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Trigeminal Neuralgia – where are we today?

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Abstract

Introduction: Trigeminal neuralgia (TN) is one of the most crippling facial pain syndromes, which has a significant impact on quality of life. This chronic disorder presents as brief shock-like paroxysmal severe, stabbing pain with rapid onset in the distribution of trigeminal nerve (CNV). The aim of this article was to review the recent literature about the epidemiology, pathogenesis, diagnosis, treatment methods and the important advances in all these fields.

Etiology and pathomechanism: The best known and tested theory on the genesis of the trigeminal neuralgia seems to be a nerve compression at the nerve root entry-zone. However there are other theories like the trigeminal convergence-projection theory, the bioresonance hypothesis or the ignition theory that are trying to explain the etiology of TN.

Treatment: Available treatment methods consist mainly of medications and surgical procedures. Surgical treatment may be divided into 2 categories: destructive and non-destructive. Among these interventions we can distinguish percutaneous rhizotomy stereotactic radiosurgery and microvascular decompression. All of them are very efficacious, however MVD is approved as the gold standard in the treatment of TN. Botulinum neurotoxin type A injections are not the first line for treatment, but it may be an attractive

alternative for classic pharmaceutical or surgical therapy, as it's safe and effective. Acupuncture is also proposed in recent studies as a valuable treatment option, even though there is little well-designed research.

Conclusion: Much remains to be learned about the diagnosis, pathomechanism and methods of treatment of neuropathic pain and the efficacy of each of them. Further evidence-based studies are needed, as the amount of reliable materials is still not sufficient and lots of them have yet to be examined.

Keywords: trigeminal, neuralgia, MVD, rhizotomy, neuropathic pain

Introduction

Trigeminal neuralgia (TN) also reffered as *tic douloureux*, prosopalgia, Fothergill's disease or the suicide disease is a chronic disorder characterized by relapsing seizures of piercing facial pain in the skin area innervated by trigeminal nerve (CNV).[1] The first full and the most complete description of TN was given in 1773 by previously mentioned John Fothergills. However, the first attempts to describe this disease took place many years before as evidenced by the manuscripts of Galen, Aretaeus of Cappadocia or 11th century work by Avicenna, who mentioned similar symptoms and called them „tortura oris".[2]

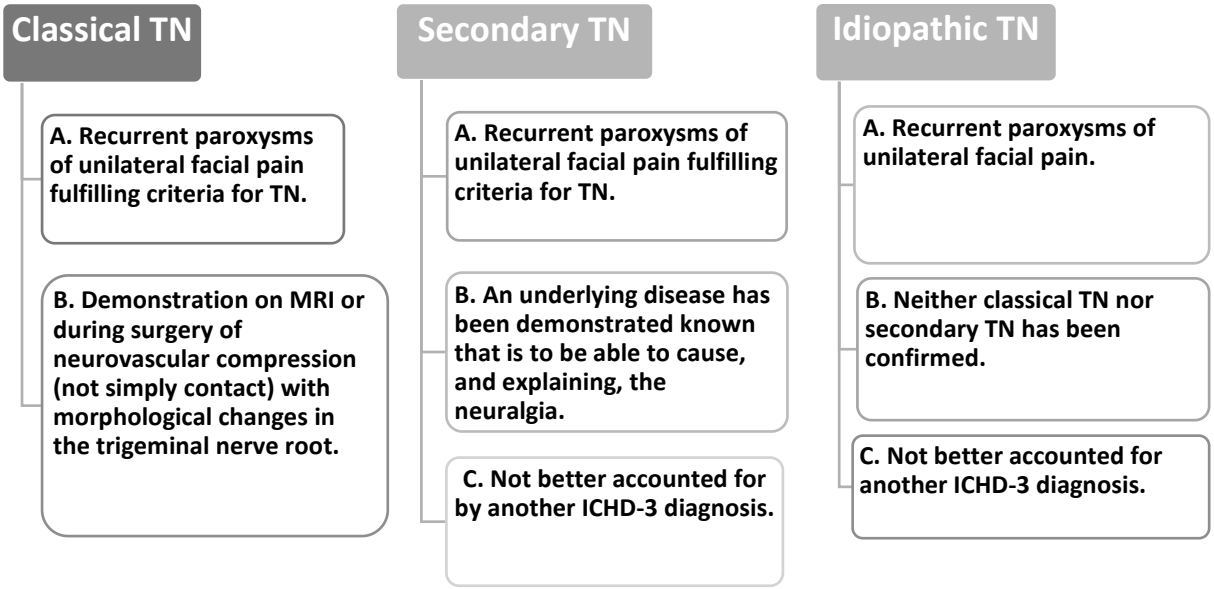
Tab. 1 Diagnostic criteria for TN according to ICHD-3.[3]

A	Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond and fulfilling criteria **B** and **C**.	
B	Pain has all of the following characteristics:	1. lasting from a fraction of a second to two minutes
		2. severe intensity
		3. electric shock-like, shooting, stabbing or sharp in quality
C	Precipitated by innocuous stimuli within the affected trigeminal distribution.	
D	Not better accounted for by another ICHD-3 diagnosis.	

According to European Academy of Neurology (EAN) based on etiological factors we can distinguish 3 types of trigeminal neuralgia[4]:

I. idiopathic TN (ITN) – without ultrastructural modifications of CNV root and no neurovascular conflict diagnosed
II. primary or classical TN (PTN/TN1) – caused by neurovascular conflict with ultrastructural changes of CNV root
III. secondary TN (STN/TN2) – arose as a result of neurological disorders (e.g. cerebellopontine's angle tumors)

Fig. 1 Diagnostic criteria for differentiation types of TN according to ICHD-3.[3]



The scientists also differentiate two phenotypes: solely paroxysmal TN (with convulsive pain only) and TN with constant, uninterrupted pain.[5] This terminology and nomenclature have been shared in the third edition of the International Classification of Headache Disorders (ICHD-3).[3]

Epidemiology

Prosopalgia is considered a rare disease as its prevalence ranges from 12.6/100,000/year to 27/100,000/year which corresponds with 0.015% of general population[6], however some sources claim that it may reach the 0.07%.[7] The disorder may affect people in any age but it occurs more often in those over age 50, with slightly higher frequency ranging from 1:1,5 to 1:2 among the female population.[1] TN as a rule is not connected with a familial inheritance, although we can find in the literature over 164 reported cases of familial trigeminal neuralgia.[8] The maxillary (V2) and mandibular (V3) nerves are more frequently affected than the opthalmic nerve (V1), which is seized only in 5% of cases. Predominantly, TN pain is unilateral and usually right-sided. However, around 4% cases are bilateral, although the attacks rarely affects both sides in the same time.[9]

Etiology and pathomechanism

Most of the theories on the subject of the origin of trigeminal neuralgia assumed a nerve compression at the nerve root entry-zone (REZ) for various reasons such as an abnormal artery or vein, anatomical abnormalities, vascular malformations, aneurysm, vessel aggregations, multifarious cysts and tumors.[6] Anatomical variations focus mainly on vascular sector and especially on the superior cerebral artery (SCA).[10] Nonetheless, changes in other anatomical structures are suspected to be the cause of trigeminal neuralgia. In the midst of these changes the scientists point out e.g. inferior alveolar nerve[11], infraorbital nerve[12] or foramen ovale and rotundum[13,14].

The other hypothesis, called the trigeminal convergence-projection theory, claims that constant or repeated nociceptive stimulation of head and neck region converge in spinal nucleus of CNV (subnucleus caudalis) what leads to promotion of vasoactive substances and

neurotransmitters. Obtained situation is causing the decreased threshold of contiguous second-order neurons that perceive stimuli other than this coming from nociceptive receptors. Signals coming from this excited neurons are transmitted to the somatosensory cortex and may be further interpreted as pain.[15,16]

The bioresonance hypothesis states that the trigeminal nerve, which is submerged in cerebrospinal fluid (CSF), vibrates at its own specific frequency. When the structures surrounding the CNV vibrate at similar frequency, the resonance of the trigeminal nerve occurs. The disproportions in frequency values may lead to nerve fibers' damage and cause a wide spectrum of electrophysiological changes what finally can result as a pain feeling.[17]

The ignition theory affirms that the damaged or injured afferent neurons of trigeminal root or trigeminal ganglion reveal itself as hyperexcitability of the axons which leads to synchronized discharge activity causing pain paroxysms.[16,18]

Treatment

Pharmacological treatment

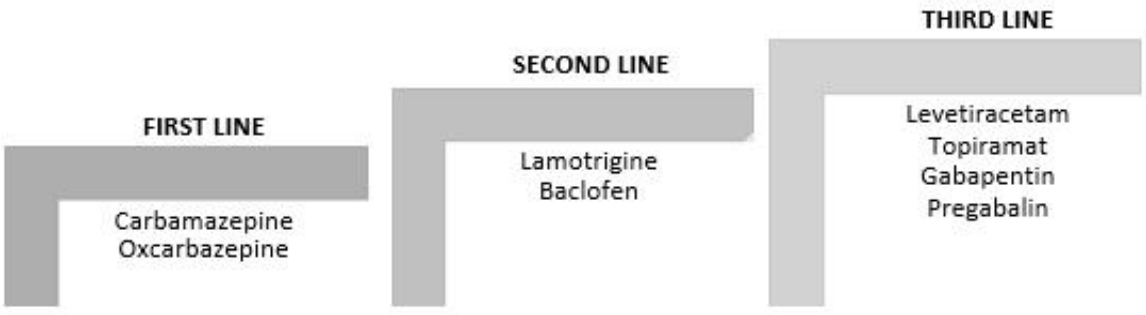
The first line drugs for controlling symptoms of classic TN are carbamazepine and oxcarbazepine. Recommended dose of carbamazepine are 200-1200 mg daily and for oxcarbazepine are 600-1800 mg daily.[19] Carbamazepine is considered the gold standard for the initial medical treatment of TN.[4] Its mechanism relies on stabilizing sodium channels in an inactive state, what effects in reducing the excitability of neural membranes. Carbamazepine has also been shown to potentiate gamma aminobutyric acid (GABA) receptors, what is suspected to boost its efficacy in neuropathic pain.[19]

Second-line therapy is based on very little evidence.[20] Drugs included in this group are lamotrigine, baclofen, and pimozide. These medicaments should be taken into account when reaching full dosage of sodium channel blockers is impossible because of side effects.[21]

Third-line therapy covers newer antiepileptic drugs (AEDs), which have been being tested within the past few years. Those are gabapentin, pregabalin, topiramate and levetiracetam.[22]

Doses of the drugs should be reasonably increased to the maximum allowed daily dose until appropriate reduction of symptoms is obtained. If maximal allowed doses are reached without achieving satisfactory results, a surgical procedures should be considered as a treatment option.[23]

Fig. 2 Medical therapies for trigeminal neuralgia treatment.[1,10,24]



Acupuncture

This therapeutic method is commonly used for diverse conditions, including chronic

diseases and pain control. There are reports in the literature that show the utility of acupuncture in treating neuropathic pain, including neuralgias, however there are not many studies with good methodology. Regardless of the type, a manual (MA) or the electro-acupuncture (EA), are the subject of research into their usefulness in treatment of TN.[25,26]

In 2020 Zhao et al. proposed a protocol for systematic reviews and meta-analysis for further researches on efficacy and safety of acupuncture for TN treatment.[27]

Jie Gao et al. in their RCT performed on 116 patients with ITN showed the potentially positive effects of manual acupuncture, such as reducing pain, improving quality of life and cognitive functions.[28]

Hu et al. in their meta-analysis, including 33 studies, assessed the efficiency of MA and/or EA in the therapy of PTN. The study shows that both MA and EA seem to be more significant than carbamazepine in improving response rate (RR) and reducing recurrence. Furthermore, the MA has more positive influence on alleviating pain intensity than carbamazepine itself. Anyhow, the combination of carbamazepine and acupuncture appears to be more influential for improving RR than carbamazepine alone. [29]

Nonetheless, considering limitations of the studies and their low standard of methodology, the level of all currently available evidence using the GRADE system should be considered as ‘low’ or ‘very low’.[29,30]

Percutaneous rhizotomy

There are three widespread procedures of rhizotomy, all of which require a needle to be inserted through an foramen ovale in order to damage the fibers of the trigeminal nerve: radiofrequency thermal rhizotomy (PRR, creates an injury throughout heat application), chemical rhizotomy (PRGR, works by glycerol injection into trigeminal cistern) and mechanical rhizotomy or micro-compression (PBC, is based on compression of a Gasserian ganglion by inflated balloon).[31] Usually a needle is punctured 25 mm laterally to the labial fissure and is guided mesially to the ramus of the jaw into the foramen ovale with the help of fluoroscopic imaging. To confirm the position of the needle, the operators are using a lateral radiograph.[32]

Radiofrequency thermocoagulation

Lesioning with the use of the radiofrequency owes its genesis to Rethi, who attempted to electrocoagulate the TN and rootlets of trigeminal ganglion in 1913. However, it was Sweet, who paved the way in the use of thermocoagulation to aim the trigeminal rootlets with succes in 1975.[33]

After a short-lasting induction, usually with the use of propofol, a needle with an obturator is introduced into the foramen ovale, however there are authors that are describing accessing through the foramen rotundum. Adjustment of the placement in the foramen is achieved with the help of the fluoroscopy. When the position is confirmed, the obturator is removed and the electrode is introduced. The patient is awakened, and his sensory and motor responses are being tested. Electric impulses are usually acquired at 0.2 to 1 V (50 Hz for 0.2 milliseconds). The stimulating electrode is then substituted with the thermocouple, and lesions are made at a maximum of 0.5 V at 5 and 75 cycles per second with the temperature ranging from 55°C to 80°C for 0.5 to 2 minutes. Individual techniques differ from the utilization of a single lesion to the use of extra lesions with the purpose of producing hypalgesia in the aimed branch.[34,35]

Kanpolat et al. in their long-term trial performed 2138 percutaneous radiofrequency rhizotomies on 1600 patients. The obtained results showed pain relief in 92% of patients who underwent a single procedure or with multiple procedures at 5 years follow-up. At 10-year check-up, 52.3% of the patients who underwent a single procedure and 94.2% of the patients who underwent multiple procedures had experienced pain relief. At 20-year follow up the rates were respectively 41% and 100%. [36]

Primary response rate to PRR is described at 97.6% to 99%. After 6 months, there is a 83.3% to 89.9% response rate.[36,37]

Data on recurrence rates vary from 38.2% at 1 year to 10% at 6.5 years follow-up.[32]

The main limitations preventing more widespread use of RF are the frequency and severity of side effects.[34]

Glycerol injections

The first full description of this technique was given by *Håkanson* in 1981.[38] This method was further developed, with only minor changes by Arias and by Bergenheim.[39] The pain relief is caused by demyelination and axonal fragmentation.[40]

The procedure consists of needle insertion through the oval foramen with the help of the Härtel trajectory assisted by fluoroscopy. When the spontaneous cerebrospinal fluid flow is obtained, cisternography is performed by iohexol injection to verify a correct needle position. Subsequently, the cistern is emptied, and 0.1 to 0.4 mL of anhydrous glycerol is injected, followed by needle removal. After that, the patient is kept in a sitting position for an hour with the head positioned depending on which trigeminal branch is affected.[41]

Chen et al. in their study performed on an impressive group of 4012 patients who have undergone PRGR procedure. A complete initial pain relief was reported in 3926 (97.9%) patients, a partial improvement in 114 (2.8%) patients and no effect was observed only in three (0.08%) patients. Recurrence was reported in 594 (18.82%) patients and the rates were the highest during the first 3 years postoperatively. The complete success rate was assessed at 81.18% for 10 years after intervention.[42]

Ordinarily reported impediments from PRGR include dysesthesias (average, 8.3%), corneal numbness (average, 8.1%), and masseter weakness (average, 3.1%).[34]

In the work of Pollock the only existing and statistically significant prognostic positive effect of treatment was pain during the glycerol injection. [43] Burchiel in his paper pointed out that the success rates of PRGR depends on primary degree of sensory loss.[44]

One advantage of PRGR in comparison with PBC is that it is less invasive because the needle used in PRGR is much thinner and compression of anatomical structures is not required. What's more, the PRGR can be performed under local anesthesia and sedation and general anesthesia is not required like in the PBC. The major drawback of PRGR is that it is technically more complicated and harder to perform than PBC, hence the experience of the surgeon can be crucial in the outcome. [45]

Balloon compression

PBR owes its origins to work of Shelden and Pudenz, although their original purpose was to decompress the semilunar ganglion.[34] Continuing their work, Taarnhøj in 1952 performed the retro-gasserian ganglion decompression on 10 patients through a infratemporal approach and achieved satisfying results.[46] Further researches led to the hypothesis that the

alleviation of the pain is more likely caused by an operative trauma rather than decompression itself. Notwithstanding, it wasn't until 1983 that Mullan and Lichtor, after finding out that postoperative facial numbness was related to more effective pain reduction and continuing work of their antecedents, introduced transdermal balloon compression, which was further modified by Brown. [47,48] In its actual form, PBR is considered as an effective treatment option for TN.[34]

The placement of catheter in the center of the porous aims for second-division or multidivisional pain, when the lateral placement targets third-division pain and the mesial placement focuses more on the symptoms coming from first-division. The balloon is dilated with iohexol for 60 to 180 seconds to a pressure of approximately 1000 to 1200 mm Hg, which may be roughly 0.3 to 0.8 ml, what results in a pear shape visible on radiograph.[34,41]

Brown et al. in their study performed on group of 50 patients with TN achieved exquisite results in reducing initial pain relief rated at 96%.[48] Average rates of complete pain relief at 6 months and 3 years were respectively 91% and 69%, and other authors in their studies has reported similar results.[34,48,49] PBR is especially useful in patients with first-division pain in view of the fact that it does not damage the small myelinated fibers which are responsible for the blink reflex and because of which it does not provoke the corneal keratitis. [50] On the other hand, the recurrence rates after applying this method are relatively high – averaging 26%, with a mean time to recurrence of 18 months.[34,48]

According to the work of AAN/EFNS from 2008, there have been 4 uncontrolled case studies of transdermal rhizotomies and the results showed that initial pain relief is achieved in 90% of patients, however it's not permanent and this rates gradually decrease in the following years, and after 5 years approximately only half of patients are pain free.[51] The most common complication reported are sensory disturbances in the area of innervation of the CN V (50%), hereafter dysesthesias (6%), anesthesia dolorosa (4%), corneal numbness with risk of keratitis (4%), aseptic meningitis (0.2%), and negligible mortality.[51,52] Percutaneous procedures are believed to be less invasive and have favorable balance of profits and potential complications.[22]

Botulinum injections

Botulinum neurotoxin is a powerful tool in the treatment of several orofacial pathologies, including trigeminal neuralgia. Botulinum toxin type A (BTX-A) relaxes striated muscle by inhibiting acetylcholine's release from presynaptic nerve terminals. As a result, the neuromuscular junction is blocked. One of the theories proposes that BTX-A pain therapy is based on relieving muscle trigger points. Literature sources mention that around 72% of patients have myofascial trigger points. On the grounds of this report it can be concluded that BTX-A might be useful in 70% of patients with TN.[53,54]

Increasing evidence confirms that BTX-A injection is efficient and may be particularly useful in the treatment of patients before surgery or patients who are unwilling to undergo more invasive procedures.[6] The efficiency of Botulinum toxin treatment is determined on the basis of the guidelines of the American Academy of Neurology. Following the published data, BTX-A treatment is effective in trigeminal neuralgia (level A evidence). It is confirmed by two class I studies.[55]

In clinical trials no significant difference between dosages of BTX-A was noticed. Maximum effectiveness was observed between 6 weeks and 3 months after the injection

procedure. The most common side effects were: facial asymmetry, headaches, haematoma, oedema, itching and pain. All complaints were temporary. Facial asymmetry may remain constant for 6 - 7 weeks. The other conditions resolved in 1 week.[53]

BTX-A injection is a promising therapeutic strategy for treatment of TN. According to recent studies this type of therapy is safe and efficacious for patients with classical as well as drug-resistant idiopathic trigeminal neuralgia.[56]

Microvascular decompression (MVD)

Microvascular decompression (MVD) among all surgical procedures is considered as the most effective method of trigeminal neuralgia treatment. MVD is recommended for patients with classic TN, who suffer from drug-resistant pain. It is advised for the patients with TN in good general health condition or for patients who are refractory to less invasive techniques such as rhizotomy or radiosurgery.[19,57]

The treatment procedure is performed under general anesthesia. The surgery consists in retrosigmoid craniotomy and microsurgical posterior fossa exploration, which enables the identification of the trigeminal nerve and the compressive blood vessels (usually arteries, but in some cases veins may cause the compression. To maintain the separation the most common method is based on placing teflon pads between the nerve and the vessel. In the case of the vertebrobasilar artery (VBA) compression some authors describe using an aneurysm clip (2 patients), brainstem auditory-evoked potentials-BAEPs (2 studies) or facial nerve monitoring with electromyography- EMG (1 study).[32,57]

Although this type of therapy is the most invasive and technically demanding, it provides the highest long-term pain relief outcomes that have been reported in the current literature. The overall rate of immediate post-operative pain relief is 80.3% to 96%. One prospective study demonstrated that 92.5% of patients were pain free at 28 month follow-up. Another study showed that during 38 months of follow-up, 85% of patients had satisfying pain control. After 5 years, 72% to 85% had good pain control. Barker et al. in their study of MVD with long-term follow-up performed that after 10 years in 70% patients pain didn't occur. Sindou et al. in the study with very long-term follow-up found that after 15 years 73.4% were still free of pain. Male patients with postoperative pain relief, no venous compression and shorter TN duration might have better outcomes. Bilateral pain implies worse treatment outcomes.[32,57]

The frequency of complications is low. Complications such as new burning or aching pain, sensory loss and hearing loss appear in 2–10%. Aseptic meningitis, as the most common, occurs in 11%. There is a low rate of serious complications: cerebrospinal fluid leaks, infarction, hematoma (4%), cranial nerve dysfunction (2%), stroke (0.3%). Although complication rate is low, MVD has a risk of death reported at around 0.15-0.8%. [19,24]

MVD is an effective operation, but unfortunately there are no standardized surgical procedures for trigeminal neuralgia without neurovascular compression (NVC). The therapy of TN without NVC is based on trigeminal root compression or internal neurolysis, which are considered as very destructive. These surgical procedures may cause permanent trigeminal nerve damage. Also the long-term efficiency wasn't identified. The study with 19 patients demonstrated that 360-degree circumferential arachnoid dissection may be an alternative method of treatment of TN for patients without NVC.[58]

Stereotactic radiosurgery (gamma knife/cyber knife)

Gamma knife radiosurgery (GKRS) has been recently regarded as an effective way of the treatment of trigeminal neuralgia. This outpatient and non-invasive procedure is using a highly focused type of radiation. During such therapy a high dose of convergent beams of radiation (70-90 Gy) is delivered at the trigeminal root entry zone. Stereotactic radiosurgery leads to the axonal degeneration and necrosis and also disturbs pain signals. [19,20,24]

Pain relief is progressive and appears over a few weeks or months.[59] In the systemic review provided by the American Academy of Neurology (AAN) and European Federation of Neurological Societies (EFNS) there was presented 3 case series of gamma knife therapy, where 69% of patients were pain free at a year after GKRS. Also 52% were still pain free after 3 years.[19]

Taich et al. in their study state that after gamma knife radiosurgery 79% of patients responding to treatment reported pain relief. The average duration of achieving pain relief was 2,5 months. They also report that pain relief wasn't improved with high doses of radiation.[60] In another large study Kondziolka et al. showed that 89% of patients reported pain relief an average of 1 month and total pain relief was achieved on average in 5 months.[61] Martinez Moreno et al. reported that 76% of patients remained free of pain at 7 years.[62] In another studies 30% to 51.5% still showed pain relief at 10 years.[32] In a multifactor analysis performed that initial response is associated with TN1, older age and prior percutaneous procedures.[60] Also, positive response to medication is a predictor of better outcomes.[32]

Considering the efficiency of repeat GKRS current studies demonstrate that the efficiency wasn't decreased in patients who had to repeat GKRS. However, after the next cyber knife procedure new sensory symptoms may develop (dysesthesia, paresthesia or numbness).[60]

The most common side effects are facial numbness (9-37%) and sensory loss or paresthesia (6-13%) that can develop with a delay (up to 6 months). (7) Reporting facial numbness is associated with higher dose of radiation (90Gy) and previous stereotactic radiosurgery.[60]

Stereotactic radiosurgery provides lots of advantages, because of its non-invasive character. Anesthesia is not required , therefore it's a good option for patients with other health problems or who don't want to undergo invasive surgery. Thanks to this method, patients with multiple medical contraindications who can't go for MVD, have the chance to recover from the persistent pain. Unfortunately the GKRS is expensive and its widespread use is limited.[19]

Tab. 2 Advantages and disadvantages of treatment methods of TN.[30,31,55]

Method	Advantages	Disadvantages
Pharmacotherapy	Noninvasive Nondestructive Accesibility	Deferred pain relief Side effects of chronic medications
Acupuncture	Noninvasive Nondestructive	Low evidence of effectivness
Radiofrequency thermocoagulation	Minimally invasive Immediate pain relief	Destructive
Glycerol injection	Minimally invasive Immediate pain relief	Destructive
Balloon microcompression	Minimally invasive Immediate pain relief	Destructive Risk of masseter weakness Risk of diplopia
Botulin injection	Minimally invasive Immediate pain relief	Risk of facial asymmetry (lasting up to 7 weeks) Relatively short duration of effects
Microvascular decompression	Immediate pain relief The highest efficiency The longest lasting results	Most invasive Risk of mimic and mastication muscles weakness Risk of hearing loss
Stereotactic radiosurgery	Minimally invasive	Destructive Deferred pain relief

Summary

Trigeminal neuralgia is one of the most severe forms of pain that has been reported in medical literature since ancient times. It's a chronic, very disabling condition of neuropathic facial pain which presents with recurrent attacks of stabbing pain in the distribution of the fifth cranial nerve. Lancinating pain is triggered by minimal stimulation (light touch, talking or chewing).

Diagnostic tests are necessary to distinguish three etiologic categories: idiopathic (nothing may be found), classical (neurovascular compression at the trigeminal root near its entry into the pons and secondary (related to major neurological diseases such as multiple sclerosis (MS) or tumors). In each case, MRI should be performed in order to exclude these pathologies in the region of cerebellopontine angle.

First-line therapy involves pharmaceutical drugs. Carbamazepine and oxcarbazepine are still the first-choice medical treatment. In case of ineffectiveness, surgical procedures should be considered. Surgical treatment may be divided into 2 categories: destructive and non-destructive. Among these interventions we can distinguish percutaneous rhizotomy (radiofrequency thermal rhizotomy, balloon compression and glycerol injections), stereotactic radiosurgery and microvascular decompression. All of them are very efficacious however MVD is known as a medically proven method of removing the cause of trigeminal nerve decompression. The neurologist should work in a collaboration with the neurosurgeon and the patient to determine what kind of surgical therapy and when need to be performed.

Gamma knife or rhizotomies may be offered to patients who can't be candidates for MVD or who are reluctant to undergo this surgery. Patients with classic TN more often achieve successful outcomes in recovery and remission in comparison to patients with atypical symptoms.

Botulinum toxin A promising results may provide a safe and effective alternative strategy for patients with drug-resistant classical and idiopathic TN. Acupuncture is also proposed in recent studies as a valuable treatment option, even though there is little well-designed research.

There is still an ongoing debate within the pathogenesis of trigeminal neuralgia. Nowadays, neurovascular conflict is the most common and accepted theory. Other mechanisms should still be taken into consideration to find a complete explanation of the cause of the TN. Less explored theories or the new ones may lead to alternative and successful treatment procedures.

All things considered, there is still much remains to be learned about the diagnosis, pathomechanism and methods of treatment of neuropathic pain and the efficacy of each of them. Further comprehensive, evidence-based research is needed, as the amount of reliable materials is still not sufficient and lots of them have yet to be examined.

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