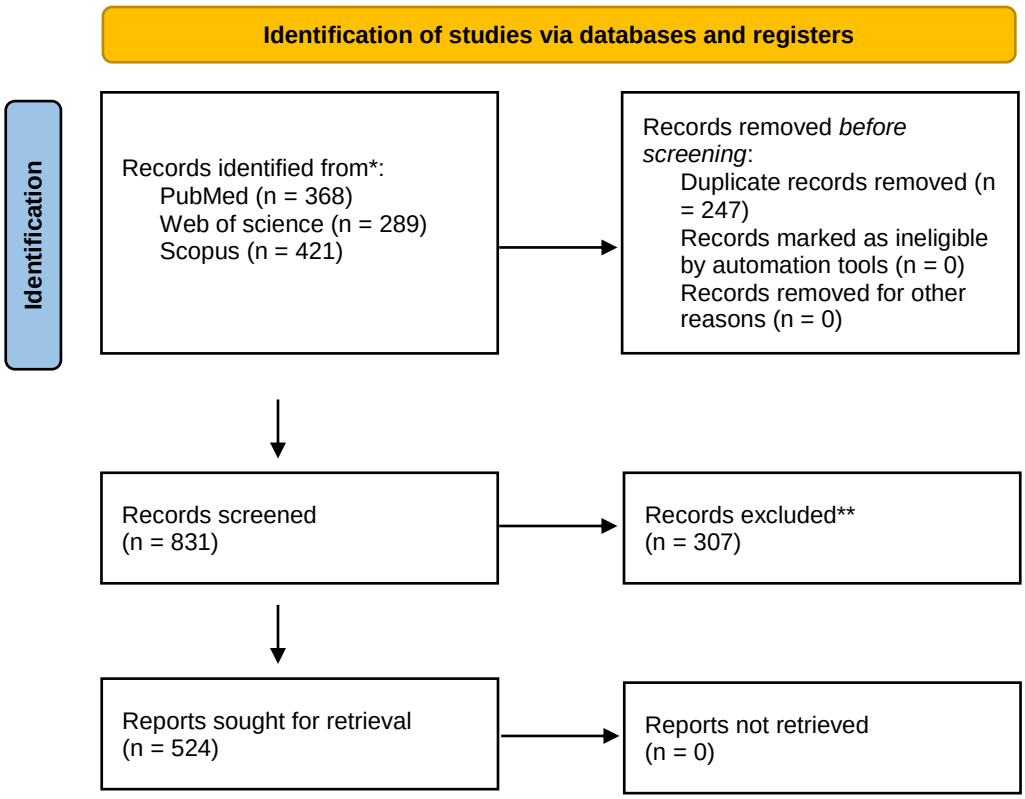
considered to have symptomatic TN. Both types of pain can be experienced by a patient, sometimes at the same time, and both can be extremely painful. Pain can be triggered by even mild stimulation, such as talking, chewing, or even touching the skin above. The discomfort is usually localized to one side of the body and comes on and off throughout the day. (6-9) Typically, a clinical diagnosis of TN is obtained after all other possible causes have been ruled out. In contrast to other neuropathic illnesses, TN may resolve spontaneously in as many as 63% of patients with entire lack of symptoms for several years. (10) Although TN is not lethal, the crippling effects of simply the threat of an attack can still be felt by sufferers.

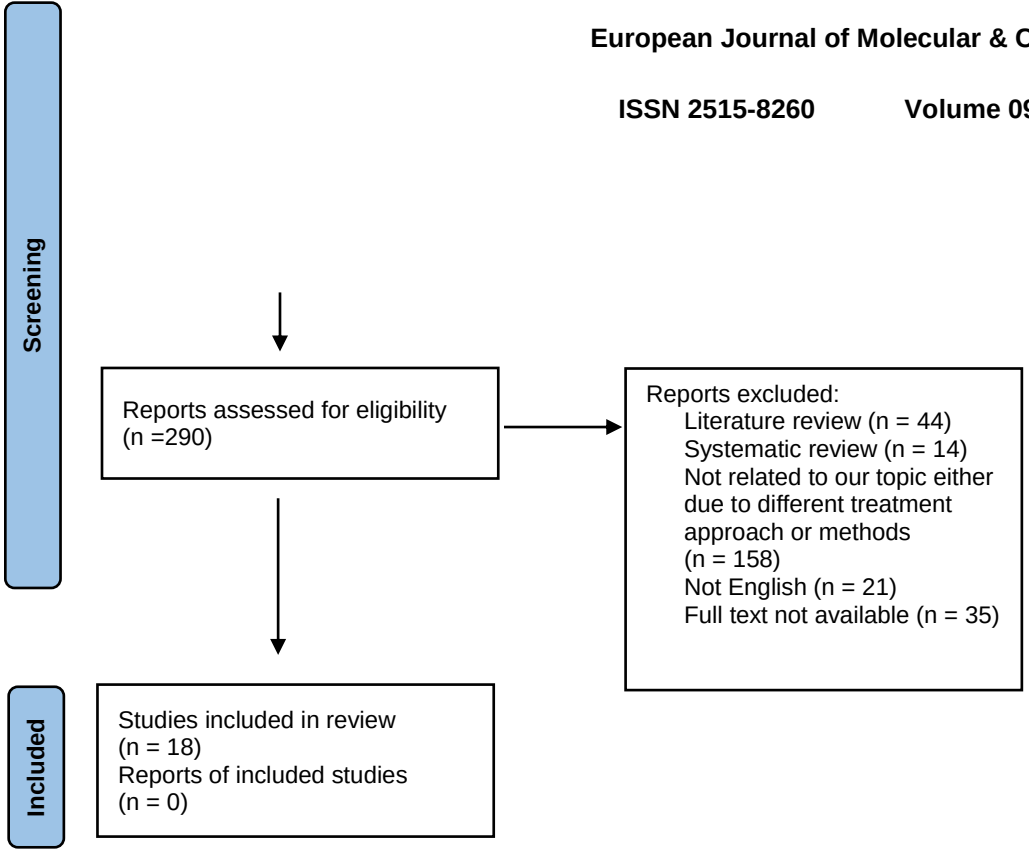
Materials and Method

This systematic review was done following the criteria of the Cochrane Handbook for Systematic Reviews of Interventions. The authors also followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to conduct this systematic review.

The databases used included PubMed, web of science and Scopus. Searches were conducted for articles published from 2000 to July 30, 2022. (Table1) An electronic search was done to answer this review's focus question, "What are the recent advances in diagnosis and management of trigeminal neuralgia?" with the keyword's trigeminal neuralgia, Facial pain, Chronic pain, Neuropathic pain, Anti-convulsant. Microvascular decompression.

Table 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only





Discussion

Medications, surgery, and alternative methods can all be used to treat TN. When treating TN, medical pharmacotherapy is the treatment of choice at the outset. Anticonvulsants and tricyclic antidepressants, for example, comprise the backbone of treatment. The drug carbamazepine is commonly used as a first treatment for TN. However, several medications have shown effectiveness in refractory situations, including baclofen, gabapentin, lidocaine, and misoprostol. In the short-term at least, anticonvulsant medicine is effective in improving the quality of life for the vast majority of patients. Neurosurgical intervention can be helpful for patients who are unable or unwilling to undergo medicinal treatment. Trigeminal nerve root microvascular decompression, rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, and chemical neurectomy are the most common types of procedures. Medically intractable cases may also benefit from botulinum toxin injections, according on the available research. (11-13) When conventional treatments fail to alleviate pain, neuromodulation and peripheral nerve field stimulation are two potential alternative therapies that deserve more research.

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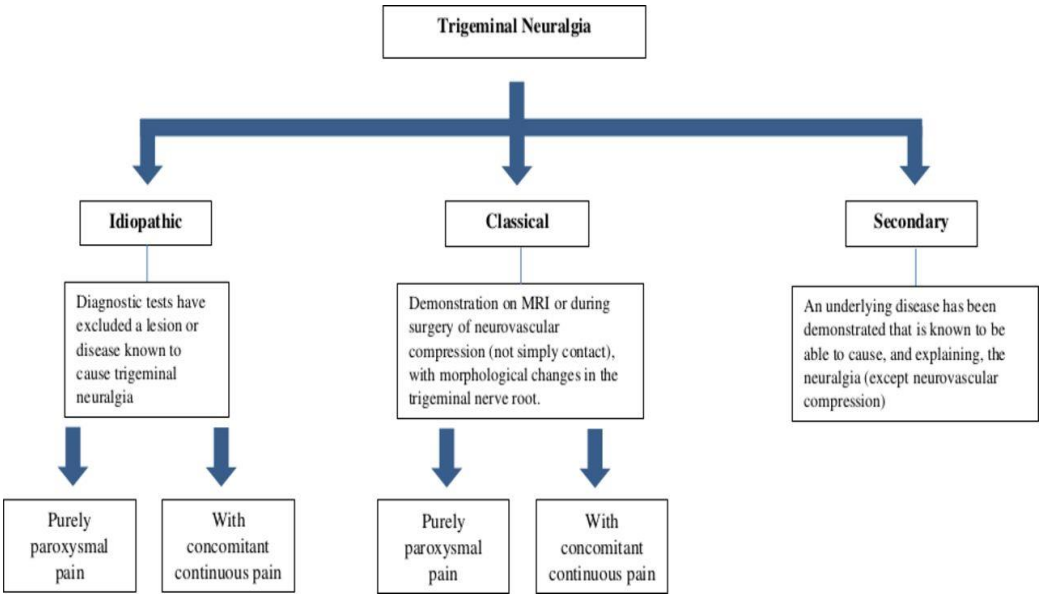

(Picture courtesy of Lambru et al. Trigeminal neuralgia. A practical guide.2021)

Pharmacological Therapy

The American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) determined that according to current evidence-based treatment guidelines, carbamazepine (level A) and oxcarbazepine (level B) are effective for controlling the pain of classical TN. Even in the more recent publication guidelines by the European Academy of Neurology (2019), carbamazepine remains strongly recommended as a first-line long-term treatment of TN. (14) The mechanism of action of carbamazepine is the blockage of voltage-gated sodium channels in a frequency-dependent manner. Although carbamazepine is considered the gold standard and has been shown to increase overall pain relief long term, it does not come without drawbacks. It is associated with several adverse effects including drowsiness, dizziness, rash, liver damage, and ataxia. (15,16) Furthermore, there are multiple drug interactions, and there is the risk of potentially life-threatening skin conditions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Despite these problems, carbamazepine remains the only Food and Drug Administration (FDA)-approved medication for treatment of classical TN due to its proven efficacy and effectiveness in randomized controlled trials (RCTs). On the other hand, oxcarbazepine is essentially an analog of carbamazepine and has the same mechanism of action but provides better tolerability, predictable metabolism, and much fewer drug interactions. In comparable studies, oxcarbazepine was proven to be equally as effective in the reduction of pain attacks and intensity as carbamazepine. (17) The EAN suggests that although there is only low-quality evidence in the literature, oxcarbazepine remains strongly recommended due to high confidence from clinical experience. Lamotrigine is also proposed; however, there is insufficient evidence from RCTs to truly comment on its effectiveness for the treatment of TN.. Moreover, gabapentin has been shown to be effective in treating many other neuropathic pain conditions including postherpetic neuralgia. Yet, the evidence supporting its use for the treatment of TN is

limited, and there is only low-quality evidence. Nevertheless, it is suggested that it can improve the pain and functional health status of patients with TN and there are few if any side effects. Other drugs that have been proposed for the treatment of TN include baclofen (specifically for those with multiple sclerosis who develop TN), topiramate, pregabalin, levetiracetam, and valproic acid. However, their support rests on small, open-label studies, and it would be prudent to proceed with caution.

Combination of two or more of the drugs listed above is a tried and tested option with good results. However, there is no solid proof that suggests one pairing is superior to another. For this reason, it is recommended to titrate these medicines slowly and reach maximal acceptable dosages before considering surgical management (19). Local anesthetic (LA) injections, particularly in TN patients with a specific trigger location, have been demonstrated to provide some short-term respite from pain for weeks to months. While some articles are highly effective and applicable, others are not. Botulin toxin A injections have also been observed to help reduce pain severity and frequency for those with TN. Proof of botulin toxin A's efficacy and safety came from a single randomized, placebo-controlled trial. This finding was supported by a meta-analysis of the available data, which also indicated that further large-scale, well-designed RCTs are warranted. (20)

The medications used to treat TN are primarily used to treat other medical conditions, namely epilepsy. Carbamazepine, which stabilizes sodium channels in an inactive state, is the gold standard and has been shown to be most efficacious according to one high-quality meta-analysis. Other studies have shown rates of 100% symptom relief in 70% of patients. Common side effects include tiredness, dizziness, and poor concentration, while some serious complications include agranulocytosis, aplastic anemia, and drug-drug interactions through hepatic cytochrome P450 induction. Oxcarbazepine is an alternative first-line therapy shown to have similar efficacy with fewer side effects. Second-line medications include baclofen, a GABAB receptor agonist, and lamotrigine, a sodium channel inhibitor. Baclofen acts by depressing excitatory neurotransmission and can be used alone or in conjunction with carbamazepine. Like carbamazepine, common side effects include sedation, faintness, fatigue, and nausea. Sudden discontinuation of this drug can lead to withdrawal consisting of seizures and hallucinations. Lamotrigine is an anticonvulsant that is also used to treat bipolar disorder. This medication was shown to have a beneficial response in TN that was proportionate to plasma levels up to a maximum dose of 400 mg/day in an open-label study of 15 patients. Another small double-blind placebo-controlled crossover trial showed that 400 mg lamotrigine therapy in conjunction with carbamazepine was more effective than placebo. (21) Similar to those of antiepileptics, side effects can include sleepiness, dizziness, headache, and vertigo. Skin rash may develop in 7–10% of patients and typically resolves with continued treatment, though 1 in 10,000 patients develop Stevens-Johnson syndrome in which the medication should be discontinued immediately. Newer medications including levetiracetam, topiramate, gabapentin, pregabalin, and botulinum toxin A are used as third-line therapies. A recent Cochrane systematic review, however, concluded that

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there is not enough evidence demonstrating significant benefit from non-anticonvulsants for treating TN. (22) Surgical Therapy Surgical management for TN patients should be reserved for those who have either failed medical treatment with at least 3 medications, suffer intolerable side-effects, or have suffered relapse of symptoms. It has been estimated that up to 50% of this patient population will require surgery at some point. Surgical options consist of destructive and nondestructive (microvascular decompression) modalities. (23) Microvascular decompression (MVD) is the most invasive surgical option though most successful for permanent treatment of pain. It has a low risk of sensory loss and is a good option for otherwise healthy patients and those who have failed less invasive treatments. Long-term studies have shown that this method provides lasting pain relief in more than 70% of patients. This procedure also provides the highest long-term patient satisfaction and lowest rate of pain recurrence in comparison to other surgical treatments.

The three types of rhizotomy include mechanical (balloon compression of the Gasserian ganglion), chemical (glycerol injection of the trigeminal cistern), and radiofrequency thermal (application of heat to damage the trigeminal nerve ganglion). Access to the trigeminal ganglion for these techniques is gained by threading of a cannula through the foramen ovale. Balloon compression offers immediate pain relief in 80–90% of patients and time free from medications from 2 to 3 years (24). Glycerol rhizotomy has a similarly high short-term success rate, with over 90% of patients obtaining initial relief and over 50% of patients remaining pain free at three years (25). Thermocoagulation rhizotomy also provides a high initial success rate of 90%, though recurrence occurs in 25% of cases. Though less invasive than microvascular neuralgia, these percutaneous procedures have the risk of sensory loss in the trigeminal distribution (50%), dysthesias (6%), anesthesia dolorosa (4%), a feared complication consisting of numbness and pain in the targeted dermatome), corneal numbness leading to keratitis (4%), aseptic meningitis (0.2%), and very small risk of mortality. Gamma knife radiosurgery (GKRS) is used in treatment centers as a surgical alternative for poor surgical candidates or those refusing more invasive therapy. This is a stereotactic, outpatient procedure that utilizes high doses (70– 80 Gy) of submillimeter radiation beams focused on the trigeminal root entry zone which causes necrosis over time and thus decreases pain signals. A systematic review demonstrated a 69% success rate at 1 year and 52% at 3 years after surgery.

Emerging Therapy Neuromodulation via motor cortex stimulation (MCS) and deep brain stimulation (DBS), though currently off label, have been described in literature as possible treatments for refractory cases. Use of MCS has been documented to bring effective pain relief in 75–100% of patients undergoing treatment for neuropathic pain syndrome. However, the patients studied were mostly those with complex regional pain syndrome and only a few had classic TN. DBS has also been practiced as treatment for pain refractory to medical and surgical methods since 1997. The posterior hypothalamus has been hypothesized to act as a switchboard for the neuropsychological circuits of pain behavior and the neuro vegetative system; thus, it has been the target of DBS treatment for pain. Yet, no evidence has been shown for DBS as sole therapy

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for refractory TN. While peripheral nerve/field stimulation is used to treat chronic, neuropathic, and refractory pain for a wide variety of conditions, literature involving TN is lacking. However, a few promising studies have been conducted in small sample sizes. A case report published by Abd-Elsayed et al. in 2015 described a TN patient who was refractory to conservative medical management as well as trigeminal nerve blocks. (26) Following implantation of a peripheral nerve stimulator with a supraorbital, infraorbital, and frontoparietal leads, the patient had complete resolution of her pain and a significantly increased quality of life. This case study shows that peripheral nerve stimulation could be a promising alternative treatment for refractory TN and merits further research.

Although pharmaceutical options represent the first line of treatment for TN, reports estimate that 50% of patients will eventually require surgical management to relieve the pain. The surgeries are reserved for TN, in which a neurovascular conflict can be determined. As previously mentioned, an MRI focusing on the posterior fossa is usually necessary to determine the cause of the compression, such as tumors or lesions, large vessels, or other vascular malformations. Microvascular decompression (MVD) is usually the first-choice treatment. It entails performing a craniotomy and posterior fossa exploration to decompress the nerve by resetting the vascular loop or other irregularity affecting the trigeminal nerve, thereby positioning or providing a more normal anatomy. Studies have shown that pain relief after the operation is usually immediate, and it leads to the longest duration of pain freedom in comparison with other procedures. (27) In the event that the aforementioned method doesn't work, or if the patient is resistant to it, trigeminal ganglion peripheral lesioning procedures are used. These procedures effectively injure or kill the nerve fibers thought to be responsible for TN pain. Glycerol rhizotomy, mechanical rhizotomy, and radiofrequency rhizotomy are all viable options for this surgical procedure. Caustic glycerol is injected around the nerves that exit or enter the trigeminal ganglion; a procedure known as rhizotomy. Balloon compression of the trigeminal ganglion can produce a mechanical rhizotomy. Finally, percutaneous radiofrequency rhizotomy allows for the selective destruction of the underlying sensory nerve fibers by means of heat. Many different types of surgical procedures can alleviate pain almost instantly. Although all of these methods are effective, with patients reporting relief from pain in the majority of cases, balloon compression provides more sustained relief for patients, along with fewer long-term complications, reduced morbidity, and no fatalities.(28,29) Finally, TN can be treated with stereotactic radiosurgery using cutting-edge technology like Gamma Knife, CyberKnife, and linear accelerators with multileaf collimator capabilities (LINAC-MLC).(30-33) However, it has been reported that the pain-relieving effects may take up to six months to kick in. When other forms of treatment for TN have failed or when patients are not good surgical candidates, peripheral neurectomy may be considered as a last resort.

Conclusion

Medication, surgery, and complementary therapies are all available as treatment options. The preferred initial treatment for TN is medical medication. Anticonvulsants and tricyclic

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antidepressants serve as the cornerstones of treatment. Carbamazepine is the first-line treatment for TN; however, additional medications, including baclofen, gabapentin, lidocaine, and misoprostol, have shown success in resistant patients. Most patients react at least briefly to anticonvulsant drug treatment. Neurosurgical intervention may benefit patients who cannot tolerate or do not respond to pharmacological therapy. Microvascular decompression of the trigeminal nerve root, neuro-ablation via rhizotomy with radiofrequency thermocoagulation, mechanical balloon compression, and chemical neurectomy are the most common techniques. There are some indications that botulinum toxin injections may also be effective in medically resistant patients. Neuromodulation and peripheral nerve field stimulation are potential alternatives to conventional pain treatments that warrant additional investigation.

There are numerous options available, ranging from conventional medicine and peripheral blocks to surgical techniques. We now have access to cutting-edge, innovative methods that show great promise. The only way to prove that these methods work is with large-scale randomized controlled trials. The ideal method would be to provide long-lasting relief from pain with minimal side effects that could be performed in a single outpatient visit.

Conflicts of Interest- None

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