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Trigeminal Neuralgia: Pharmacological and Surgical Treatment

Alice Madureira Fontoura Alves

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Autora

Alice Madureira Fontoura Alves

alicemad97@gmail.com

Mestrado Integrado em Medicina

Instituto Ciências Biomédicas Abel Salazar, Universidade do Porto

Orientação

Professora Doutora Dalila Maria Rodrigues Gonçalves Veiga Mora

Médica Assistente Hospitalar de Anestesiologista – Serviço de Anestesiologia do Centro Hospitalar Universitário do Porto

Professora Auxiliar Convidada do Instituto Ciências Biomédicas Abel Salazar, Universidade do Porto

Coorientação

Dr. Carlos Jorge da Silva Andrade

Médico Assistente Hospitalar de Neurologia – Serviço de Neurologia do Centro Hospitalar Universitário do Porto

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Autora | Alice Madureira Fontoura Alves

Assinado por: Dalila Maria Rodrigues Gonçalves Veiga Mora
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Orientação | Professora Doutora Dalila Maria Rodrigues Gonçalves Veiga Mora

Coorientação | Dr. Carlos Jorge da Silva Andrade

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RESUMO

Introdução: A nevralgia do trigémeo é uma doença debilitante que se carateriza por dor de curta duração, severa, em facada e que provoca episódios recorrentes de dor facial. Investigação recente possibilitou uma melhor compreensão da sintomatologia, fisiopatologia e tratamento da nevralgia do trigémeo, o que permitiu proceder a alterações na classificação e no prognóstico desta doença.
Objetivos: A revisão da literatura recente da nevralgia do trigémeo foi realizada numa perspetiva de compreender a sua clínica, fisiopatologia e classificação. Foi realizada uma revisão da eficácia e segurança do diagnóstico e, principalmente, de opções de tratamento para a nevralgia do trigémeo.
Métodos: A pesquisa bibliográfica foi realizada na plataforma eletrónica *PubMed*, tendo por base as palavras-chave: *trigeminal neuralgia*, trigeminal neuralgia treatment, surgical treatment*.
Resultados: O tratamento de primeira-linha para a nevralgia do trigémeo inclui a carbamazepina ou oxcarbazepina. Apesar de terem eficácia semelhante, a oxcarbazepina apresenta menos efeitos-laterais. A terapêutica de segunda-linha deverá ser considerada quando o tratamento com a carbamazepina e a oxcarbazepina é ineficaz ou pouco tolerado. Outros fármacos como lamotrigina, gabapentina, pregabalina, baclofeno e toxina botulina tipo A poderão ser utilizados em monoterapia ou em associação à carbamazepine ou à oxcarbazepina. A cirurgia, por sua vez, é recomendada quando o controlo da dor é ineficaz com os fármacos ou quando a terapêutica médica é pouco tolerada. A descompressão microvascular é a primeira opção cirúrgica para doentes com nevralgia do trigémeo clássica. Na ausência de compressão neurovascular em exames de imagem, os procedimentos ablativos são os recomendados, nomeadamente: termocoagulação por radiofrequência, compressão por balão, rizotomia com glicerol, neurolise interna e radiocirurgia com *gamma-knife*. A admissão de doentes em meio hospitalar poderá justificar-se nos casos de exacerbações agudas da nevralgia do trigémeo para rehidratação, terapêutica endovenosa e titulação de fármacos anti-epiléticos. Neste sentido, a lidocaína ou fosfenitoína podem ser utilizados para o controlo agudo da dor. Outros fármacos como os agonistas da serotonina, sumatriptano, antagonistas dos recetores N-metil-D- aspartato e a toxina botulínica poderão ser também utilizados, contudo apresentam pouca evidência.
Conclusão: De facto, verificaram-se alterações importantes no que concerne ao diagnóstico e classificação da nevralgia do trigémeo. Além disso, foram atualizadas recomendações no que diz respeito ao tratamento farmacológico e cirúrgico. Porém, são necessários mais estudos de elevada qualidade que permitam aprimorar a abordagem e o tratamento de forma a colmatar as lacunas existentes do conhecimento atual.

ABSTRACT

BACKGROUD: Trigeminal neuralgia is a debilitating disease characterized by very severe, short-lasting stabbing pain that provokes recurrent episodes of facial pain. Recent research has led to new understandings into trigeminal neuralgia symptomatology, pathophysiology, and treatment, also allowing a modification in the classification and prognosis of the condition.

OBJECTIVE: Review of recent literature of TN in a comprehensive perspective of its clinical, pathophysiology, classification. Research into the efficacy and safety of diagnosis and mainly treatment options for TN.

METHODS: Exhausting bibliographic research was performed on the electronic database PubMed using terms: trigeminal neuralgia*, trigeminal neuralgia treatment, surgical treatment**.**

RESULTS: First-line therapy of trigeminal neuralgia includes carbamazepine or oxcarbazepine. Despite having similar efficacy, oxcarbazepine caused less side-effects. Second-line treatment should be considered when carbamazepine and oxcarbazepine become ineffective or poorly tolerated. Pharmaceuticals such as lamotrigine, gabapentin, pregabalin, baclofen, phenytoin and botulinum toxin type A can be used as monotherapy or as an add-on treatment with carbamazepine or oxcarbazepine. Surgery is recommended when pain is inadequately controlled with drugs or if medical therapy is poorly tolerated. Microvascular decompression is the first-line surgery offered to patients with classical trigeminal neuralgia. When neurovascular compression on neuroimaging is absent, then ablative procedures may be required; procedures such as: radiofrequency thermocoagulation, balloon compression, glycerol rhizolysis, internal neurolysis and gamma knife surgery. Inpatient admission might be necessary in patients with acute exacerbations of trigeminal neuralgia, for procedures such as: rehydration, intravenous treatment and titration of anti-epileptic drugs; lidocaine or fosphenytoin can be used to briefly relieve the pain. Other treatment options include serotonin agonist, sumatriptan, N-methyl-D-aspartate receptor antagonist and botulinum toxin, albeit with very limited evidence.

CONCLUSION: There were important changes regarding diagnosis and classification of trigeminal neuralgia. Also, recommendations concerning pharmacological and surgical treatment have been updated. Further studies are required to improve management and treatments, finding high quality evidence to rectify the existent gaps.

Abbreviations

BC: Balloon compression

CSF: Cerebrospinal fluid

CT: Computer tomography

EAN: European Academy of Neurology

GKS: Gamma knife surgery

GR: Glycerol rhizolysis

IASP: International Association for the Study of Pain

ICHD: International Classification of Headache Disorders

ICHD-3: International Classification of Headache Disorders third edition

HIS: International Headache Society

IN: Internal neurolysis

MRI: Magnetic resonance imaging

MS: Multiple sclerosis

MVD: Microvascular decompression

NMDA: N-Methyl-D-aspartate

NRS: Numerical rating scale

NVC: Neurovascular contact

PIFP: Persistent idiopathic facial pain

PTR: Percutaneous trigeminal rhizotomy

RCT: Randomized controlled trials

REZ: Root entry zone

RFTC: Radiofrequency thermocoagulation

SUNA: Short lasting unilateral neuralgiform headache with cranial autonomic symptoms

SUNCT: Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

TACs: Trigeminal autonomic cephalalgias

TN: Trigeminal neuralgia

VAS: Visual analogue scale

VGSC: Voltage-gated sodium channels

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1 INTRODUCTION

Trigeminal neuralgia is a neuropathic facial pain syndrome characterized by painful episodes triggered by innocuous stimuli such as: chewing, brushing teeth, talking or face touching. It negatively affects the quotidian life of patients. [1 2]

Trigeminal neuralgia was firstly described by the known philosopher John Locke in 1677. In 1756, Nicolaus Andre entitled the term "tic doulourex" for the condition that represents trigeminal neuralgia. Dr. John Fothergill provided the first complete and accurate description of TN. During his remarkable research work with patients, Dr. Fothergill suspected that TN could stem from cancer, instead of a convulsive condition. His suspicious arose from the untreatable and chronic nature of the pain. [3–5]

The IASP classified TN as a neuropathic pain and there should be objective signs which confirm the presence of a subjacent lesion or disease of the nervous system. For the secondary type of TN this requirement would be appropriate, although it doesn´t account for classical TN. In order to account for TN variants the ICHD developed a new classification consisting of 3 diagnostic types. The most common, classic neuralgia must show morphological changes (atrophy and/or displacement) in the nerve root, secondary to neurovascular compression. Secondary *TN,* as the name suggests, has an underlying aetiology. When there isn´t an identifying cause it is considered *idiopathic* TN.[1], [6]

Constant research and technological innovation have increased our understanding of TN, especially in recent years. For example, high-definition MRI studies showed that trigeminal REZ NVC changes in the trigeminal nerve´s anatomy were associated with symptomatic TN of the affected side. [7] A prospective study showed that direct artery contact produces constant trauma on the trigeminal nerve entry in the pons consequently, a degeneration of the local axons and demyelination can happen in this weak point. [8]

Trigeminal neuralgia could potentially be progressive and have poor prognosis, with slow deterioration over time, although recent studies didn´t confirm the apparent progressive character of this disease. Nevertheless, some studies indicate a good prognosis for the patients who were surgically treated. [9] This condition is associated with increasing anxiety and depression Some individuals may experience suicidal thoughts resulting in poor quality of life. This could be direct consequence of the pain or due to drug side effects. Thus, patients should be offered psychotherapy like cognitive behavioural therapy, so they can learning coping skills to deal with their pain. [10,11]

Expert management of medical therapy is mandatory for this disease because most treatment medicines are anticonvulsants, often administered in high doses to relieve the pain.

Moreover, there is weak supporting evidence for pharmacological treatment of TN. Treatment of TN with medicine can be difficult due to the lack of efficacy, adverse drug interactions and side effects.[12–14] The first-line treatment for TN is usually anticonvulsants drugs, such as carbamazepine or oxcarbazepine. Occasionally, a second medication is prescribed. Surgical techniques become the preferred treatment option when higher doses of medicine could yield sub-optimal pain suppression and/or induce noteworthy side effects. [15]

In this review, based on an exhausted review of the literature, we focused on classical TN and will provide recent, evidence-based knowledge concerning pharmacological and surgical treatment options for typical TN. In addition, we researched potential new treatment medicines, like botulinum toxin A and vanguard medications used on acute exacerbations of TN.

2 METHODS

An extensive literature research was conducted on the electronic platform *PubMed* for: scientific articles, especially systematic reviews, meta-analysis and clinical randomized-controlled trials, prospective, retrospective, and open-label studies to provide an update on definition, pathophysiology, epidemiology, classification, pharmacologic and surgical treatment of trigeminal neuralgia. Investigative articles were privileged to assess the most significant results on the literature considering this topic. Articles were mainly selected according to their relevance of content. Only relevant articles published since 2012 were used for my research, using the search keywords: *trigeminal neuralgia, management of trigeminal neuralgia, pharmacologic treatment of trigeminal neuralgia, surgical treatment of trigeminal neuralgia.*

3 EPIDEMIOLOGY

According to population-based studies, the lifetime prevalence of trigeminal neuralgia is estimated to be between 0,16% and 0,3%. [16] [17]. The annual incidence of this condition ranges between 4 to 29 per 100 000 per person. [18–20] The prevalence of TN is higher in women than men (3:4). [19,21] The right side of the face is more affected than the left side (R: 56% vs L: 41%). The second and third branches of the fifth cranial nerve are usually more involved.[21] The incidence of TN increases with age, with the average age of onset being between 53 and 57 years; however there has been TN reported from early age to elderhood. [21,22]

4 PATHOPHYSIOLOGY

Trigeminal neuralgia is composed of three main branches. The ophthalmic branch (V1) is the first one in the rostral-caudal order. This branch provides the sensory innervation of the upper part of the face and the two thirds of the anterior scalp, from the level of the palpebral fissure to the area of coronal suture, along with the eye and parts of the nasal cavity.

The maxillary branch (V2) is also a sensory branch. It reaches the upper teeth and correspondent gingiva, the palate and mucous membranes of the maxillary sinus, the nasal cavity, as well as the middle portions of face and skull above the mouth and below the forehead.

The mandibular branch (V3) is the only nerve with both sensory and motor fibres. The sensory portion of V3 innervates buccal mucosa, mandibular teeth and the chin area. The motor fibres of V3 supply all mastication muscles, which are responsible for controlling biting and chewing mechanisms. Additionally, it gives sensory fibres to the anterior two-thirds of the tongue. [23]

Neurovascular compression is an important mechanism underlying the pathophysiology of classical trigeminal neuralgia. It is thought that a blood vessel, either vein or artery (in the cerebellopontine cistern), can cause compression of the proximal site of sensory trigeminal root near of the brainstem (REZ). The transition from peripherical Schwann myelin cell to central oligodendroglia myelin represents an anatomical gap, and neurovascular contact makes this zone more susceptible to demyelination. To test this hypothesis several biopsy specimens of the disrupted tissue were taken during a surgical procedure. As predicted, most of the axons located in the severely affected area suffered a process of demyelination with direct apposition of demyelinated axons; while dysmyelination and remyelination was observed in the nearby axons due to possible microvascular ischemic injury. [24] [25] [26] These changes may induce episodes of re-excitation, slowing conduction on the fibres action potential, hence acting like an ectopic action potential through the contiguous fibres.[27]

The mechanism of touch-evoked pain can be explained by the relation between the fast myelinated Aβ fibres and the Aδ fibres, fibres of nociceptive pathway. The first fibres activate the second ones inducing the paroxysms of painful episodes. After some time, the spontaneous discharges cease and are unable to restart for a while (the refractory period).

Voltage-gated sodium channels are involved in the treatment of TN. Among their subclasses, Nav.1.3 was down-regulated, Nav.1.7 was up-regulated and there was a correlation between Nav.1.7 and Nav.1.8 in patients with TN. Consequently, this alterations of quick activation and inactivation can account for the maintenance of the action potential. These findings suggest that besides neurovascular compression, sodium channels may have an important role in TN physiopathology. [28]

Some patients report concomitant persistent pain before the onset or after the paroxysm episodes of pain. This means that among the paroxystic events some patients still have continuous pain. Its mechanism is still uncertain, however *Obermann et al.* developed an electrophysical study, and discovered that the central hyperactivation of sensory transmission could facilitate concomitant persistent pain. Also, the data in this study suggests this phenotype is very prevalent in TN, mainly in women, and is associated with sensory abnormalities rather than paroxystic TN.[29,30] A recent study using neuroimaging demonstrated that root's atrophy of trigeminal nerve was more common in patients' with continuous pain; and suggested that this might emerge from the loss of axons, and abnormal activity of denervated nociceptive trigeminal second-order neurons.[31]

5 CLASSIFICATION

New classifications were published, in 2018, by both the IHS and IASP for trigeminal neuralgia to affiliate the two classifications. The ICHD-3 criteria demands that TN must include recurrent paroxysms of unilateral facial pain limited to the distribution(s) of one or more divisions of the TN, (lasting from a fraction of a second to two minutes), having a severe intensity and electric shock-like, shooting, stabbing or sharp in quality. It can be triggered by innocuous stimuli within the area of the injured trigeminal distribution. Moreover, concomitant persistent pain of moderate intensity confined to the distribution(s) of the affected nerve division(s). [1]

Trigeminal neuralgia is subdivided into classical (due to neurovascular compression), idiopathic (absent of neurovascular contact or neurovascular contact with no morphological changes of the trigeminal root) and secondary (due to an underlying disease).

The classical subtype is the most frequently found, and accounts for nearly 75% of the cases. Classical TN can be diagnosed when there is an anatomical change, such as nerve root atrophy and/or displacement due to neurovascular compression provoked mainly by arteries in the root entry zone. These atrophic changes include demyelination, loss of neurons, and modifications in microvasculature. [1] A prospective study that aimed to analyse the NVC in TN, revealed that both sides, symptomatic and asymptomatic, showed NVC, although severe NVC was more prevalent on the painful side and more often provoked by arteries than veins in the REZ. [32]

The diagnosis of the idiopathic type, which accounts nearly 10% of cases, is made when there are no evident abnormalities identified by electrophysiological tests or MRI. Furthermore, both Idiopathic and classical TN are subdivided into purely paroxysmal pain or with concomitant continuous pain, depending on whether there are pain free intervals or continuous/ near-continuous interictal pain between the attacks. Contact between a blood vessel and trigeminal

nerve and/or nerve root of heathy patients is often observed during neuroimaging. When there is neurovascular contact, although without evidence of morphological changes (atrophy, displacement) in the nerve root, then this condition is considered idiopathic. [1]

In addition, IHS classifies secondary TN when there is an underlying disease that may explain the neuralgia, recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia; either purely paroxysmal or associated with concomitant continuous/ near-continuous pain and not better accounted for by another ICHD-3 diagnosis. In this case a significant amount of individuals will show sensory changes. Established causes include tumour in the cerebellopontine angle, arteriovenous malformation and multiple sclerosis. [1,14]

6 Clinical Features

Trigeminal neuralgia is defined as a short-lasting facial pain, that is characteristically described as stabbing, electrical shock-like, shooting, or sharp. The paroxysm episodes usually last seconds. They can relapse after a refractory period, increased frequency in a day and appear consecutively many paroxysms of pain.[33]

About half of the patients suffering from TN present with concomitant persistent pain: an aching, dull or burning pain that usually is less intense than paroxysmal pain; is localised in the same area and accompanies the paroxysmal attacks. This condition is more prevalent in women.[30]

7 Trigger factors and Refractory period

In most patients with TN there is a refractory period after paroxysmal episodes.[34] Although much of this mechanism is still relatively unknown, it was proposed that it could be associated with hyperpolarisation of the sensory neurons. [35]

The background of TN suggests that it is precipitated by innocuous sensory stimuli to the injured side. These stimuli are instigated by daily life activities such as touching the face, or the upper lip with a ribbon of tissue. In addition, some studies showed that triggering manoeuvres prompt pain in 91-99% of the patients with TN. [21,36,37] A study demonstrated that light touching stimuli was considered vigorous enough to prompt TN while thermal or painful stimuli were less effective at triggering it.[34] The trigger factors often mentioned were: light touching, chewing, cold wind, talking, brushing teeth, drying face, eating, drinking, and shaving.[30,38] The affected side of the pain not always matches with the site of sensory trigger.[39] Common trigger zones (intraoral or extraoral) for TN were higher in the nasal wing, upper and lower lip, chin, cheekbone, nasolabial

fold, and alveolar gingiva.[37] Triggered attacks are usually followed by a period of seconds or minutes in which painful attacks can´t be evoked (refractory period).

8 Localisation

Trigeminal neuralgia most often involves the distribution of maxillary and mandibular branches of trigeminal nerve, with nearly a quarter of the cases involving the ophthalmological branch. The symptoms predominantly occurred on the right side of the face, with slightly lower incidence on the left. Secondary TN usually appears in patients with an average age of onset a few years early than the ones with classic TN. Atypical facial pain presents some different characteristics such as dull and continuous pain and should prompt identification of differential diagnosis. Bilateral pain is rare in classical TN and can be a manifestation of multiple sclerosis. [11,14,40].

9 Frequency and duration of attacks

There is high variability on the duration and frequency of TN episodes. In the majority of patients (74%) pain lasted from less than a second to 2 minutes; a minority of patients described pain attacks with a duration up to 10 minutes.[41] Additionally, around 70% of patients reported a series of paroxysms up to 1 hour, which can complicate diagnosis. [21] The frequency of attacks varied from a few attacks in some patients to hundred attacks daily approximately 40% of patients reported more than 10 attacks a day.[21] Variety is also characteristic of the remission-relapsing pattern of the attacks in TN. Patients mostly experienced periods of remission: around 37% of patients experienced months of remission while 63% reported years of remission.[21]

It is important to differentiate TN from other diagnosis. TACs can present as a paroxysmal short-lasting pain episodes such as SUNCT and SUNA. The underlying mechanisms for TACs unify the importance of the trigeminal autonomic reflex with parasympathetic activation, and clinical appearance with strictly unilateral pain in the distribution of the trigeminal nerve, also cranial autonomic features in the same side as the pain. The ophthalmic branch is the one that predominantly experiences most pain. Persistent idiopathic facial pain (PIFP) causes continuous, deep facial pain localized in a circumscribed area of the face; and is not accompanied by sensory loss or neurological deficits. [23]

10 Associated cranial autonomic symptoms

Generally, TN doesn´t include cranial autonomic symptoms, such as tearing or rhinorrhea. Some cases reported autonomic symptoms, which could present a challenge to differentiating TN from other entities of TACs. *Rasmussen et al.* described in his study that a population of 98 patients

out of 229 reported facial autonomic symptoms, namely: lacrimation (31%), rhinorrhea (9%), hypersalivation (7%), facial swelling/flushing (5%). [38] Also, *Maarbjerg et al.* documented that 48 out of 158 patients underwent ipsilateral cranial autonomic symptoms.[30] In both cases, these symptoms registered were predominantly in patients with implicated V1. Instead, *Sjaastad et al.* during their investigation of 19 patients with V1 TN reported these symptoms: lacrimation (42%), conjunctival injection (16%) and rhinorrhoea (11%); although these autonomic symptoms were moderate in all patients.

11 Diagnosis

Trigeminal neuralgia diagnosis is essentially clinical and established on the ICHD, that subdivides TN into three categories: classical, secondary or idiopathic. [1] In order for a disorder to be diagnosed as TN it must fulfil two criteria: the pain must occur on at least one trigeminal nerve division, and the pain must not be accompanied by other neurologic conditions or spread beyond the distribution of TN. In addition, the pain features must obey two out of three criteria: (a) severe intensity; (b) either sharp, electric, shock-like, or stabbing in quality; and (c) paroxysmal occurrences lasting from one second up to two minutes.[1] Furthermore, trigeminal pain must be provoked by innocuous stimulus of the affected side. [1] The classical diagnosis implies paroxysmal painful attacks provoked by neurovascular compression without another cause for the pain. There should be non-continuous periods of remission between pain cycles. [1]

Neuroimaging is recommended to differentiate classic from symptomatic TN as soon as TN is clinically suspected (MRI or CT). MRI presents higher sensitivity (75-95%) and specificity (26-86%).[7] [14] MRI with or without contrast is a useful tool to evaluate TN and surrounding structures because of its superior accuracy. It can identify neurovascular compression of the TN. [14] It can identify an etiology in up to 15 % of patients, which include cerebellopontine angle tumours and MS plaques. Clinical evaluation using MRI is paramount since you can find evidence of NVC in roughly 17% of the general population with an MRI. Around 99,94% of people with NVC found using imaging are asymptomatic. [42] [43]

Although secondary TN in MS is mostly related with a pontine demyelinating plaque, a study from *Truini et al.* discovered that the frequency of NVC and its relation with pontine demyelinating plaque was higher on the affected side (54% vs 0%; p=0.0001); after examining 1628 patients with MS. Thus, the underlying causes of MS are: inflammatory demyelination due to autoimmune processes, and mechanical demyelination due to NVC. [44]

12 Treatment

12.1 Acute treatment for exacerbations

Usually, single TN episodes are too brief to be treated. [11] In contrast, the increase of episode frequency which defines acute exacerbations of TN can be a serious medical issue leading to dehydration and anorexia, since drinking and eating can trigger the pain. Thusly, this condition could at times justify the hospitalization of patients, to undergo rehydration and/or titration of antiepileptic drugs.

It is essential to manage pain treatment and adjust medication, until a neurosurgical intervention is considered. Opioids showed no benefit in acute exacerbation of TN. Intravenous infusion of fosphenytoin and lidocaine could potentially be effective in managing pain, although concrete evidence is lacking. [45]

The algorithm for acute pain management preconizes a complete patient's evaluation including pain characterization. It is important to search red-flags symptoms or signs to exclude life-threatening causes. If the patient has an established diagnosis of TN and the pain episode is identic to anterior attacks, then it is suitable to treat adequately. It is recommended to start with the interventions with: the highest proven efficacy first, lowest cost second, less severe side-effects last.[45] *Bendtsen* et al. recommended intravenous fosphenytoin and lidocaine during acute exacerbations of pain (very low quality of evidence)[11]

A systematic review of analgesic options in acute exacerbations of primary trigeminal neuralgia of *Moore et al*. (2019) includes: lidocaine, anticonvulsant (phenytoin or fosphenytoin), serotonin agonist (sumatriptan), or other options with lower proven efficacy: NMDA receptor antagonist, BTX-A. The primary outcome of this review was to assess the efficacy of each treatment option, that could provide 50% pain relief in 24h of administration. The evidence for effective analgesic treatment in TN exacerbations is very low (see TABLE I). [45]

12.1.1 Lidocaine

Lidocaine is a drug with anaesthetic potential and is a voltage-gated sodium channel blocker. In higher doses, it can decrease transduction of C-fibre of pain signals, and can inhibit ectopic discharges from damaged neurons, without impacting normal sensory function. It has a short duration of action, and therefore has a higher safety profile concerning cardiac and neurological toxicity than other anaesthetics. [45]

In a RCT cross-over double-blind from *Kanai et al.* (2006) included 25 patients with second-division TN that were randomized to be given two sprays (0,2 ml) with lidocaine 8% or saline placebo in the affected nostril using a dose spray. After 7 days, patients were crossed over to

receive the other treatment. The pain triggered by touching or moving face was measured using a 10 cm VAS before and 15 min after treatment. Intranasal lidocaine 8% spray demonstrated significantly decreased VAS from 8,0 (2.0) cm to post-spray: 1.5cm (1.9) cm while the placebo spray didn´t prove the same, 7.9 (2.0) cm to 7.6 (2.0) cm. Furthermore, 23 patients using lidocaine and 1 patient on placebo reported significant pain relief. Lidocaine analgesic effect persisted for 4.3hours. There were no serious side effects reported, only: local irritation, burning, numbness of the nose and eye. [46]

Another RCT cross-over double-blind placebo-controlled experiment analysed the response to intraoral application of 8% lidocaine in 24 patients with oral TN pain. These patients were randomized to have either intraoral application of 8% lidocaine or saline placebo on the painful territory. The NRS was used before and 15 minutes after the treatment for pain assessment. Patients who received intraoral lidocaine, on average experienced a significant pain score reduction from 5 to 1 (P = 0.001). In contrast, those who received the placebo on average did not report a reduced NRS score (from 5 to 5) (p = 0.093). Remarkably, 19 of the 24 patients, noticed marked or moderate relief of pain after lidocaine treatment. Lidocaine analgesic effect persisted for 2,8 hours. [47]

12.1.2Phenytoin and fosphenytoin

Anticonvulsants used in TN treatment such as carbamazepine, oxcarbazepine, lamotrigine and gabapentin are not suitable for acute exacerbations, as they require prolonged oral administration with a titration period. Exceptionally, there are some anticonvulsants which can be used intravenously, such as phenytoin and its prodrug fosphenytoin; although there are not enough case studies to support this.

Phenytoin is a use-dependent selective antagonist of VGSC; also blocks voltage-gated calcium channels. In contrast, fosphenytoin is a phenytoin prodrug with a better side-effect profile. The loading dose for the two drugs is 15-18 mg/kg over 30 min. Its use requires monitoring during infusion. Some expected side-effects are: dizziness and ataxia, hypotension and uncommonly heart blockage. [48,49]

Case series described by *Cheshire et al.* (2001) included 3 patients with untreatable TN, who were previously medicated with carbamazepine. Fosphenytoin was used in each case, first diluted to 5–10 mg PE/ml in 5% dextrose with 0.45% NaCl then injected through an intravenous catheter. The concentration of fosphenytoin is expressed as phenytoin sodium equivalents (PE), as way to prevent molecular weight-based adjustments from the familiar phenytoin.

The first case was a 66-year-old woman. She presented with exacerbation of painful attacks during a two-week period, and even increasing the dosage of carbamazepine to 200mg three times a day did not provide symptom relief. She then received a dosage of 18 mg/kg of fosphenytoin for 20 minutes which provided total pain relief for 2 days. She chose microvascular decompression (MVD) and was pain-free for 2.5 years. The second patient was an 80-year-old man with TN for 4 years, who presented with 4 days of severe exacerbation of pain. He received 100mg PE of fosphenytoin I.V. at intervals of 10 minutes with a planned maximum limit of 10 doses. After each dose was administered, he received a pain assessment. The assessments showed an incremental improvement, complete remission after the final dose of 11mg/kg. There were no hemodynamic changes or noticeable side effects. After 20 hours, pain reappeared because he stopped taking his recommended medication. Four weeks later, he underwent percutaneous balloon compression of the TN. He was pain-free for 7 months and did not even need to take his medication. The third patient was a 75-year-old woman with TN for 14 years, who presented with an exacerbation of TN for 5 months. She received the same treatment regimen as the second patient. She received a 14mg/kg dose and was completely pain-free for 2 days. Afterward, her pain subsided with a Gasserian balloon compression procedure. She was pain-free for 3 months. Some central nervous side-effects were reported on two of the cases: on the first case mild tinnitus and ataxia of gait were reported, and on case three dizziness was reported. [49]

12.1.3NMDA receptors

N-Methyl-D-aspartate receptors are glutamate-gated ion channels, which perform a pivotal role in the regulation of synaptic function in the brain. Magnesium is an antagonist of NMDA receptors, and this ion is also present in the receptor central pore in normal physiological states. Magnesium is released upon nociceptive stimulus NMDA receptors allow calcium influx and nociceptive signal is transmitted to the dorsal horn level in spinal cord. These receptors are the key of central sensitisation, which include features like allodynia and hyperalgesia. These aren´t a significant part of classical TN but can be observed in other sub-types. The benefits of magnesium sulphate infusion are: its low cost and minimal side-effects. [45]

A case report with very weak evidence used a magnesium sulphate (MgSO4) infusion to control an acute exacerbation of TN in a 65-year-old man. He arrived at the emergency department with a VAS score 10/10, and he received a MgSO4 infusion of 30mg/kg for 30 minutes. He reported substantial post-infusion pain reduction from 10/10 to 2/10. There were no side effects reported. [50]

12.1.4Serotonin agonists

Sumatriptan is a serotonin (5-hydroxytriptamine) agonist, particularly serotonin $5-HT_{1B}$ and $5-HT_{1D}$ receptors. Its administration can be oral, intranasal, subcutaneous or rectal. Triptan is commonly used as a first-line rescue agent in migraine. However, it can also have a crucial role in the acute management of TN exacerbations. Its mechanism of action is thought to be vasoconstriction of dilated meningeal vessels. It also inhibits the release of vasodilatory peptides from trigeminal sensory neurons, and reduces the transmission of pain from the trigeminal dorsal horn in the pons. [51–53] Sumatriptan can reduce transmission of pain in pons in TN. Furthermore, its vasoconstrictor effect can lower the vascular compression of the trigeminal nerve root. The nasal administration can be a good choice for patients who can´t tolerate oral or injected medication. One of the adverse effects of sumatriptan is the increase of blood pressure, and must therefore be used with precaution in patients with arterial hypertension and/or coronary heart disease. [45]

A RCT cross-over double-blind study from *Kanai et al.* (2006) examined the efficacy of sumatriptan in triggered TN paroxysms in 24 patients, who were randomized to receive subcutaneous doses of either 3mg (1mL) of sumatriptan or 1mL of saline placebo. After 7 days, the same patients took the opposite treatment. Pain attacks triggered by innocuous stimulus were assessed using VAS before and 15 minutes after treatment. Results of subcutaneous sumatriptan showed a significant decrease on average in VAS from 8.3 to 2.4. On the saline control group there was no significant decrease, 8.5 to 8.1. The effect of sumatriptan lasted for a median of 7.9 hours (range:1-20 hours). Out of 24 patients, 12 (50%, $p < .01$) reported no pain after sumatriptan treatment. Side-effects such as mild increase of blood pressure, fatigue and nausea were documented. [54]

12.1.5Botulinum toxin

Zuniga et al. described the use of BTX-A injection in TN in the trigger zones. An open label study including 12 patients who were evaluated weekly for 8 weeks. A dose range from 20-50 units in trigger areas was used. Results showed that 10 of the 12 patients (83%) underwent pain relief “after some minutes” of the administration. Likewise, better pain control occurred at higher doses. The number of paroxysms and pain scores were not described within the first 24 hours. At week 8, there was however, a notable decrease of pain in the VAS score, and a decline in the number of paroxysms. A 64-year-old woman who had a VAS of 10 and around 30-40 paroxysms of pain per day, received 40 units in the left frontotemporal, and 5 units into the peribuccal and zygomatic areas. She reported a pain score of 0 at 24 hours and no painful paroxysms. She maintained a VAS of 0 for 70 days. Transient facial asymmetry was observed in one case. [55]

12.2 Long-term therapy

Management of TN include medical pharmacological, surgery and complementary approaches. The first option should be pharmacological with anticonvulsants, considered the core of treatment. Carbamazepine is the first-line choice for treatment of TN, because of its high efficacy. Alternatively, oxcarbazepine can be used as first-line medication with a similar efficacy, and less side effects than carbamazepine. [56] Although these medications showed good potential efficacy in TN treatment, their side effects lead up to 40% of the patients to discontinue usage.[57], [58,59]

According to EAN guidelines, lamotrigine, baclofen, pregabalin, gabapentin, phenytoin and BTX-A are considered second-line therapy. When these medicines prove ineffective or cause serious side-effects, they can be combined with either carbamazepine or oxcarbazepine. It is also suggested that doses should be carefully adjusted, depending on the severity of pain and side-effects, as well as whenever partial or complete remission occur (see TABLE II and III). [11,33]

Recently, new third-generation antiepileptic drugs, namely eslicarbazepine and lacosamide, have been considered to treat neuropathic pain; mainly in refractory cases of TN due to their safety profile, reduced number of side-effects, and fewer drugs interactions. [60,61]

12.2.1First line therapy

12.2.1.1 Carbamazepine

Carbamazepine is an inhibitor of voltage-gated sodium channels. It reduces the neural membrane's excitability and inhibits the repetitive firing or reduction of propagation of synaptic impulses. When the dose is optimized there is a noticeable improvement in around 75% of patients.[19] The initial dose is 200mg and its typical dosage range is from 200 to 1200 mg.[62,63]

Once remission occurs, the dosage should be diminished after pain control. Sometimes, long release carbamazepine is needed for patients with painful nocturnal episodes. [29,35] The most common side effects of carbamazepine are: sedation, dizziness, nausea, vomiting, diplopia, memory loss, ataxia, increase of hepatic enzymes and hyponatremia. The amount of possible carbamazepine side effects as well as its interaction with other drugs can make it difficult to properly regulate the dosage in elderly people. Unusual severe side effects that could occur are: leukopenia, aplastic anaemia, allergic rash, systemic lupus erythematosus, hepatotoxicity. Carbamazepine is also associated with HLA-B*1502 allele, which can lead to Stevens-Johnson syndrome and/or toxic epidermal necrolysis. This occurred mainly in the Han Chinese, but not in Caucasian patients. In patients of Han Chinese descent, a test for the HLA-B*1502 allele should be performed prior to treatment with carbamazepine. It is prudent to require complete blood count,

serum sodium, and liver function tests some weeks after initiating therapy to prevent these carbamazepine-induced complications over time. [29] [63,64]

In 1969, *Nicol et al.* conducted a double-blind randomized investigation lasting 4 years. This study evaluated the efficacy of carbamazepine in 44 patients with TN who, either begun with 200 mg of carbamazepine or a placebo. Twenty-seven patients (73%) who were treated with carbamazepine from the start or after an unsuccessful trial with a placebo revealed a clinical response ranging from good to excellent. Ten of the patients (27%) treated with carbamazepine had either a poor result or showed no alterations. Of the 7 patients receiving only placebo, 6 had an excellent or good response. There were some side effects reported like: drowsiness, staggering gait, minor upset stomach, constipation, and tremulousness. [65]

In 1966, *Campbell et al.* conducted a double-blind randomised controlled trial that lasted 8 weeks in which 70 patients were randomised into two different cross-over regimens with carbamazepine up to 800 mg. The patients passed two periods of fortnights, alternating between carbamazepine and a placebo. The pain was scored into different categories. The group who began with carbamazepine showed an average improvement of 58% (51/89) in their first period on the drug. In contrast, patients who first started the trial with a placebo only showed an average improvement of 41% (27/66) after the first dose of carbamazepine. This indicated a better outcome for patients who received carbamazepine before the placebo. In addition, treatment downgrade was more evident in patients on the placebo than on carbamazepine. In the first period, the carbamazepine group improved 68% while the placebo group only improved 26%. When accounting for the triggering factors: the carbamazepine group experienced a reduction in triggers of 68% and only 2% downgrading, the placebo group experienced a reduction in triggers of 40% and downgrading of 20%; both statistically significant figures (p=0.05). There was statistically significant evidence to support an effective reduction of pain and the number of pain paroxysms using carbamazepine over placebo.

In 1968, *Killian et al.* conducted a double-blind study to evaluate the role of carbamazepine in TN. The study included 42 patients and similar tablets containing 200mg of carbamazepine or a placebo which were randomized and administered for 5 days each. The starting dose was either 400 mg or 600mg per day and whenever necessary increased by 200mg every 48 hours. The most effective dose was continued for 3 months. Of the 30 patients who suffered from TN, 24 were observed by the double-blind technique; all demonstrated a disappearance or decrease in trigeminal pain with a dosage of 400 mg 600mg a day. Around 70% of the patients experienced a significant response to carbamazepine, having complete or satisfactory results for an average of 13 and up to 36 months. On the placebo group the response was nil or minimal. A minimal percentage of patients only experienced partial response to carbamazepine, however the number wasn´t

enough to say that this was indeed related to the medication. During the use of carbamazepine some side effects were documented: vertigo, drowsiness, diastolic hypertension, bradycardia, rash, including some laboratory findings: leukopenia, transient or persistent and abnormal liver function.[66]

12.2.1.2 Oxcarbazepine

Oxcarbazepine is a keto-analogue of carbamazepine that is quickly converted into the 10-monohydroxy metabolite, its pharmacologically active form. This metabolite doesn´t cross through the liver cytochrome system; it explains why oxcarbazepine has a better side-effects profile and has less pharmacological interaction than oxcarbazepine. In addition, patients had a better tolerance to oxcarbazepine than carbamazepine. The starting dose for oxcarbazepine is 300mg twice a day and typical doses range from 300mg to 1800 mg. Whenever a patient experiences an allergy related to the use of carbamazepine, precaution should be taken due to possible cross-reactivity between these two drugs. [56(p)] Common side-effects of oxcarbazepine are: dizziness, drowsiness, fatigue, ataxia, hyponatraemia and skin reaction.

In 2007, *Gomez-Arguelles et al.* performed prospective open-label study, which evaluated the efficacy and tolerability of oxcarbazepine in patients with TN who had were unresponsive to treatment with carbamazepine. The study included 35 patients with idiopathic TN who received oxcarbazepine monotherapy treatment for at least 12 months. The endpoints measurements taken were: mean pain, responder rate, pain-free patients. The maintenance dose was 773.7 mg/day. Results showed significant diminishing in pain scores following 12 weeks of treatment ($p < 0.05$) compared with baseline. In addition, results showed a significant reduction in pain frequency ($p<0.01$) after 12 months; responder rate was 65,7% and pain-free rate 37.1%. [67]

12.2.2 Second-line therapy

12.2.2.1 *Lamotrigine*

Lamotrigine acts at VGSC, by stabilising neural membranes and inhibiting the release of excitatory neurotransmitters. [68] [69] This drug can be used in patients who can´t take neither carbamazepine or oxcarbazepine, or as an alternatives an adjuvant medication to increase efficacy. Lamotrigine usually has less side effects than carbamazepine and oxcarbazepine. [63] The starting dose of lamotrigine is 25mg two times a day and its dosage range is 25mg- 400mg. Common side effects reported are: sleepiness, dizziness, headache, vertigo, and ataxia. Another possible life-threatening event, albeit rare in only 1:10000 of patients, was Stevens-Johnson syndrome. Slow-dose titration protocol can help prevent these events, reducing to the rate of severe rashes down

to 0,1%-0,01%. [70] Lamotrigine is not suitable to for controlling severe TN exacerbation due to slow dose titration when there is a necessity for rapid pain control. [63]

In 1997, *Zakrzewska et al.* conducted a double-blind placebo controlled cross-over trial to evaluate lamotrigine's antineuralgic properties. This trial included 14 patients with refractory TN. For 31 days, patients took a regular dose of either carbamazepine or phenytoin. Each stage of the trial lasted for 2 weeks (days 1-14), then a 3-day washout period on placebo (days 15-17). The dose of lamotrigine used for maintenance was 400mg (days 21-31) and it proved to be superior to the placebo (p=0,011). This was based on the analysis of the efficacy index which compared the number of patients with better results while taking lamotrigine with those with better results taking the placebo. The parameters used to assess the efficacy of both treatments were: use of escape medication, total pain scores and global evaluations. Out of the 13 patients included, 11 had better results while taking lamotrigine than while taking the placebo. Also, global evaluations indicated that patients had a better outcome from lamotrigine than from the placebo (p = 0.025). Some side-effects reported with both lamotrigine and the placebo were mainly dose-dependent effects on central nervous system. Lamotrigine seems to have antineuralgic properties. [68]

12.2.2.2 Gabapentin

Gabapentin is a GABA receptor agonist that has its role on presynaptic calcium channels of neurons, inhibiting the release of excitatory neurotransmitters. RCTs showed efficacy on neuropathic pain. It is also effective relieving TN symptoms in patients with MS. The loading dose is 300mg/day and its dose range is 300mg-3600mg. Moreover, this drug has benefits such as: quick titration, no known interactions with other medicine, and a relatively good side-effect profile. Side-effects included: mild somnolence, dizziness, headache, confusion, nausea, hyperlipidaemia and ankle edema. [58]

A meta-analysis of *Yuan et al.* (2016) aimed to assess the efficacy of gabapentin on the relief of TN. There were 14 RCTs with a total of 1156 patients. The three things used to measure the outcome were: total effective rate, life satisfaction Index B and adverse reactions. The total effective rate of gabapentin therapy group was similar to carbamazepine therapy group (OR = 1.600, 95% CI 1.185, 2.161, p = 0.002). The effective rate of gabapentin after a duration of 4 weeks of therapy was superior to the carbamazepine therapy (OR = 1.495, 95% CI 1.061, 2.107, p = 0.022, heterogeneity: x2 = 7.12, p = 0.625, I 2 = 0.0%). After 10 months of treatment, the same groups showed similar efficacy (OR = 0.723, 95% CI 0.236, 2.222, p = 0.572, heterogeneity: x2 = 0.00, p = 0.996, I 2 = 0.0%). Moreover, life satisfaction improvement was also higher in the gabapentin group

after a 4-week treatment (SMD = 0.966, 95% CI 0.583, 1.348, p < 0.001). Additionally, this meta-analysis demonstrated that the number of adverse effects in the gabapentin group was significantly lower relative to the carbamazepine group (OR = 0.312, 95% CI 0.240, 0.407, p < 0.001). However, and as a result of the poor methodological quality of available studies there was not enough quality evidence to conclude that gabapentin efficacy and adverse effects count was superior to carbamazepine.[71]

12.2.2.3 Pregabalin

Pregabalin is a GABA's analogue with a similar structure and mechanism of action at the alpha-2-delta (α2-δ) sub-unit of voltage-gated calcium channels. Even though it has a valuable use in reducing neuropathic pain in some patients, there is insufficient evidence to support its use to treat TN. [72] Pregabalin´s starting dose is 150mg and dosage range of 150mg-600mg. Reported side-effects included: dizziness, confusion, somnolence, ataxia, increased risk of infection, gastrointestinal symptoms, weight gain [63]

A prospective, open-label study intended to assess the efficacy of pregabalin treatment in TN with or without concomitant facial pain (53 patients with TN, 14 of which with concomitant chronic facial pain). These patients received PGB 150mg-600mg daily and were prospectively followed for 1 year. The primary studied outcomes were a high number of pain-free patients or with a reduction of pain intensity by more than 50 % and lower frequency of episodes by more than 50% after 8 weeks. The secondary outcome was durable pain relief after 1 year. Out of the 53 patients, 39 (74%) of them showed an improvement after 8 weeks with a mean dose of 269.8 mg/day (range 150–600 mg/day). Of these 39 patients, 13 (25%) of them experienced complete pain relief and 26 (49%) others described pain relief of more than 50% (< 0.001). In addition, 32 out of 39 (82%) patients suffering from TN without concomitant facial pain presented better response rates compared to those with concomitant chronic facial pain 7 out of 14 (50%) ($X^2 = 5.4$, p=0.02). Concomitant chronic facial pain seems to be a clinical predictor of poor treatment outcome. The most common adverse effects with pregabalin were: dizziness, somnolence, headache, peripheral edema and dry mouth.[73]

12.2.2.4 Baclofen

Baclofen is a skeletal muscle relaxant. This drug is a GABA-b agonist that acts by activating GABA-b receptors and depressing excitatory neurotransmission. [56(p),69] This medication seems to be effective in managing pain in patients with TN. Its initiating dose is 15mg and dosage range of 15mg-90mg. Baclofen can be taken alone or as an add-on therapy with carbamazepine. When used as an

adjuvant therapy with carbamazepine it is recommend to decrease the dose of carbamazepine to 500mg/day to keep the synergetic effect.[74] Some side effects of this drug are: drowsiness, dizziness, weakness, fatigue, nausea, hypotension, and constipation. Withdrawal symptoms after sudden discontinuation of this medication have been documented, including hallucinations and seizures.[75] Patients suffering from MS can obtain additional benefits from baclofen due to its muscle relaxant property. [76]

A double-blind cross-over study assessing the effects of baclofen and long-term follow-up was performed on 10 patients with classic trigeminal neuralgia. Seven out of ten patients showed significantly diminished painful paroxysm when on baclofen than when taking the placebo ($t = 2.75$; $p < 0.05$). An open trial in another 50 patients with TN refractory who could not tolerate carbamazepine demonstrated attack relief in 37 (74%) patients using baclofen ($t = 3.53$; $p < 0.01$). Twelve patients were only using baclofen. Twenty-five patients received a combination of baclofen with previously unsuccessful doses of either carbamazepine or phenytoin ($x2 = 10.32$; $p < 0.01$). A one-to-five-year (mean, 3.0 years) follow-up was performed on 60 patients: 18 (30%) of them who used baclofen for one to five years were pain-free, 10 (17%) were on remission after 3 to 6 months, 13 (22%) became refractory to baclofen after 1 to 18 months, and 2 (3%) had a good response to baclofen. Baclofen seems to be a useful drug in the treatment of TN according to the results.[77]

12.2.2.5 Botulinum toxin A

BTX-A is classified as an exotoxin produced by the bacteria Clostridium Botulinum. The mechanism of action of BTX-A is still unknown. It is thought that it leads to the release of anti-nociceptive neuropeptides like substance P, glutamate and calcitonin-gene related peptide, which provoke central inhibition and peripheral sensitization. [78] BTX-A interferes with neural transmission by inhibiting the release of acetylcholine by the neuromuscular junction at the presynaptic motor neurons, prompting muscle paralysis. Additionally, this exotoxin can inhibit the release of acetylcholine from cholinergic nerve terminals, thusly inhibiting secretion from glands. [79] Its role in the treatment of migraine, tension type headache, and postherpetic neuralgia has been studied. [80,81]

BTX-A is recommended as add-on therapy for medium-term treatment of TN. [11] It is used with a starting dose of 25-195 units and its dose range of 25-195 units (very low quality of evidence). [63]

A systematic review and meta-analysis of randomized controlled trials conducted by *Morra et al.* (2016) aimed to assess the efficacy and safety of BTX-A therapy in TN. The follow-up ranged from 8 to 12 weeks and included 178 patients, 99 in the BTX-A group and 79 in the placebo control

group. The outcome measures assessed were: the proportion of responders with more than 50% decrease in mean pain score from baseline to endpoint, the frequency of attacks per day, and associated adverse effects. The dosage varied from 25U to 100U, and the routes of administration were: intradermal, submucosal or subcutaneous. Results demonstrated that the overall effect was higher on the BTX-A group than on the placebo group in terms of proportion of responders (risk ratio RR = 2.87, 95 % confidence interval CI [1.76, 4.69], p<0.0001) with no significant heterogeneity detected (p = 0.31; I2 = 4 %). Also, VAS score was significant lower for the BTX-A group at the end of first month (MD = -2.89, 95 % CI [-4.66,– 1.12], P = 0.001), the second month (MD = -2.47, 95 % CI [-3.96,–0.99], p = 0.001), and the third month (MD = -3.43, 95 % CI [-5.21,–1.64], p = 0.0002) with no heterogeneity detected. [82] Furthermore, mean paroxysms frequency was also significantly lower for the BTX-A group (MD = -29.79, 95 % CI [-38.50,–21.08], p < 0.00001) with no significant heterogeneity (p = 0.21; I2 = 36 %). Adverse effects included facial asymmetry and edema/hematoma at the local of the injection. [82]

Another open label of *Li et al. (*2014) researched the long-term effects and safety of BTX-A to treat trigeminal neuralgia. This study incorporated 88 patients and the primary measured outcomes were the severity of the pain (estimated using VAS) and the frequency of pain attacks daily. The secondary measured outcome was the overall response to the treatment, evaluated by the Patient Global Impression of Change. Multiple doses were assessed: ≤50U in 43 cases, 50–100 U in 32 cases and ≥100 U in 13 cases. In 81 patients, the treatment seemed to be effective within 1 month and all the 88 patients (100%) showed improvement with treatment at 2 months. The symptoms showed improvement and the frequency of painful attacks was reduced in all the patients. The period in which TN was considered completely controlled was at 3 months in 46 patients. The efficacy of the treatment slowly diminished after 3 months; at 14 months 38,6% of patients had a prevalence of effective treatment and 22 patients (25%) had totally controlled treatment. No significant difference was detected in the prevalence of effective treatment and pain attack frequency among the different groups at identical time points between 1 and 14 months (p>0.05). Noted reactions included: local swelling at the site of injection, muscle relaxation but were considered mild side effects that disappeared in a short period. [83]

12.2.3 Third-generation anticonvulsants

12.2.3.1 Lacosamide

Lacosamide is a third-generation anticonvulsant drug with a safe side-effect profile. Its mechanism of action seems to be related with slow inactivation of VGSC both peripheral (Nav 1.7 and Nav 1.3) and central (Nav.16), leading to stabilization of hyperexcitable neuronal membranes,

thus inhibiting neuronal firing. [84–87] Approved dosage levels vary from 200mg-400mg daily. [88] It is commonly used in the treatment of epilepsy and possibly has been used to treat neuropathic pain.

The advantages of lacosamide include: excellent oral bio-availability, minimal serum protein binding, fewer interactions with other drugs, and reduced number of side-effects. Common, dose-related side-effect were: dizziness, headache, nausea, asthenia and slightly increase in PR interval in ECG the last one being associated with cardiac arrythmias and atrioventricular blocks, but specially in patients with cardiovascular risk factors. [89]

A study reported a case of a 60-year-old man with TN refractory who received previous treatments with gabapentin, carbamazepine, lamotrigine and pregabalin and due to occurrence of sever leukopenia. Lacosamide was proven to be effective without any side-effects. The dosage used was 100mg twice daily and complete pain relief (VAS score:0) was achieved after 3 weeks of therapy without any side-effects. [60]

12.2.3.2 Eslicarbazepine acetate

Eslicarbazepine is a third-generation anticonvulsant that targets VGSC, however its affinity for VGSC is around 15-to 5-fold fold lower than that of carbamazepine and oxcarbazepine. Eslicarbazepine demonstrated higher selectivity by blocking VGSC during the slow inactivation phase in comparison with carbamazepine and oxcarbazepine.[90] Side-effects include drowsiness, dizziness, vertigo, ataxia, abnormal coordination, diplopia, fatigue and headache. [91,92]

A retrospective, open-label study was conducted on 18 patients for 21.1 months to assess the efficacy, tolerability and safety of eslicarbazepine in the treatment of TN. The primary measured outcome was the differences in the intensity of pain paroxysms before and after treatment with eslicarbazepine. The secondary measured outcomes were the tolerability and safety of eslicarbazepine. Median pain intensity improved from 9.5 to 2.5 VAS ($p < 0.001$) and the median of pain paroxysms frequency improved from 70 episodes per week to 0.37 ($p<0.001$). Out of 18 patients, 16 showed a responder rate of 88.9% and 8 of them (44,4%) were asymptomatic after treatment. Side-effects reported were: lightheadedness, severe dizziness, hyponatremia, and gastric disturbances, ataxia, confusion, somnolence, insomnia and myoclonus. Responder rate was 77.8% in 14 patients (after six months), and 61.1% in 11 patients (after 1 year).[61]

12.3 Surgical treatment

Surgical treatment is recommended in case of refractory pain after pharmacological treatment. There are three types of surgical interventions offered.

First, there is an invasive non-ablative procedure named MVD, which involves the decompression of conflicting blood vessels while opening via suboccipital craniotomy.

Second, there is an invasive and ablative procedure by penetrating foramen ovale with a canula and after controlled lesion of the trigeminal ganglion or root by mechanical (BC), thermal (RFTC*) or* chemical way (GR) and split of the fascicles located in fossa posterior of the trigeminal nerve (IN).

Lastly, there are non-invasive ablative technique like stereotactic radiosurgery, as GKS*,* which focuses radiation at the entry zone of trigeminal root. [63] Repetitive ablative procedures are common in clinics. [93]

The *EAN* guideline mentions that although there are no studies that can rigorously identify the number of medicines that should be tried before surgery, pharmacological therapy with adequate doses and regular monitoring should be performed before surgery is considered to treat TN. Based on very low quality of evidence, surgery should be recommended in cases of refractory pain to medication or if pharmacological treatment is not tolerated (see TABLE IV and V). [11]

12.3.1Microvascular decompression

MVD requires a retrosigmoid craniotomy that provides a passage to the cerebellopontine angle and the exploration of the fossa posterior to identify the affected trigeminal nerve and the conflicting blood vessel. [33,94]

This technique affords the longest pain-free duration compared to other surgical procedures. The *EAN* guideline reveals that based on low-quality evidence although extensive clinical experience, MVD is strongly recommend over GKS in patients with classical TN who can receive posterior fossa surgery. Other guideline mentions a weak recommendation, based on a low quality evidence, for MVD over neuroablative procedures (RFTC, BC, IN and GR). [11]

Literature yielded 21 studies that include 5149 patients who were followed on average from 3 to 10.9 years. The pain relief reported ranged from 80-88%, follow-up pain-free varied from 62-89% and recurrence rates stated ranged from 4-38%. Some severe, albeit rare, complications of this treatment that should be mentioned were: death (0-3%), edema, haemorrhage, or stroke (0-6%), anaesthesia dolorosa (0-0.2%) and meningitis (0-4%). Other less severe, and less common complications were: cranial nerve palsy (4%), hearing loss (1-8%), and facial hypoesthesia (3%). [11], [9596,96–99,99,100,100–115]

Four non-randomized prospective studies were conducted, and they compared long-term (>1year) impact of first-time MVD with first-time GKS numbering 561 patients (MDV N = 287; GKS, N = 274). In fact, MVD showed superiority over GKS with a considerable effect size at both medium and long term. At 1-2 years post-operatively, 68-88% of patients who underwent MVD had no pain without additional medical treatment, while only 24-71% experienced no pain after being submitted to GKS. At 4-5 years, the pain-free percentages were 61-88% for MVD and 33-56% for GKS. [11,116], [117,118]

One non-randomized prospective study involved 256 patients with refractory TN who were submitted to 405 surgical procedures. This study had as endpoints: response rate, time to pain recurrence and surgical complications. Of a total of 256 patients, 172 under the age of 70 were eligible for surgery and had the chance to choose between MVD, GR or RFTC. Out of these 172 patients, 95 underwent MVD and 77 opted for either GR (38) or RF (39). MVD seemed to be the procedure with the highest percentage of pain freedom (85.6%) at 3 years comparing to the 3-year success rate in patients who underwent GR (54,8%); and those who opted for percutaneous RF (70,7%) ($p<0,01$). There was no statistically significant difference between GR and RFTC at 3 years ($p>0,05$). There were some adverse effects reported: CSF leaks in MVD, temporary hemifacial anaesthesia after GR, and anaesthesia dolorosa on various procedures.

12.3.2Ablative procedures

Ablative techniques are favoured when: there is no evidence of NVC on neuroimaging, when the patients are poor candidates for MVD surgery (such as patients with MS), or when they can´t tolerate surgery due to significant comorbidities and advanced age. [11,94]

PTR requires insertion of a needle via percutaneous into Meckel´s cave through foramen ovale and then causing partial ablation of trigeminal nerve. Nearly 70-85% of patients reported an initial response to these procedures with the response rate at 5 years around 55–65%. [94]

PTR can also offer some alleviation in patients who didn´t respond to MVD or who present atypical symptoms besides showing the higher response in patient with classical symptoms.

The ablative techniques (RFTC, BC and GR) offer on average 3-4 years of pain relief and recurrent ablative procedures are usually necessary. High rates of complications are particularly connected with repeated procedures. No evidence was found on which procedure should be preferred over another. [11] Besides adverse effects associated to ablative procedures, it is important to mention anaesthesia dolorosa. Although it can be a rare complication, it is associated with surgical trauma via rhizotomy or thermocoagulation of the trigeminal ganglion. This condition is characterized by painful anaesthesia or hypersthesia in the distribution of the trigeminal nerve, or

one of its divisions, or occipital nerve. It is provoked by an injury of the nerve or its central connections and manifests as persistent pain with reduced sensory loss in the distribution of the nerve. [119]

There were no RCTs identified, nevertheless there some non-randomized cohort studies were found: 7 for RFTC, 3 for GR, 5 for BC, and 1 for IN.

12.3.2.1 Glycerol Rhizolysis

The principle of this procedure consists of the neurotoxicity of glycerol when in contact with the post-gasserian fibres of the TN. [120] The literature search yielded 3 studies with a total of 289 patients, whose follow-up lasted from 4.5 to 8 years. Acute pain relief rate was achieved in around 75% of them. The registered pain free rate at mean follow-up decreased to 19-58%, and recurrence rates ranged from 41 to 84%. Some important complications were noticed such as facial hypoesthesia or paresthesia. [11,121–123]

12.3.2.2 Percutaneous Balloon Compression

This procedure is based on compression of retrogasserian fibres of trigeminal ganglion in Meckel´s cave and damages small unmyelinated and weakly myelinated nociceptive fibres. [124] There were 5 eligible studies conducted on a total of 755 patients. Follow-up varied from 4.2 to 10.7 years. The reported acute pain relief was accomplished in more than 95% and pain-free rate at mean follow-up diminished to 55-80% (mean: 67%). Also, recurrence or failure rate ranges from 20-51.7%. In this group there were some complications identified as facial hypoesthesia or paraesthesia in 14.6% (110/755) and trigeminal motor weakness in 4.5% (34/755). [11,124–128]

12.3.2.3 Radiofrequency thermocoagulation

This surgery requires a heat source applied on the trigeminal nerve sensory axons to achieve thermoalgic anesthesia of the injured territory. The current recognized mechanism of action considers that the weakly myelinated Aδ and amyelin C are thermo-sensitive fibres. [129] The literature search established 7 studies that included 4533 patients. The medium follow-up ranged from 3 to 9.3 years. The acute pain relief was obtained in more than 90%of the cases. The reported follow-up pain-free ranged from 26-82% and recurrence or failure varied from 16-74%. The complications linked to this technique were: facial hypoesthesia or paresthesia, corneal hypoesthesia, keratitis, trigeminal motor weakness, anaesthesia dolorosa and cranial nerve palsy. [11,123,130–135]

12.3.2.4 Internal neurolysis

Internal neurolysis is a technique in which all segments of the trigeminal nerve are separated longitudinally along its fibres between the pons and the porus trigeminus.

The search included 1 study with 26 patients. [136] The average follow-up was 3.6 years. The acute pain relief was reached in 85% of patients. The pain relief rate at mean follow-up decreased to 72% and recurrence rate was 27%. Reported complications were: facial hypoesthesia (96%), CSF leak (4%), and anesthesia dolorosa (4%). [11 136]

12.3.2.5 Gamma knife surgery

This technique aims a focused beam of radiation at the trigeminal root in the posterior fossa. It is used a stereotaxic apparatus underneath local anaesthesia followed by CT and MRI to achieve a 3D localization of the target area.

There were 8 studies that encompassed 1168 patients. The follow up ranged from 3.1 to 5.6 years. The acute pain relief rate was obtained in less than 80% of cases. Also, pain-free rate at mean follow-up diminished to 30-66% and recurrence or failure rates varied from 18% to 52.2%.[11] The time to get pain alleviation ranged from 1 day to 24 months in the selected series. This procedure was considered the one with lowest incidence of morbidity when compared with all other surgeries. The major complication was facial hyposthesia or paresthesia (184/1168; 15,8%). [11,118–122 137,138–142 143]

In order to treat TN with radiation therapies, new strategies involve fractionation of the radiation dose and to select parts of the trigeminal nerve outside the root entry zone. [94]

13 PROGNOSIS

TN is considered a crippling disease that can diminish the quality-of-life of the affected individuals. The progress of this condition varies. Some patients may have episodes that last weeks or months, with subsequently pain-free intervals. Other patients will remain with concomitant persistent facial pain concomitantly. Furthermore, in some patients, pain paroxysms will become worsts over time, with fewer and shorter pain-free intervals before the attacks reappear.

Furthermore, medicines might lose their efficacy over time. Thus, it remains essential to diagnose TN quickly and accurately, so treatment plan can be promptly developed to lead to a better prognosis. [144]

14 CONCLUSION

Summarising, TN is still a challenge for healthcare providers. Nevertheless, constant research has led to an advancement in its classification based on the neuroimaging findings. Currently, TN is subdivided into three subgroups: classical, idiopathic and secondary, depending on the imaging findings. Also, there were noticeable improvements in the description and pathophysiological mechanisms involved in TN, particularly NVC.

TN can be significantly disabling for patient's personal and professional life. Some drugs used as rescue analgesic treatment in acute exacerbations of TN acutely improved the pain. Of course, when a patient presents with an acute exacerbation of TN, it is important to do a complete examination, focusing on the nature of a patient's pain and the presence of red-flags. After ruling out life threatening causes, if there is a previous diagnosis of TN and characteristic pain are consistent with primary TN it is prudent to treat adequately. Although there are several drugs that can provide acute pain relief like lidocaine, sumatriptan, phenytoin/fosphenytoin, BTX-A and magnesium sulphate there is weak evidence to support their use. Some TN patients will need hospitalization to be treated with rehydration, titration of anti-epileptic drugs and intravenous infusions of fosphenytoin and lidocaine.

Concerning to long-term treatment, carbamazepine and oxcarbazepine are the firstline therapy. While other drugs as lamotrigine, gabapentin, pregabalin, baclofen and BTX-A may be used as either monotherapy or combined with carbamazepine or oxcarbazepine. Regarding new treatment options, BTX-A it has a potential benefit as add-on therapy in some cases, although lack of sufficiently strong evidence. Dosages must be adapted regarding patient's pain severity and side effects and recommendations concerning titration must be given. Also, novel third-generation anticonvulsants have been considered off-label to apply in cases of refractory TN with a safe profile, like eslicarbazepine and lacosamide. Although RCTs are needed to evaluate these drugs efficacy in TN.

Likewise, surgical treatment has provided promising results. It can be proposed when pain is refractory to medical therapy or poorly tolerated. Among the types of surgery, MVD is the first-line in those patients in which NVC has been confirmed. While neuroablative procedures are preferred if MRI doesn't show NVC.

Hence, pathophysiology of TN should be further investigated. Thus, more studies are required with larger sample size and RCTs to satisfactorily confirm the efficacy of medical treatment in the management of TN, as well as finding better options that are proven effective and well tolerated. Neurosurgical prospective studies are needed to report outcomes and subsequent complications rates.

A multi-disciplinary approach to the diagnosis and treatment of TN is crucial to improve patients´outcome and their quality-of-life. It should be managed in multi-disciplinary centres with a skilled team including a neurologist, neurosurgeon, pain experts, nurses and psychologists to help patients cope with their pain. Patients who suffer from TN are more likely to experience depression, anxiety, and suicidal thoughts. Moreover, besides experiencing a high level of pain, they also suffer disability and activity limitation, especially when eating. The intensity and unpredictability of these attacks leads to patients developing improper coping mechanisms which often translate into anxiety, depression, lack of confidence in managing with flares of their condition and harmful responses which explains their difficulty in maintaining a good quality-of-life and in dealing with TN. Thus, strategies including cognitive behavioural therapy can help patients to adequately manage their pain, mental health, and well-being and to develop coping skills. It is necessary to perform more studies that include standardized outcomes such as quality-of-life on functional and emotional status and patient general improvement.

Furthermore, an adequate clinical evaluation should be meticulously performed, in order to triage the patients from the onset of their condition. The clinicians need to be aware of the various types of facial pain disorders to distinguish this facial neuralgia from the other spectrum of headaches. Likewise, information leaflets should be delivered about their disease and treatment and follow-up visits should be conducted to provide support and closely monitor possible side-effects. Although imaging studies have been a precious tool on diagnosing and deciding which treatment is more suitable for the patient, further evaluation with advanced imaging techniques is needed to accurately determine the route of trigeminal nerve and the surrounding blood vessels and to rule out secondary causes of TN.

The constant efforts by clinicians, investigators and pharmaceutical industry will contribute to give these patients new therapeutical options with higher efficacy, specificity, tolerability, and less side-effects.

15 TABLES

15.1 TABLE I | Acute analgesic treatments in trigeminal neuralgia

TABLE I | Acute analgesic treatments in trigeminal neuralgia

GIC: global impression of change; IV: intravenous; NRS: numerical rating scale; PE: phenytoin equivalents; RCT: randomised controlled trials SC: subcutaneous; VAS: visual analogue scale;

Drug	Author	Year	Method	Route	Dosage	Outcome measures	Efficacy within 24 hours	Adverse effects
Lidocaine	*Kanai et al*	2006	RCT cross-over double-blind	Nasal spray	Active: 8% 0,2 mL, Control: 0,2 mL saline	VAS assessed 15 minutes after intervention;	Active: VAS 8.0 to 1.5, Control: 7.9 to 7.6, Duration: 4.3 h	Local irritation (stinging,burning numbness), bitter taste or numb throat.
	Niki et al	2014	RCT cross-over double - blind	Oral mucosa	Active: 8% 0.2 ml, Control: saline 0.2 mL	NRS	Active: NRS 5 to 1, Control: 5 (no change), Duration: 2.8 h	Numbness (active, control), bitterness.
Fosphenytoin	*Cheshire*	2001	Case series	I.V. Infusion	14 (11-18) mg/kg (PE) over 20-180 min	Pain relief	Instant pain relief after infusion	Mild and transient dizziness, tinnitus, ataxia.
Magnesium sulphate	*Soleimanpour et al*	2014	Case report	I.V. Infusion	30 mg/kg	VAS	VAS: 10 to 2 (30 min after infusion)	Nil
Sumatriptan	*Kanai et al*	2006	RCT cross-over double-blind	S.C.	Active: 3 mg (1 mL) Control: 1 mL saline	VAS assessed 15 minutes post-intervention;	Active: VAS 8.3 to 2.4, Control: 8.5 to 8.1, Duration: 7.9 h	Mild hypertension, fatigue, nausea.
Botulinum Toxin	*Zuniga and colleagues*	2008	Prospective observational	S.C.	20-50 Units	VAS with 8 weeks	10 of the 12 patients reported relief "after some minutes"; 1 patients: VAS 10 to 0 in 24h	Transient facial asymmetry.

Adapted from: D. Moore, M. S. Chong, A. Shetty, e J. M. Zakrzewska, «A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia», Br. J. Anaesth., vol. 123, n. 2, pp. e385–e396, Ago. 2019, doi: 10.1016/j.bja.2019.05.026.

15.2 TABLE II | Preventive treatments in Trigeminal Neuralgia

TABLE II | Preventive treatments in Trigeminal Neuralgia

NA: not applicable

Drugs	Iniciating dose	Dose range	Daily dose needed	Frequency	Titration	Tapering	Side-effects
First-line drugs							
Carbamazepine	200 mg	200-1200 mg	200-1800 mg	Two to four times per day	Increase by 200 mg every 3 days	Decrease by 200 mg every 7 days	Drowsiness, fatigue, ataxia, diplopia, dizziness, nausea, cognitive slowing, hiponatraemia, leucopenia, thrombocytopenia, skin reactionsm abnormal liver function tests.
Oxcarbazepine	300 mg	300-1800 mg	300-2700 mg	Twice daily to four times a day	Increase by 300 mg every 3 days	Decrease by 300 mg every 7 days	Dizziness, drowsiness, tiredness, headache, nausea, ataxia, hyponatraemia, skin reaction
Second line drugs or add-on							
Lamotrigine	25 mg	25-400 mg	100-400 mg	Twice a day	Increase 25 mg for 2 weeks, 50 mg for 1 week, then increase by 50 mg every week	Decrease 50 mg every 7 days	Drowsiness, dizziness, tiredness, headache, gastrointestinal symptoms, irritability, sleep disorders, tremor, cognitive slowing, rash
Gabapentin	300 mg	300-3600 mg	600- 3600 mg	Three times a day	Increase 300 mg every 3 days	Decrease 300 mg every 7 days	Dizziness, fever, confusion, tiredness, ataxia, increased risk of viral infection, gastrointestinal symptoms, weight gain; use carefully with opioids
Pregabalin	150 mg	150-600 mg	150-600 mg	Twice a day	Increase 150 mg every 7 days	Decrease 100 mg every 7 days	Dizziness, confusion, somnolence, ataxia, increased risk of infection, gastrointestinal symptoms, weight gain
Baclofen	15 mg	15-90 mg	15- 70 mg	Three times a day	Increase 15 mg every 7 days	Decrease 15 mg every 7 days	Dizziness, drowsiness, confusion, euphoria, hallucinations and gastrointestinal symptoms
Botulinum toxin type A	25-195 units	25-195 units	50-100 units	Every 12 weeks	NA	NA	Transient facial asymmetry, transient oedema or haematoma at injection site, transient drooling and difficulty chewing.

Adapted from: L. Bendtsen et al., «European Academy of Neurology guideline on trigeminal neuralgia», Eur. J. Neurol., vol. 26, n. 6, pp. 831–849, Jun. 2019, doi: 10.1111/ene.13950.

15.3 Table III | Summary of RCTs assessing pharmacological treatment in trigeminal neuralgia

Table III | Summary of RCTs assessing pharmacological treatment in trigeminal neuralgia

BTX-A: botulinum toxin type A; RCT: Randomized Controlled Trials; TN: trigeminal neuralgia; VAS: visual analogue scale;

Drugs	*Authors*	Year	*Method*	*Number of patients and intervention*	*Duration of trial*	*Results*
Carbamazepine	*Killian et al*	1968	RCT, double blind, crossover, single centre	24 patients were randomised to carbamazepine titrated to sufficient dose versus placebo	3 months	All patients on carbamazepine group showed a clear response (either disappearance or reduction of pain); On placebo group the response was nil or minimal in all patients.
	Campbell et al	1966	RCT, double blind, crossover, multicentre	70 patients were randomised up to 800mg of carbamazepine into 2 different crossover regimens; each period had a duration of 2 weeks and both carbamazepine and placebo were taken for two separated periods	8 weeks	The pain severity and number of pain attacks statistically improved in carbamazepine regim compared with placebo regim
	Nicol	1969	RCT, double blind, single centre	44 patients were randomised to carbamazepine up to 2400mg or placebo; if there was no response to the first treatment, they were switched to the other drug (either carbamazepine or placebo)	4 months	Excelente or good response was seen in 27 (73%) patients on carbamazepine while 6 (25%) patients showed an excellent or good response to placebo;
Oxcarbazepine	*Gomez-Arguelles et al*	2007	Prospective, open-label study	35 patients underwent treatment with oxcarbazepine monotherapy with mean maintance dose of 773.7 mg/day. Outcomes measures were mean pain frequency, responder rate, pain-free patients.	12 months	Results showed significant reduction in main scores ($p<0.05$)and pain frequency ($p<0.01$) after 12 months. Responder rate was 65,7% and pain-free rate was 37,1%.
Lamotrigine	Zakrzewska et al	1997	RCT, double blind, crossover, multicentre	14 patients were randomised to lamotrigine up to 400 mg vs placebo; each period took 2 weeks with a 3-day washout period between; primary endpoint was the use of escape medication, total pain score, and patient's global evaluation of pain.	31 days	Lamotrigine showed to be more effective than placebo in 85% (11) of patients.

Adpated from: *L. Bendtsen et al., «Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia», Lancet Neurol., vol. 19, n. 9, pp. 784–796, Set. 2020, doi: 10.1016/S1474-4422(20)30233-7*

Table III | Summary of RCTs assessing pharmacological treatment in trigeminal neuralgia (continued)

BTX-A: botulinum toxin type A; RCT: Randomized Controlled Trials; TN: trigeminal neuralgia; VAS: visual analogue scale;

Drugs	*Authors*	Year	*Method*	*Number of patients and intervention*	*Duration of trial*	*Results*
Gabapentin	Yuan et al	2016	RCT, multicentre single-centre studies	1156 patients were randomised to gabapentin up to 3600 mg vs carbamazepine up to 2400 mg; The outcome measure mostly used was the effective dose when comparing response to gabapentin vs carbamazepine	4-10 weeks	Response was similiar to both gabapentin and carbamazepine (odd ratio 1.6 [95% CI 1·2 to –2·2], p=0,002)
Pregabalin	*Obermann et al*	2007	Prospective, open-label study	The efficacy of pregabalin was assessed in 53 patients with or without concomitante facial pain receiving pregabalin 150-600 mg daily. Primary outcome was the number of patients free of pain or with a reduction of pain intensity by more than 50% and the reduction in more than 50% of attack frequency. Secondary outcome was sustained pain relief after 1 year.	1 year	39 (74%) of patients improved with a mean dose of 269,8mg of pregabalin: 13 (25%) presented a complete pain alliviation and 26 (49%) showed a reduction in more than 50%.
Baclofen	*H. Fromm*	1984	Double blind, cross over clinical trial	A double blind study with 10 patients with typical trigeminal neuralgia and an open trial with 50 patients was conducted to evaluate the efficacy of baclofen.	5 years	In the double blind-study, results showed significant reduced of frequency of the paroxysms in 7 of 10 patients. In the open study, results demonstrated a significant decrease in 74% (37/50) of the attacks ($p < 0.01$);
Botulinum toxin type A	*Morra et al*	2016	RCT, double blind, multiple single-centre studies	Meta-analysis of 4 RCT including 178 patients randomised to BTX-A 25–100 units or placebo injected intradermally, in submucosa, and subcutaneously; primary outcomes were proportion of patients with >50% reduction in mean pain score from baseline to endpoint, alteration in mean number of paroxysms, and in mean VAS score	8-12 weeks	72 (77%) participants responded to BTX-A and 21 (26%) responded to placebo (risk ratio 2·9 [95% CI 1·8 to 4·7], p<0·001); mean difference in VAS score was lower at 2 months in the botulinum toxin type A group vs placebo (–2·8 [95% CI –4·0 to –1·0], p=0·001); mean difference in paroxysms was lower in the botulinum toxin type A group vs placebo (–29·8 [95% CI –38·5 to 21·1], p<0·001)
	Li et al	2014	Open-label study	An open-label incorporated 88 patients under different doses (≤50, 50-100 and ≥100U) of BTX-A to assess its therapeutic effect. Primary endpoint was pain intensity (assessed by VAS) and pain paroxysmic frequency per day. Secondary endpoint was patient's overall response to treatment.	14 months	81 patients responded to treatment within 1 month of and at 32 months, 88 patients had a 100% prevalence of effective treatment. In 46 patients, TN was completely controlled at 3 months. At 14 months, prevalence of effective tretament was 38,6% and 22 (25%) patients reported TN completely controlled.

Adpated from: *L. Bendtsen et al., «Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia», Lancet Neurol., vol. 19, n. 9, pp. 784–796, Set. 2020, doi: 10.1016/S1474-4422(20)30233-7*

15.4 TABLE IV | Summary of outcomes from single intervention trials

TABLE IV | Summary of outcomes from single intervention trials

BC: ballon compression; F/U: follow-up; GKS: gamma knife surgery; GR: glycerol rhizolysis; IN: internal neurolysis; MVD: microvascular decompression; RFTC: radiofrequency thermocoagulation.

	Interventions	MVD	GKS	RFTC	BC	GR	IN
Efficacy data	Number of studies	21	8	7	5	3	1
	Total of patients	5149	1168	4533	755	289	26
	Mean/median F/U (years)	3-10.9	3.1-5.6	3-9.3	4.2-10.7	4.5-8	3.6
	Pain free at F/U	62%-89%	30-66%	26%-82%	55-80%	19-58%	72%

Adapted from: *L. Bendtsen et al., «European Academy of Neurology guideline on trigeminal neuralgia», Eur. J. Neurol., vol. 26, n. 6, pp. 831–849, Jun. 2019, doi: 10.1111/ene.13950.*

15.5 TABLE V | Reported complications from included studies

TABLE V : Reported complications from included studies

BC: balloon compression; GKS: gamma knife surgery; GR: glycerol rhizolysis; IN: internal neurolysis; MVD: microvascular decompression; RFTC: radiofrequency thermocoagulation.

	Interventions	MVD	GKS	RFTC	BC	GR	IN
Complications (%)	Facial sensory changes	3	16	19	15	40	96
	Corneal hypoaesthesia	0.3	0	6.6	0.7	6.6	0
	Hearing loss	1.8	0	0.1	0	0.3	0
	Motor weakness	0	0	6.2	4.5	1.7	0%
	Cranial nerve palsy	4.1	0.2	0.8	1.6	0	0
	Meningitis	0.4	0	0.02	5.7	0	0
	Cerebrospinal fluid leak	2	0	0.1	0	0	3.8
	Anesthesia dolorosa	0.02	0	0.6	0.1	0.7	3.9
	Mortality	0.3	0	0	0	0	0

Adapted from: L. Bendtsen et al., «European Academy of Neurology guideline on trigeminal neuralgia», Eur. J. Neurol., vol. 26, n. 6, pp. 831–849, Jun. 2019, doi: 10.1111/ene.13950.

16 BIBLIOGRAPHY

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202
2. Parreira E. Recomendações Terapêuticas para Cefaleias da Sociedade Portuguesa de Cefaleias – 2021. *Sinapse*. 2021;21(supplement 1):3-100. doi:10.46531/sinapse/GU/200048/2021
3. Patel SK, Liu JK. Overview and History of Trigeminal Neuralgia. *Neurosurg Clin N Am*. 2016;27(3):265-276. doi:10.1016/j.nec.2016.02.002
4. Pearce JMS. Trigeminal neuralgia (Fothergill's disease) in the 17th and 18th centuries. *J Neurol Neurosurg Psychiatry*. 2003;74(12):1688-1688. doi:10.1136/jnnp.74.12.1688
5. Verma G. Role of Botulinum Toxin Type-A (BTX-A) in the Management of Trigeminal Neuralgia. *Pain Res Treat*. 2013;2013:1-6. doi:10.1155/2013/831094
6. Cruccu G, Finnerup NB, Jensen TS, et al. Trigeminal neuralgia: New classification and diagnostic grading for practice and research. *Neurology*. 2016;87(2):220-228. doi:10.1212/WNL.0000000000002840
7. Antonini G, Di Pasquale A, Cruccu G, et al. Magnetic resonance imaging contribution for diagnosing symptomatic neurovascular contact in classical trigeminal neuralgia: A blinded case-control study and meta-analysis. *Pain*. 2014;155(8):1464-1471. doi:10.1016/j.pain.2014.04.020
8. Lutz J, Thon N, Stahl R, et al. Microstructural alterations in trigeminal neuralgia determined by diffusion tensor imaging are independent of symptom duration, severity, and type of neurovascular conflict. *J Neurosurg*. 2016;124(3):823-830. doi:10.3171/2015.2.JNS142587
9. Heinskou TB, Maarbjerg S, Wolfram F, et al. Favourable prognosis of trigeminal neuralgia when enrolled in a multidisciplinary management program - a two-year prospective real-life study. *J Headache Pain*. 2019;20(1):23. doi:10.1186/s10194-019-0973-4
10. Maarbjerg S, Benoliel R. The changing face of trigeminal neuralgia—A narrative review. *Headache J Head Face Pain*. 2021;61(6):817-837. doi:10.1111/head.14144
11. Bendtsen L, Zakrzewska JM, Abbott J, et al. European Academy of Neurology guideline on trigeminal neuralgia. *Eur J Neurol*. 2019;26(6):831-849. doi:10.1111/ene.13950
12. Cruccu G, Gronseth G, Alksne J, et al. AAN-EFNS guidelines on trigeminal neuralgia management: Trigeminal neuralgia management. *Eur J Neurol*. 2008;15(10):1013-1028. doi:10.1111/j.1468-1331.2008.02185.x
13. Tolle T, Dukes E, Sadosky A. Patient Burden of Trigeminal Neuralgia: Results from a Cross-Sectional Survey of Health State Impairment and Treatment Patterns in Six European Countries. *Pain Pract*. 2006;6(3):153-160. doi:10.1111/j.1533-2500.2006.00079.x
14. Gronseth G, Cruccu G, Alksne J, et al. Practice Parameter: The diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies. *Neurology*. 2008;71(15):1183-1190. doi:10.1212/01.wnl.0000326598.83183.04
15. Di Stefano G, Truini A, Cruccu G. Current and Innovative Pharmacological Options to Treat Typical and Atypical Trigeminal Neuralgia. *Drugs*. 2018;78(14):1433-1442. doi:10.1007/s40265-018-0964-9

16. Mueller D, Obermann M, Yoon MS, et al. Prevalence of trigeminal neuralgia and persistent idiopathic facial pain: A population-based study. *Cephalalgia*. 2011;31(15):1542-1548. doi:10.1177/0333102411424619

17. Sjaastad O, Bakketeig LS. The rare, unilateral headaches. Vågå study of headache epidemiology. :9.

18. Koopman JSHA, Dieleman JP, Huygen FJ, de Mos M, Martin CGM, Sturkenboom MCJM. Incidence of facial pain in the general population. *Pain*. 2009;147(1):122-127. doi:10.1016/j.pain.2009.08.023

19. Katusic S, Beard CM, Bergstralth E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. *Ann Neurol*. 1990;27(1):89-95. doi:10.1002/ana.410270114

20. Hall GC, Carroll D, Parry D, McQuay HJ. Epidemiology and treatment of neuropathic pain: The UK primary care perspective. *Pain*. 2006;122(1):156-162. doi:10.1016/j.pain.2006.01.030

21. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal Neuralgia - A Prospective Systematic Study of Clinical Characteristics in 158 Patients. *Headache J Head Face Pain*. 2014;54(10):1574-1582. doi:10.1111/head.12441

22. Zakrzewska JM, Wu J, Mon-Williams M, Phillips N, Pavitt SH. Evaluating the impact of trigeminal neuralgia. *Pain*. 2017;158(6):1166-1174. doi:10.1097/j.pain.0000000000000853

23. Edvinsson JCA, Viganò A, Alekseeva A, et al. The fifth cranial nerve in headaches. *J Headache Pain*. 2020;21(1):65. doi:10.1186/s10194-020-01134-1

24. Love S. Trigeminal neuralgia: Pathology and pathogenesis. *Brain*. 2001;124(12):2347-2360. doi:10.1093/brain/124.12.2347

25. Marinković S, Todorović V, Gibo H, et al. The Trigeminal Vasculature Pathology in Patients With Neuralgia. *Headache J Head Face Pain*. 2007;47(9):1334-1339. doi:10.1111/j.1526-4610.2007.00933.x

26. Rappaport ZH, Govrin-Lippmann R, Devor M. An electron-microscopic analysis of biopsy samples of the trigeminal root taken during microvascular decompressive surgery. *Stereotact Funct Neurosurg*. 1997;68(1-4 Pt 1):182-186. doi:10.1159/000099920

27. Burchiel KJ. Abnormal impulse generation in focally demyelinated trigeminal roots. *J Neurosurg*. 1980;53:10.

28. Siqueira SRDT, Alves B, Malpartida HMG, Teixeira MJ, Siqueira JTT. Abnormal expression of voltage-gated sodium channels Nav1.7, Nav1.3 and Nav1.8 in trigeminal neuralgia. *Neuroscience*. 2009;164(2):573-577. doi:10.1016/j.neuroscience.2009.08.037

29. Obermann M, Yoon MS, Ese D, et al. Impaired trigeminal nociceptive processing in patients with trigeminal neuralgia. *Neurology*. 2007;69(9):835-841. doi:10.1212/01.wnl.0000269670.30045.6b

30. Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Concomitant Persistent Pain in Classical Trigeminal Neuralgia - Evidence for Different Subtypes. *Headache J Head Face Pain*. 2014;54(7):1173-1183. doi:10.1111/head.12384

31. Di Stefano G, De Stefano G, Leone C, et al. Concomitant continuous pain in patients with trigeminal neuralgia is associated with trigeminal nerve root atrophy. *Cephalalgia*. 2020;40(13):1502-1510. doi:10.1177/0333102420949206

32. Maarbjerg S, Wolfram F, Gozalov A, Olesen J, Bendtsen L. Significance of neurovascular contact in classical trigeminal neuralgia. *Brain*. 2015;138(2):311-319. doi:10.1093/brain/awu349

33. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia – diagnosis and treatment. *Cephalalgia*. 2017;37(7):648-657. doi:10.1177/0333102416687280

34. Kugelberg E, Lindblom U. THE MECHANISM OF THE PAIN IN TRIGEMINAL NEURALGIA. *J Neurol Neurosurg Psychiatry*. 1959;22(1):36-43. doi:10.1136/jnnp.22.1.36

35. Devor M, Amir R, Rappaport ZH. Pathophysiology of Trigeminal Neuralgia: The Ignition Hypothesis: *Clin J Pain*. 2002;18(1):4-13. doi:10.1097/00002508-200201000-00002

36. Cruccu G, Finnerup NB, Jensen TS, et al. Trigeminal neuralgia: New classification and diagnostic grading for practice and research. *Neurology*. 2016;87(2):220-228. doi:10.1212/WNL.0000000000002840

37. Di Stefano G, Maarbjerg S, Nurmikko T, Truini A, Cruccu G. Triggering trigeminal neuralgia. *Cephalalgia*. 2018;38(6):1049-1056. doi:10.1177/0333102417721677

38. Rasmussen P. Facial pain: IV. A prospective study of 1052 patients with a view of: Precipitating factors, associated symptoms, objective psychiatric and neurological symptoms. *Acta Neurochir (Wien)*. 1991;108(3-4):100-109. doi:10.1007/BF01418516

39. Cruccu G, Di Stefano G, Truini A. Trigeminal Neuralgia. Ropper AH, ed. *N Engl J Med*. 2020;383(8):754-762. doi:10.1056/NEJMra1914484

40. Obermann M, Katsarava Z. Update on trigeminal neuralgia. *Expert Rev Neurother*. 2009;9(3):323-329. doi:10.1586/14737175.9.3.323

41. Haviv Y, Khan J, Zini A, Almoznino G, Sharav Y, Benoliel R. Trigeminal neuralgia (part I): Revisiting the clinical phenotype. *Cephalalgia*. 2016;36(8):730-746. doi:10.1177/0333102415611405

42. Miller JP, Acar F, Hamilton BE, Burchiel KJ. Radiographic evaluation of trigeminal neurovascular compression in patients with and without trigeminal neuralgia. *J Neurosurg*. 2009;110(4):627-632. doi:10.3171/2008.6.17620

43. Jones MR, Urits I, Ehrhardt KP, et al. A Comprehensive Review of Trigeminal Neuralgia. *Curr Pain Headache Rep*. 2019;23(10):74. doi:10.1007/s11916-019-0810-0

44. Truini A, Prosperini L, Calistri V, et al. A dual concurrent mechanism explains trigeminal neuralgia in patients with multiple sclerosis. *Neurology*. 2016;86(22):2094-2099. doi:10.1212/WNL.0000000000002720

45. Moore D, Chong MS, Shetty A, Zakrzewska JM. A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia. *Br J Anaesth*. 2019;123(2):e385-e396. doi:10.1016/j.bja.2019.05.026

46. Kanai A, Suzuki A, Kobayashi M, Hoka S. Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. *Br J Anaesth*. 2006;97(4):559-563. doi:10.1093/bja/ael180

47. Niki Y, Kanai A, Hoshi K, Okamoto H. Immediate Analgesic Effect of 8% Lidocaine Applied to the Oral Mucosa in Patients with Trigeminal Neuralgia. *Pain Med*. 2014;15(5):826-831. doi:10.1111/pme.12349

48. Vargas A, Thomas K. Intravenous fosphenytoin for acute exacerbation of trigeminal neuralgia: case report and literature review. *Ther Adv Neurol Disord*. 2015;8(4):187-188. doi:10.1177/1756285615583202

49. Cheshire WP. Fosphenytoin: An Intravenous Option for the Management of Acute Trigeminal Neuralgia Crisis. 2001;21(6):5.

50. Soleimanpour H, Aghamohammadi D, Ghaffarzad A, Golzari SE, Safari S, Soleimanpour M. Novel treatment in refractory tic douloureux. *J Clin Anesth*. 2014;26(6):495-496. doi:10.1016/j.jclinane.2014.03.011

51. Goadsby PJ. Trigeminal autonomic cephalalgias. Pathophysiology and classification. *Rev Neurol (Paris)*. 2005;161(6-7):692-695. doi:10.1016/S0035-3787(05)85120-3

52. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat during activation of the trigeminovascular system. *Ann Neurol*. 1988;23(2):193-196. doi:10.1002/ana.410230214

53. Russell FA, King R, Smillie SJ, Kodji X, Brain SD. Calcitonin Gene-Related Peptide: Physiology and Pathophysiology. *Physiol Rev*. 2014;94(4):1099-1142. doi:10.1152/physrev.00034.2013

54. Kanai A, Saito M, Hoka S. Subcutaneous Sumatriptan for Refractory Trigeminal Neuralgia. *Headache J Head Face Pain*. 2006;46(4):577-582. doi:10.1111/j.1526-4610.2006.00405.x

55. Zúñiga C, Díaz S, Piedimonte F, Micheli F. Beneficial effects of botulinum toxin type A in trigeminal neuralgia. *Arq Neuropsiquiatr*. 2008;66(3a):500-503. doi:10.1590/S0004-282X2008000400012

56. Al-Quliti KW. Update on neuropathic pain treatment for trigeminal neuralgia: The pharmacological and surgical options. *Neurosciences*. 2015;20(2):107-114. doi:10.17712/nsj.2015.2.20140501

57. O'Callaghan L, Floden L, Vinikoor-Imler L, et al. Burden of illness of trigeminal neuralgia among patients managed in a specialist center in England. *J Headache Pain*. 2020;21(1):130. doi:10.1186/s10194-020-01198-z

58. Besi E, Boniface DR, Cregg R, Zakrzewska JM. Comparison of tolerability and adverse symptoms in oxcarbazepine and carbamazepine in the treatment of trigeminal neuralgia and neuralgiform headaches using the Liverpool Adverse Events Profile (AEP). *J Headache Pain*. 2015;16(1):81. doi:10.1186/s10194-015-0563-z

59. Beydoun A. Safety and Efficacy of Oxcarbazepine: Results of Randomized, Double-Blind Trials. *Pharmacotherapy*. 2000;20(8 Part 2):152S-158S. doi:10.1592/phco.20.12.152S.35254

60. Adamo D, Coppola N, Pecoraro G, Nicolò M, Mignogna MD. Lacosamide in trigeminal neuralgia: report of a case refractory to first- and second-generation anticonvulsants. *CRANIO®*. Published online August 10, 2020:1-5. doi:10.1080/08869634.2020.1804233

61. Sanchez-Larsen A, Sopelana D, Diaz-Maroto I, et al. Assessment of efficacy and safety of eslicarbazepine acetate for the treatment of trigeminal neuralgia. *Eur J Pain*. 2018;22(6):1080-1087. doi:10.1002/ejp.1192

62. Joffroy A, Levivier M, Massager N. Trigeminal neuralgia Pathophysiology and treatment. :6.

63. Lambru G, Zakrzewska J, Matharu M. Trigeminal neuralgia: a practical guide. *Pract Neurol*. 2021;21(5):392-402. doi:10.1136/practneurol-2020-002782

64. Anisha.A. Mahtani, Sethu G. Review on Trigeminal Neuralgia. *J Pharm Sci Res*. 2016;8 (6).

65. Nicol CF. A FOUR YEAR DOUBLE-BLIND STUDY OF TEGRETOL(r)IN FACIAL PAIN. *Headache J Head Face Pain*. 1969;9(1):54-57. doi:10.1111/j.1526-4610.1969.hed0901054.x

66. Killian JM, Fromm GH. in the Treatment of Neuralgia. :8.

67. Gomez-Arguelles JM, Dorado R, Sepulveda JM, et al. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. *J Clin Neurosci*. 2008;15(5):516-519. doi:10.1016/j.jocn.2007.04.010

68. Zakrzewska JM, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens LE. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain*. 1997;73(2):223-230. doi:10.1016/S0304-3959(97)00104-8

69. Obermann M. Treatment options in trigeminal neuralgia. *Ther Adv Neurol Disord*. 2010;3(2):107-115. doi:10.1177/1756285609359317

70. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. :6.

71. Yuan M, Zhou H yan, Xiao Z long, et al. Efficacy and Safety of Gabapentin vs. Carbamazepine in the Treatment of Trigeminal Neuralgia: A Meta-Analysis. *Pain Pract*. 2016;16(8):1083-1091. doi:10.1111/papr.12406

72. Rodríguez MJ, Díaz S, Vera-Llonch M, Dukes E, Rejas J. Cost-effectiveness analysis of pregabalin versus gabapentin in the management of neuropathic pain due to diabetic polyneuropathy or post-herpetic neuralgia. *Curr Med Res Opin*. 2007;23(10):2585-2596. doi:10.1185/030079907X233151

73. Obermann M, Yoon M, Sensen K, Maschke M, Diener H, Katsarava Z. Efficacy of Pregabalin in the Treatment of Trigeminal Neuralgia. *Cephalalgia*. 2008;28(2):174-181. doi:10.1111/j.1468-2982.2007.01483.x

74. Fromm GH, Terrence CF, Chattha AS, Glass JD. Baclofen in trigeminal neuralgia: its effect on the spinal trigeminal nucleus: a pilot study. *Arch Neurol*. 1980;37(12):768-771. doi:10.1001/archneur.1980.00500610048007

75. Hasan S, Khan NI, Sherwani OA, Bhatt V, Asif S. TRIGEMINAL NEURALGIA: AN OVERVIEW OF LITERATURE WITH EMPHASIS ON MEDICAL MANAGEMENT. Published online 2012:4.

76. Leandri M. Therapy of trigeminal neuralgia secondary to multiple sclerosis. *Expert Rev Neurother*. 2003;3(5):661-671. doi:10.1586/14737175.3.5.661

77. Fromm GH, Terrence CF, Chattha AS. Baclofen in the treatment of trigeminal neuralgia: Double-blind study and long-term follow-up. *Ann Neurol*. 1984;15(3):240-244. doi:10.1002/ana.410150306

78. Aoki KR. Review of a Proposed Mechanism for the Antinociceptive Action of Botulinum Toxin Type A. *NeuroToxicology*. 2005;26(5):785-793. doi:10.1016/j.neuro.2005.01.017

79. Bowen ME, Weninger K, Brunger AT, Chu S. Single Molecule Observation of Liposome-Bilayer Fusion Thermally Induced by Soluble N-Ethyl Maleimide Sensitive-Factor Attachment Protein Receptors (SNAREs). *Biophys J*. 2004;87(5):3569-3584. doi:10.1529/biophysj.104.048637

80. Frampton JE. OnabotulinumtoxinA (BOTOXÒ). Published online 2012:21.

81. Porta M, Camerlingo M. Headache and botulinum toxin. *J Headache Pain*. 2005;6(4):325-327. doi:10.1007/s10194-005-0222-x

82. Morra ME, Elgebaly A, Elmaraezy A, et al. Therapeutic efficacy and safety of Botulinum Toxin A Therapy in Trigeminal Neuralgia: a systematic review and meta-analysis of randomized controlled trials. *J Headache Pain*. 2016;17(1):63. doi:10.1186/s10194-016-0651-8

83. Li S, Lian YJ, Chen Y, et al. Therapeutic effect of Botulinum toxin-A in 88 patients with Trigeminal Neuralgia with 14-month follow-up. *J Headache Pain*. 2014;15(1):43. doi:10.1186/1129-2377-15-43

84. Beyreuther BK, Freitag J, Heers C, Krebsfänger N, Scharfenecker U, Stöhr T. Lacosamide: A Review of Preclinical Properties. *CNS Drug Rev*. 2007;13(1):21-42. doi:10.1111/j.1527-3458.2007.00001.x

85. Rogawski MA, Tofighy A, White HS, Matagne A, Wolff C. Current understanding of the mechanism of action of the antiepileptic drug lacosamide. *Epilepsy Res*. 2015;110:189-205. doi:10.1016/j.eplepsyres.2014.11.021

86. Stöhr T, Kupferberg HJ, Stables JP, et al. Lacosamide, a novel anti-convulsant drug, shows efficacy with a wide safety margin in rodent models for epilepsy. *Epilepsy Res*. 2007;74(2-3):147-154. doi:10.1016/j.eplepsyres.2007.03.004

87. Tayama T, Mori T, Goji A, Toda Y, Kagami S. Improvement of epilepsy with lacosamide in a patient with ring chromosome 20 syndrome. *Brain Dev*. 2020;42(6):473-476. doi:10.1016/j.braindev.2020.03.003

88. Biton V, Gil-Nagel A, Isojarvi J, Doty P, Hebert D, Fountain NB. Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: Analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials. *Epilepsy Behav*. 2015;52:119-127. doi:10.1016/j.yebeh.2015.09.006

89. Schultz L, Mahmoud SH. Is Therapeutic Drug Monitoring of Lacosamide Needed in Patients with Seizures and Epilepsy? *Eur J Drug Metab Pharmacokinet*. 2020;45(3):315-349. doi:10.1007/s13318-019-00601-8

90. Soares-da-Silva P, Pires N, Bonifácio MJ, Loureiro AI, Palma N, Wright LC. Eslicarbazepine acetate for the treatment of focal epilepsy: an update on its proposed mechanisms of action. *Pharmacol Res Perspect*. 2015;3(2):e00124. doi:10.1002/prp2.124

91. Villanueva V, Serratosa JM, Guillamón E, et al. Long-term safety and efficacy of eslicarbazepine acetate in patients with focal seizures: Results of the 1-year ESLIBASE retrospective study. *Epilepsy Res*. 2014;108(7):1243-1252. doi:10.1016/j.eplepsyres.2014.04.014

92. Gil-Nagel A, Elger C, Ben-Menachem E, et al. Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: Integrated analysis of pooled data from double-blind phase III clinical studies: *ESL in the Treatment of Focal-Onset Seizures*. *Epilepsia*. 2013;54(1):98-107. doi:10.1111/j.1528-1167.2012.03605.x

93. Bendtsen L, Zakrzewska JM, Heinskou TB, et al. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. *Lancet Neurol*. 2020;19(9):784-796. doi:10.1016/S1474-4422(20)30233-7

94. Tai AX, Nayar VV. Update on Trigeminal Neuralgia. *Curr Treat Options Neurol*. 2019;21(9):42. doi:10.1007/s11940-019-0583-0

95. Haridas A, Mathewson C, Eljamel S. Long-term Results of 405 Refractory Trigeminal Neuralgia Surgeries in 256 Patients. *Zentralblatt Für Neurochir - Cent Eur Neurosurg*. 2008;69(04):170-174. doi:10.1055/s-2008-1077076

96. Barker FG 2nd, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med*. 1996;334(17):1077-1083. doi:10.1056/NEJM199604253341701

97. Bond AE, Zada G, Gonzalez AA, Hansen C, Giannotta SL. Operative strategies for minimizing hearing loss and other major complications associated with microvascular decompression for trigeminal neuralgia. *World Neurosurg*. 2010;74(1):172-177. doi:10.1016/j.wneu.2010.05.001

98. Broggi G, Ferroli P, Franzini A, Servello D, Dones I. Microvascular decompression for trigeminal neuralgia: comments on a series of 250 cases, including 10 patients with multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2000;68(1):59-64. doi:10.1136/jnnp.68.1.59

99. Klun B. Microvascular decompression and partial sensory rhizotomy in the treatment of trigeminal neuralgia: personal experience with 220 patients. *Neurosurgery*. 1992;30(1):49-52. doi:10.1227/00006123-199201000-00009

100. Laghmari M, El Ouahabi A, Arkha Y, Derraz S, El Khamlichi A. Are the destructive neurosurgical techniques as effective as microvascular decompression in the management of trigeminal neuralgia? *Surg Neurol*. 2007;68(5):505-512. doi:10.1016/j.surneu.2006.11.066

101. Lee KH, Chang JW, Park YG, Chung SS. Microvascular decompression and percutaneous rhizotomy in trigeminal neuralgia. *Stereotact Funct Neurosurg*. 1997;68(1-4 Pt 1):196-199. doi:10.1159/000099923

102. Mendoza N, Illingworth RD. Trigeminal neuralgia treated by microvascular decompression: a long-term follow-up study. *Br J Neurosurg*. 1995;9(1):13-19.

103. Miller JP, Magill ST, Acar F, Burchiel KJ. Predictors of long-term success after microvascular decompression for trigeminal neuralgia. *J Neurosurg*. 2009;110(4):620-626. doi:10.3171/2008.9.17660

104. Oesman C, Mooij JJA. Long-term follow-up of microvascular decompression for trigeminal neuralgia. *Skull Base Off J North Am Skull Base Soc Al*. 2011;21(5):313-322. doi:10.1055/s-0031-1284213

105. Olson S, Atkinson L, Weidmann M. Microvascular decompression for trigeminal neuralgia: recurrences and complications. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2005;12(7):787-789. doi:10.1016/j.jocn.2005.08.001

106. Pamir M, Peker S. Microvascular Decompression for Trigeminal Neuralgia: A Long-Term Follow-Up Study. *Min - Minim Invasive Neurosurg*. 2006;49(6):342-346. doi:10.1055/s-2006-960487

107. Sandel T, Eide PK. Long-term results of microvascular decompression for trigeminal neuralgia and hemifacial spasms according to preoperative symptomatology. *Acta Neurochir (Wien)*. 2013;155(9):1681-1692; discussion 1692. doi:10.1007/s00701-013-1816-8

108. Sarsam Z, Garcia-Fiñana M, Nurmikko TJ, Varma TRK, Eldridge P. The long-term outcome of microvascular decompression for trigeminal neuralgia. *Br J Neurosurg*. 2010;24(1):18-25. doi:10.3109/02688690903370289

109. Sindou M, Leston J, Howeidy T, Decullier E, Chapuis F. Micro-vascular decompression for primary Trigeminal Neuralgia (typical or atypical). Long-term effectiveness on pain; prospective study with survival analysis in a consecutive series of 362 patients. *Acta Neurochir (Wien)*. 2006;148(12):1235-1245; discussion 1245. doi:10.1007/s00701-006-0809-2

110. Sun T, Saito S, Nakai O, Ando T. Long-term results of microvascular decompression for trigeminal neuralgia with reference to probability of recurrence. *Acta Neurochir (Wien)*. 1994;126(2-4):144-148. doi:10.1007/BF01476425

111. Tyler-Kabara EC, Kassam AB, Horowitz MH, et al. Predictors of outcome in surgically managed patients with typical and atypical trigeminal neuralgia: comparison of results following microvascular decompression. *J Neurosurg*. 2002;96(3):527-531. doi:10.3171/jns.2002.96.3.0527

112. Walchenbach R, Voormolen JHC, Hermans J. Microvascular decompression for trigeminal neuralgia: A critical reappraisal. *Clin Neurol Neurosurg*. 1994;96(4):290-295. doi:10.1016/0303-8467(94)90116-3

113. Zakrzewska JM, Lopez BC, Kim SE, Coakham HB. Patient reports of satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. *Neurosurgery*. 2005;56(6):1304-1311; discussion 1311-1312. doi:10.1227/01.neu.0000159883.35957.e0

114. Zakrzewska JM, Thomas DGT. Patient's assessment of outcome after three surgical procedures for the management of trigeminal neuralgia. *Acta Neurochir (Wien)*. 1993;122(3-4):225-230. doi:10.1007/BF01405533

115. Zhang H, Lei D, You C, Mao BY, Wu B, Fang Y. The Long-Term Outcome Predictors of Pure Microvascular Decompression for Primary Trigeminal Neuralgia. *World Neurosurg*. 2013;79(5-6):756-762. doi:10.1016/j.wneu.2012.01.040

116. Wang DD, Raygor KP, Cage TA, et al. Prospective comparison of long-term pain relief rates after first-time microvascular decompression and stereotactic radiosurgery for trigeminal neuralgia. *J Neurosurg*. 2018;128(1):68-77. doi:10.3171/2016.9.JNS16149

117. Brisman R. Microvascular Decompression vs. Gamma Knife Radiosurgery for Typical Trigeminal Neuralgia: Preliminary Findings. *Stereotact Funct Neurosurg*. 2007;85(2-3):94-98. doi:10.1159/000097925

118. Pollock BE, Schoeberl KA. Prospective Comparison of Posterior Fossa Exploration and Stereotactic Radiosurgery Dorsal Root Entry Zone Target as Primary Surgery for Patients With Idiopathic Trigeminal Neuralgia. *Neurosurgery*. 2010;67(3):633-639. doi:10.1227/01.NEU.0000377861.14650.98

119. Narouze S. Headache and Craniofacial Neuralgias. In: *Encyclopedia of the Neurological Sciences*. Elsevier; 2014:512-515. doi:10.1016/B978-0-12-385157-4.00231-1

120. Håkanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. *Neurosurgery*. 1981;9(6):638-646. doi:10.1227/00006123-198112000-00005

121. Fujimaki T, Miyazaki S. Percutaneous retrogasserian glycerol injection in the management of trigeminal neuralgia: long-term follow-up results. *J Neurosurg*. 1990;73:5.

122. Steiger HJ. Prognostic factors in the treatment of trigeminal neuralgia: Aalysis of a differential therapeutic approach. *Acta Neurochir (Wien)*. 1991;113(1-2):11-17. doi:10.1007/BF01402108

123. Oturai AB, Jensen K, Eriksen J, Madsen F. Neurosurgery for trigeminal neuralgia: comparison of alcohol block, neurectomy, and radiofrequency coagulation. *Clin J Pain*. 1996;12(4):311-315. doi:10.1097/00002508-199612000-00010

124. Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. *J Neurosurg*. 1983;59(6):1007-1012. doi:10.3171/jns.1983.59.6.1007

125. Campos WK, Linhares MN. A prospective study of 39 patients with trigeminal neuralgia treated with percutaneous balloon compression. *Arq Neuropsiquiatr*. 2011;69(2a):221-226. doi:10.1590/S0004-282X2011000200016

126. Lichtor T, Mullan JF. A 10-year follow-up review of percutaneous microcompression of the trigeminal ganglion. *J Neurosurg*. 1990;72(1):49-54. doi:10.3171/jns.1990.72.1.0049

127. Omeis I, Smith D, Kim S, Murali R. Percutaneous Balloon Compression for the Treatment of Recurrent Trigeminal Neuralgia: Long-Term Outcome in 29 Patients. *Stereotact Funct Neurosurg*. 2008;86(4):259-265. doi:10.1159/000138770

128. Skirving DJ, Dan NG. A 20-year review of percutaneous balloon compression of the trigeminal ganglion. *J Neurosurg*. 2001;94(6):913-917. doi:10.3171/jns.2001.94.6.0913

129. Sweet WH. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers Part 1" Trigeminal neuralgia. *J Neurosurg*. 1974;39:14.

130. Yoon KB, Wiles JR, Miles JB, Nurmikko TJ. Long-term outcome of percutaneous thermocoagulation for trigeminal neuralgia. *Anaesthesia*. 1999;54(8):803-808. doi:10.1046/j.1365-2044.1999.00905.x

131. Broggi G, Franzini A, Lasio G, Giorgi C, Servello D. Long-term results of percutaneous retrogasserian thermorhizotomy for “essential” trigeminal neuralgia: considerations in 1000 consecutive patients. *Neurosurgery*. 1990;26(5):783-786; discussion 786-787. doi:10.1097/00006123-199005000-00008

132. Huang Y, Ni J, Wu B, He M, Yang L, Wang Q. Percutaneous radiofrequency thermocoagulation for the treatment of different types of trigeminal neuralgia: evaluation of quality of life and outcomes. *J Huazhong Univ Sci Technol Med Sci Hua Zhong Ke Ji Xue Xue Bao Yi Xue Ying Wen Ban Huazhong Keji Daxue Xuebao Yixue Yingdewen Ban*. 2010;30(3):403-407. doi:10.1007/s11596-010-0365-0

133. Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous Controlled Radiofrequency Trigeminal Rhizotomy for the Treatment of Idiopathic Trigeminal Neuralgia: 25-year Experience with 1600 Patients. *Neurosurgery*. 2001;48(3):524-534. doi:10.1097/00006123-200103000-00013

134. Taha JM, Tew JMJ. Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. *Neurosurgery*. 1996;38(5):865-871. doi:10.1097/00006123-199605000-00001

135. Tang YZ, Wu BS, Yang LQ, et al. The Long-Term Effective Rate of Different Branches of Idiopathic Trigeminal Neuralgia After Single Radiofrequency Thermocoagulation: A Cohort Study. *Medicine (Baltimore)*. 2015;94(45):e1994. doi:10.1097/MD.0000000000001994

136. Ko AL, Ozpinar A, Lee A, Raslan AM, McCartney S, Burchiel KJ. Long-term efficacy and safety of internal neurolysis for trigeminal neuralgia without neurovascular compression. *J Neurosurg*. 2015;122(5):1048-1057. doi:10.3171/2014.12.JNS14469

137. Riesenburger RI, Hwang SW, Schirmer CM, et al. Outcomes following single-treatment Gamma Knife surgery for trigeminal neuralgia with a minimum 3-year follow-up. *J Neurosurg*. 2010;112(4):766-771. doi:10.3171/2009.8.JNS081706

138. Dhople AA, Adams JR, Maggio WW, Naqvi SA, Regine WF, Kwok Y. Long-term outcomes of Gamma Knife radiosurgery for classic trigeminal neuralgia: implications of treatment and critical review of the literature. Clinical article. *J Neurosurg*. 2009;111(2):351-358. doi:10.3171/2009.2.JNS08977

139. Longhi M, Rizzo P, Nicolato A, Foroni R, Reggio M, Gerosa M. Gamma knife radiosurgery for trigeminal neuralgia: results and potentially predictive parameters--part I: Idiopathic trigeminal neuralgia. *Neurosurgery*. 2007;61(6):1254-1260; discussion 1260-1261. doi:10.1227/01.neu.0000306104.68635.d4

140. Han JH, Kim DG, Chung HT, et al. Long-term outcome of gamma knife radiosurgery for treatment of typical trigeminal neuralgia. *Int J Radiat Oncol Biol Phys*. 2009;75(3):822-827. doi:10.1016/j.ijrobp.2008.11.046

141. McNatt SA, Yu C, Giannotta SL, Zee CS, Apuzzo MLJ, Petrovich Z. Gamma knife radiosurgery for trigeminal neuralgia. *Neurosurgery*. 2005;56(6):1295-1301; discussion 1301-1303. doi:10.1227/01.neu.0000160073.02800.c7

142. Régis J, Tuleasca C, Resseguier N, et al. Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. *J Neurosurg*. 2016;124(4):1079-1087. doi:10.3171/2015.2.JNS142144

143. Urgosik D, Liscak R, Novotny JJ, Vymazal J, Vladyka V. Treatment of essential trigeminal neuralgia with gamma knife surgery. *J Neurosurg*. 2005;102 Suppl:29-33. doi:10.3171/jns.2005.102.s_supplement.0029

144. Shankar Kikkeri N, Nagalli S. Trigeminal Neuralgia. In: *StatPearls*. StatPearls Publishing; 2022.

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