*Review*

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# Trigeminal neuralgia: An overview from pathophysiology to pharmacological treatments

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**Abstract**

The trigeminal nerve (V) is the fifth and largest of all cranial nerves, and it is responsible for detecting sensory stimuli that arise from the craniofacial area. The nerve is divided into three branches: ophthalmic (V1), maxillary (V2), and mandibular (V3); their cell bodies are located in the trigeminal ganglia and they make connections with second-order neurons in the trigeminal brainstem sensory nuclear complex. Ascending projections via the trigeminothalamic tract transmit information to the thalamus and other brain regions responsible for interpreting sensory information. One of the most common forms of craniofacial pain is trigeminal neuralgia. Trigeminal neuralgia is characterized by sudden, brief, and excruciating facial pain attacks in one or more of the V branches, leading to a severe reduction in the quality of life of affected patients. Trigeminal neuralgia etiology can be classified into idiopathic, classic, and secondary. Classic trigeminal neuralgia is associated with neurovascular compression in the trigeminal root entry zone, which can lead to demyelination and a dysregulation of voltage-gated sodium channel expression in the membrane. These alterations may be responsible for pain attacks in trigeminal neuralgia patients. The antiepileptic drugs carbamazepine and oxcarbazepine are the first-line pharmacological treatment for trigeminal neuralgia. Their mechanism of action is a modulation of voltage-gated sodium channels, leading to a decrease in neuronal activity. Although carbamazepine and oxcarbazepine are the first-line treatment, other drugs may be useful for pain control in trigeminal neuralgia. Among them, the anticonvulsants gabapentin, pregabalin, lamotrigine and phenytoin, baclofen, and botulinum toxin type A can be coadministered with carbamazepine or oxcarbazepine for a synergistic approach. New pharmacological alternatives are being explored such as the active metabolite of oxcarbazepine, eslicarbazepine, and the new Nav1.7 blocker vixotrigine. The pharmacological profiles of these drugs are addressed in this review.

**Keywords**

Facial pain, carbamazepine, oxcarbazepine, sodium channel, Nav1.3, Kv7.2

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## Basic organization of the trigeminal system

Sensory information from the craniofacial region is conveyed by the trigeminal sensory system, which is composed of peripheral structures, such as the trigeminal nerve (V) and trigeminal ganglia (TG), and central structures, such as the trigeminal brainstem sensory nuclear complex (VBSNC).[1] The trigeminal nerve is divided into three branches: ophthalmic (V1), maxillary (V2), and mandibular (V3) (Figure 1). The superior region of the head, that is, meninges and cornea are innervated mainly by the ophthalmic branch. The upper lip, maxillary teeth, and mucosa are innervated by the maxillary branch, while the mandibular branch innervates mainly

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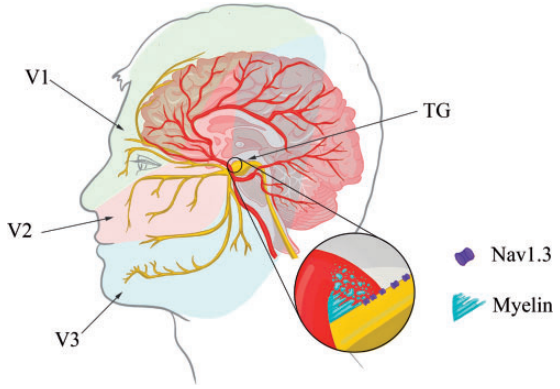


**Figure 1.** Representation of the trigeminal system and classical trigeminal neuralgia etiology. The area of innervation for the ophthalmic (V1), maxillary (V2), and mandibular (V3) branches is indicated. Neurovascular compression by the superior cerebellar arteries observed at the root entry zone of the trigeminal nerve is highlighted. This compression leads to demyelination and an upregulation of the voltage-gated sodium channels Nav1.3, as demonstrated in the magnification. TG: trigeminal ganglia.

the mandibula, lower lip, mucosa, and mandibular teeth. The V1 and V2 branches are purely sensory, whereas V3 has motor fibers which are responsible for innervation of the jaw muscles.[1] The fibers that form the trigeminal nerve are classified into nociceptive fibers (A$\delta$ and C fibers) and low-threshold mechanoreceptors (LTMs; A$\alpha$ and A$\beta$ fibers).

Within the nociceptive fibers, the C fibers are non-myelinated with a slow conductance velocity and small diameter, while the A$\delta$ fibers are myelinated and have an intermediate diameter and conductance velocity, and both fibers can be activated by noxious triggers, such as mechanical, thermal, and chemical stimuli. The proprioceptive A$\alpha$ and A$\beta$ fibers are myelinated and display fast conductance and have a larger diameter, and they are responsible for innocuous and proprioceptive stimuli.[2] In the trigeminal nerve, the proportion of unmyelinated/myelinated fibers is much lower compared to spinal nerves.[3,4] The cell bodies of those fibers are localized in the TG, while the cell bodies from the proprioceptive fibers (A$\alpha$) are localized in the mesencephalic trigeminal nucleus. They make connections with second-order neurons in the VBSNC.

The primary function of the trigeminal nucleus is to carry temperature, touch, and pain inputs from the ipsilateral side of the face to the contralateral thalamus via the ventral trigeminothalamic tract.[5] The VBSNC is divided into the main/principal sensory nucleus and spinal tract nucleus; the latter being composed by the *subnucleus oralis* (Sp5O), *subnucleus interpolaris* (Sp5I), and *subnucleus caudalis* (Sp5C). The *subnucleus caudalis* is also denominated as the medullary dorsal horn since it has a laminated structure and C- and A$\delta$ fibers project to laminae I, II, V, and VI, analogous to what occurs in the spinal dorsal horn.[4,6–8] It receives major inputs from nociceptive afferents in addition to inputs from other cranial nerves, such as the facial, glossopharyngeal, and vagus nerves (for review, see Sessle[3]). Beside this similarity between the VBSNC and the spinal dorsal horn, there are some differences, such as the transition zone Sp5I/Sp5C which is involved in the processing of nociceptive stimuli from facial deep tissues, but not in nociceptive stimuli arising from the skin.[9,10] Moreover, a group of nociceptive fibers activated from the orofacial region can also be observed within Sp5O.[11] Although both structures receive nociceptive inputs, there are some well-described differences, such as the presence and absence of a group of small interneurons (*substantia gelatinosa*) within the Sp5C and Sp5O, respectively.[11] Moreover, intrinsic fibers in the VBSNC representing the collateral incoming primary afferents can make connections between the Sp5O and Sp5C (for review, see Sessle[3] and Woda[11]). The output from these nuclei (i.e., second-order neurons) can be classified as nociceptive specific (NS), wide dynamic range (WDR), and LTMs.[12,13] The NS neurons are exclusively activated by noxious stimuli, while WDR neurons, due to their wide range of recognition, are responsive to innocuous and noxious stimuli.[14] The second-order neurons redirect the sensory information to different regions of the thalamus where sensory stimuli are processed. The thalamus sends third-order neuronal projections to the primary and secondary somatosensory cortex and insula—regions responsible for interpreting sensory information in terms of location, intensity, and duration. In addition, outputs from the thalamus can be directed to other cortical and limbic structures that are responsible for processing the cognitive, affective, and emotional components of pain.[1,12,13]

In addition, the activation of mesencephalic and bulbar structures can modulate nociceptive processing. The main inhibitory descending pathway includes structures such as the periaqueductal gray matter (GM) and the rostral ventromedial medulla (RVM), which projects to the VBSNC where the nociceptive responses are modulated.[15–17]There is growing evidence of differences between the RVM projection to the VBSNC and to the spinal dorsal horn.[18] In patients with trigeminal neuropathic pain, an increase in connectivity between the RVM and the Sp5C was reported, in addition to increased connectivity to other brain regions involved in the descending pathways, such as the anterior cingulate cortex (ACC).[19] Additionally, it has been demonstrated that there is a functional connection between the Sp5I/Sp5C zone and the RVM, and the result of a lesion of either region is attenuation of facial hyperalgesia.[20] Furthermore, it was shown that corticotrigeminal

pathways can regulate facial pain perception.[21,22] Projections from the somatosensory cortices (SI and SII) to Sp5C target the primary nociceptive afferents from the facial region.[23–25] Corticotrigeminal inhibitory effects can also be achieved through presynaptic and postsynaptic mechanisms.[26] Indeed, Castro et al.[27] demonstrated that corticotrigeminal stimulation can produce analgesia via feed-forward inhibition in the Sp5C.[27]

The prevalence of pain syndromes that affect the territories innervated by the trigeminal nerve, such as migraines and headaches, is one of the highest and ranks second only to low back pain.

## Trigeminal neuralgia: Definition and classification

Trigeminal neuralgia (TN) is the most common form of craniofacial neuropathic pain and is considered the cause of one of the most severe types of pain that a person can experience. The incidence is estimated at 4 to 13 people per 100,000/year.[28–31] The International Association for the Study of Pain describes TN as "a sudden usually unilateral severe brief stabbing recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve."[32] Pain is usually described as stabbing, paroxysmal, reminiscent of electric shock, or burning and is limited to the area innervated by one or more branches of the trigeminal nerve. In approximately 60% of the cases, there is an involvement of only one branch, the maxillary or mandibular branch, whereas in approximately 35% of the cases, both are involved. On the other hand, the ophthalmic branch is rarely affected (i.e., in fewer than 4% of patients).[33] Aging is a risk factor for the development of trigeminal pain, commonly occurring in patients over 50 years old.[34] The incidence in woman is higher, with a female–male ratio of approximately 2–3:1.[31,35] Pain attacks usually occur by stimulating trigger points, usually located in the territory innervated by the trigeminal nerve. Examples of stimuli that trigger attacks of pain include a slight touch of the face, tooth brushing, and activation of the masticatory and facial muscles during speech and feeding. Each episode of pain is followed by a refractory period that can last from a few seconds to several minutes. When attacks of pain become very frequent, patients become unable to perform their daily activities, and even avoid eating and communicating for fear of triggering a new crisis. This, in turn, can lead to a severe impairment of life quality and mental health in these patients.[36,37]

The etiology of TN and the underlying mechanisms of this condition are still poorly understood and based on the etiology, TN is classified into idiopathic TN, classic TN, and secondary TN. The first is characterized by unknown causes, and in approximately 10% of patients, even after surgical procedures or magnetic resonance imaging, the disease remains without a diagnosed cause.[38] Classic TN is associated with neurovascular compression (NVC) in the trigeminal root entry zone, which causes nerve root atrophy or displacement.[38–40] Secondary TN may be caused by an underlying disease such as tumors or artery malformations and has been associated with multiple sclerosis (multiple sclerosis patients show a 20-fold high prevalence of TN).[41,42] Classical TN has distinct features regarding both pathophysiology and therapeutic approaches, which will be covered in the ensuing section.

## Pathophysiology of classical TN

According to the International Classification of Headache Disorder-3 Classical TN is caused by NVC, most frequently by the superior cerebellar artery of the trigeminal nerve roots into the pons.[31,34,40] This compression usually results in the demyelination of nerve fibers, which then start firing ectopically (Figure 1).[40,43,44] The NVC hypothesis is supported by evidence that after surgical procedures that lead to microvascular decompression, the majority of patients achieve sustained pain relief.[45–47] Notwithstanding this evidence, NVC can also be observed in asymptomatic patients.[48,49] Several alterations have been described as a result of the vascular compression, including focal demyelination at the entry zone of the trigeminal nerve, atrophy or hypertrophy of peripheral axons, and damage to Schwann cells as well as to peripheral myelin.[50–53] The "ignition hypothesis," proposed by Devor et al., [54] aims to correlate the structural changes with paroxysmal pain attacks, which are characteristic of the condition. It states that after trigeminal root damage, partially damaged neurons trigger a stimulus induced burst of activity, making them hyperexcitable and susceptible to cross excitation as a result from the physical proximity of the neurons to the root compression site.[55] Therefore, the drastic increase in posttrigger neuronal activity recruits additional neighboring neurons leading to a rapid accumulation of electrical activity, which can be amplified by ephaptic interaction among neurons, since the myelin sheath is damaged and nerve fibers maintain close contact among them.

There is accumulating evidence that voltage-gated sodium channels (VGSCs) play a crucial role in the generation of ectopic activity in trigeminal afferents. Several preclinical studies using a model of TN by constriction of the infraorbital nerve already demonstrated a dysregulation in VGSCs, which includes an upregulation of Nav1.3 and a downregulation of Nav1.7.[56,57] These findings are in accordance with clinical studies which have shown that patients with TN present the same profile of dysregulation in VGSCs.[58,59] In addition, there is

evidence of a mutation in the SCN8A gene (which encodes Nav1.6) in a TN patient.[60] The alteration of a methionine in the position 136 to a valine (M136V) led to an increase in the peak current, without changing any biophysical properties of the channel. As the Nav1.6 channel is important for the activation of resurgent currents, this gain of function mutation facilitates the repetitive firing of action potential in neurons. Thus, VGSCs have been considered the main target for pain control in TN.

In a preclinical model of TN (i.e., constriction of the infraorbital nerve), a dysregulation of the voltage-gated potassium channel Kv7.2 has been reported and this appears to be a key factor in cold allodynia/hyperalgesia associated with this model.[61,62] Specifically, an upregulation of the Kv7.2 channel was observed in the infraorbital nerve of constricted animals,[62] and the authors suggested that this may act as a compensatory mechanism to dampen the excitability of neurons after nerve injury. It is important to point out that this channel is responsible to generate M-currents (i.e., muscarinic currents), that are slowly activating, noninactivating voltage-gated potassium currents, which are activated at subthreshold potentials.[63] M-currents help to modulate the firing properties of neurons since they serve to stabilize the membrane potential and control neuronal excitability.[63,64]

Neuroimaging studies have shown that patients with TN have alterations in brain structure, function, and connectivity, which were demonstrated by different approaches.[65–69] Resting-state functional magnetic resonance imaging (rs-fMRI) is a tool that can acquire data in the absence of stimulus and is based on blood-oxygen-level-dependent (BOLD) blood flow signals.[70,71] rs-fMRI can yield a wealth of data and measurements, such as amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo), which can provide information about brain activity and synchrony, respectively.[72,73] White matter volume changes were observed in the brainstem, corpus callosum, cingulum, corona radiata, and superior longitudinal fasciculus.[65] Moreover, it was also demonstrated that GM undergoes volume changes. A decrease in GM was detected in both primary and secondary somatosensory cortices, ACC, dorsolateral prefrontal cortex, ventral orbitofrontal cortex, insula, and thalamus.[65,67] In addition to structural changes, fMRI studies demonstrated different patterns of brain activation in patients with TN when compared to healthy controls.[66,68,69,74–76] A different pattern of activation was also observed in TN patients who report pain after stimulation of trigger zones versus patients who do not.[68] Patients with pain evoked by light tactile stimulation showed a bilateral activation of the primary and secondary somatosensory cortices, the ACC, and the prefrontal cortex, contralateral activation of insula and thalamus, ipsilateral activation of the medial cingulate cortex and spinal trigeminal nucleus, and activation of the medial brainstem, including the periaqueductal gray.[68] Conversely, TN patients without pain present a different pattern of brain activation, including the bilateral activation of the precentral cortex, contralateral supplementary motor area, prefrontal cortex, thalamus, and insula activation, and ipsilateral activation of medial cingulate cortex.[68] Analysis of local spontaneous brain activity using ALFF and ReHo demonstrated that TN has a characteristic spatiotemporal BOLD signal property. Wang et al.[66] demonstrated a bilateral increase in ALFF in the temporal and occipital cortices, and in the left middle frontal regions and middle cingulate gyrus; and a decrease in the right inferior temporal gyrus and medial prefrontal cortex. Similar ALFF analysis revealed an increase of ALFF bilaterally in the inferior cerebellum and fusiform gyrus[74] and a reduction in the posterior cingulate cortex, dorsolateral prefrontal cortex, insula, and lateral temporal region.[69] Moreover, the posterior cingulate cortex-medial prefrontal cortex circuit and the dorsolateral prefrontal cortex-hippocampal region circuit presented an abnormal interaction in the default mode network in TN patients.[69] For the ReHo analysis which reflects temporal synchronization of the BOLD signal, TN patients showed an increase in ReHo in the anterior cingulate, middle and inferior temporal gyrus, medial and superior frontal gyrus, right fusiform gyrus, and right thalamus and a decrease in the left amygdala, the parahippocampal gyrus, cerebellum, and insula.[75] Collectively, these studies demonstrated that TN may be associated with brain alterations with a complex spatiotemporal pattern activity, highlighting impairments in major brain areas that are part of the "pain matrix." It has been suggested that changes in brain structure in TN patients have a correlation with disease duration and is related to a worse prognosis. Thus, effective pain control in the initial state of the disease may have implications in the course of TN.

## Pharmacological treatment: Carbamazepine mechanisms of action and effectiveness

TN treatment is initially pharmacological in the form of monotherapy; however, combined therapy with different drugs may be used when the efficacy of monotherapy is low.[77,78] Patients not responsive to pharmacological treatment or those who present with severe side effects are candidates for more invasive strategies such as nerve block or surgery.[30]

### Studies on heterologously expressed channels

The main pharmacological class used to control pain in patients with TN is anticonvulsants. Although carbamazepine (CBZ) and oxcarbazepine (OXC) are recommended as first-line therapy,[79] their comparative efficacy lacks evidence in TN. Either one may be switched or combined with pregabalin, gabapentin, topiramate, and/or baclofen.[30] CBZ is currently the only drug approved by the Food and Drug Administration (FDA) for TN treatment, with 70% effectiveness in reducing pain.[80,81] Moreover, for long-term treatment, CBZ and OXC are recommended as the first choice.[79] CBZ blocks VGSCs resulting in inhibition of action potentials, reduction of synaptic transmission, and stabilization of the membrane potential in hyperexcitable neurons.[77,82,83] This effect is achieved in a use- and voltage-dependent manner because CBZ binds to the inactivated channels with higher affinity than to channels in the open or resting state.[84–86] Several studies demonstrated that anticonvulsants share a common binding site with local anesthetics in the alpha subunit of the VGSC.[86–89] Residues W1716 and F1764 (which comprise the external pore loop and the pore-lining part of the S6 segment of domain IV, respectively) interact to form the binding pocket for CBZ and local anesthetics.[86,90] It was proposed that the CBZ binding site is located at the junction of the widened external vestibule and the narrow part of the channel pore, which is able to recognize the two phenyl groups in the structure of the drug.[85,90] When CBZ binds to this region, the channel gating property is modified and the channel is stabilized in its inactivated state to prevent $Na^+$ ion influx.[86] Furthermore, external application of CBZ effectively blocked the sodium current, while internal application had no effect, suggesting that the region for binding and unbinding could be different than for local anesthetics.[85] Studies using whole-cell patch clamp in mouse neuroblastoma cells (N1E-115) showed that CBZ and OXC shift the voltage dependence of fast inactivation of endogenously expressed VGSC.[91,92]

It was previously demonstrated in HEK293 cells expressing the Nav1.3 channel that CBZ is able to modulate persistent $Na^+$ current. Moreover, a hyperpolarizing shift in the steady-state inactivation curve was observed in a concentration-dependent manner.[93] Fast and slow inactivation of sodium currents was evaluated in Chinese Hamster Ovary cells expressing Nav1.3, and both CBZ and OXC shifted the voltage dependence of slow inactivation toward more hyperpolarizing potentials.[91] Mutations in the pore region of the Nav1.3 can lead to pharmacoresistance to CBZ and OXC, as observed in patients with cryptogenic pediatric partial epilepsy.[94] The alteration of lysine at position 354 to a glutamine (K354Q) led to nonresponsiveness to CBZ and OXC, suggesting that this is a crucial region for the effects of both drugs.[94] As noted earlier, TN patients exhibit an upregulation of Nav1.3, which raises the question whether genomic differences in SCN3A gene may influence the effectiveness of CBZ in these patients.

When the effect of CBZ on half voltage for inactivation on different alpha subunits VGSCs was examined, a strong modulation was observed in the Nav1.6 channel, while a weak modulation in the Nav1.3 channel was seen.[95] It is worth noting that the Nav1.6 subunit is highly expressed in the axonal initial segments and nodes of Ranvier, and due to its fast recovery from inactivation may facilitate action potential initiation and propagation.[96,97] Moreover, it was found that CBZ blockade depends only on the availability of inactivated channels[95] and produced a greater degree of inhibition of Nav1.6 compared to OXC (70.4% vs. 46.7%, respectively).[98]

Jo and Bean evaluated the effect of internal and external application of CBZ on HEK293 cells expressing hNav1.7. These authors found that external, but not internal, application of CBZ was able to block $Na^+$ currents in whole-cell recordings.[99] They observed a difference in inactivation behavior of the channels when examined in the whole-cell versus an inside-out configuration, and in such inside-out recordings, application of CBZ was able to block sodium current.[99] A whole-cell patch clamp study demonstrated that application of CBZ at 100 μM was unable to produce inhibition of resurgent sodium current in HEK293 cells expressing Nav1.7; however, a higher concentration (200 μM) did block these currents.[100] Furthermore, OXC was also able to inhibit sodium currents of hNav1.7 and caused a hyperpolarizing shift in the activation and inactivation properties of Nav1.7 channels.[101] Thus, although both CBZ and OXC are able to block Nav current, the effect can be achieved with a lower concentration with OXC.[102] It should be noted that the differences in the analgesic properties of CBZ and OXC may in part be related to actions on other voltage-gated ion channels, such as voltage-gated calcium channels (VGCCs),[103,104] and thus, their ability to modulate several neurotransmitter systems involved in pain modulation (for review, see Tomić et al.[105]).

Point mutations in the Nav1.7 channel in patients with chronic pain disorders often show a hyperpolarizing shift in the voltage dependence of activation.[106–108] Interestingly, a family with inherited erythromelalgia (IEM) that carried the Nav1.7 V400M mutant was responsive to CBZ[109] because a shift in the voltage dependence of activation and in the steady-state inactivation in the V400M mutant were both normalized by CBZ.[109]

### *Effects in isolated neurons*

In neurons, CBZ was able to reduce tetrodotoxin-resistant (TTX-R) sodium currents in dorsal root ganglion neurons, including TTX-R Nav1.8 currents, an important component for pain transmission.[110–114] Furthermore, CBZ was more effective toward blocking Nav1.8 currents in a use-dependent manner, suggesting an interaction with the inactive state of Nav1.8.[110,115] Whole-cell recordings in TG neurons demonstrated that CBZ treatment was able to reduce the peak amplitude of TTX-R sodium current in a concentration-dependent manner, without affecting the half voltage for activation.[116] Meanwhile, the same study observed that CBZ was able to shift the half voltage for slow inactivation to more hyperpolarizing potentials, suggesting a decrease in channel availability during repetitive depolarization.[116] This fits with the idea that CBZ appears to exhibit a higher affinity for the inactivated conformation of the VGSC than the resting conformation.[84,117] Along these lines, studies investigating the effects on TTX-sensitive currents suggest that CBZ binds and stabilizes the channels in the inactivate state.[115] This suggests a shift in the voltage dependence, reducing the population of channels that is available for opening.

It is noteworthy that VGSCs also contain ancillary beta subunits ($\beta1$–$\beta4$), which can modulate the biophysical properties of the channel. CBZ reduced the amplitude of fast transient sodium currents ($INa_T$) in both $\beta_1^{-/-}$and $\beta_2^{-/-}$ knockout mice, with no difference from their wild-type littermates.[118] Moreover, in $\beta_2^{-/-}$ animals but not in $\beta_1^{-/-}$mice CBZ was able to shift the voltage dependence of activation of $INa_T$, suggesting that the presence of $\beta_2$ subunit can modulate the effect of CBZ.[118] In addition to effects on $INa_T$, the authors also evaluated the effect of CBZ on persistent sodium currents ($INa_P$), a type of current that does not inactivate during prolonged depolarization. CBZ was able to reduce the $INa_P$ independently of the expression of $\beta$ subunits and to induce a strong shift in the voltage dependence of $INa_P$ to more hyperpolarizing potentials in $\beta_1^{-/-}$ animals. An intriguing finding obtained in this study was that CBZ produces a paradoxical effect in $\beta_1^{-/-}$ mice, increasing the $INa_P$ at more hyperpolarizing potentials and reducing it at more depolarizing potentials which results in an ineffective block of repetitive firing in $\beta_1^{-/-}$ mice.[118] These data suggest that the loss of beta subunits could affect the cellular response to CBZ. Altogether, these data point out a number of peculiarities in the mechanism of action of CBZ, and perhaps this is responsible for its superior efficacy in TN pain control.

### *In vivo effects*

Along with in vitro studies, several in vivo studies already demonstrated the effectiveness of CBZ and OXC in animal models of pain. In an animal model of TN induced by constriction of the infraorbital nerve, treatment with CBZ was able to reduce spontaneous pain[119] and thermal hyperalgesia, without changing the mechanical threshold in doses that do not cause motor deficit.[120,121] Likewise, in a TN model consisting of compression of the trigeminal nerve root, CBZ treatment was able to reduce facial mechanical allodynia.[122,123] These studies demonstrated the effectiveness of CBZ in reducing evoked and spontaneous pain in different animal models of TN.

The main pharmacokinetic characteristics of CBZ and OXC are an important point of consideration, since they may influence treatment response. After oral administration CBZ presents a lower time to reach the peak concentration (0.5 h) with a peak concentration of 37.8 μg/mL and an elimination half-life of 3.38 h, whereas OXC takes 1 h to reach the peak concentration with a maximum concentration of 30.6 μg/mL and 8.99 h of half-life.[124,125] Although the metabolites of CBZ and OXC are very similar, metabolic pathways are quite different. CBZ is metabolized by cytochrome P450 oxidative processes and leads to autoinduction, which results in changes in elimination over time. On the other hand, OXC is metabolized by cytosolic enzymes, presenting a lower potential for drug interactions.[126,127] While CBZ and OXC are the first-line drugs recommended for TN, there is not much known about their comparative efficacy in TN.[79] Furthermore, both drugs are associated with frequent and/or severe side effects, but the latter is suggested to have greater tolerability.[128–133] A systematic review of the effectiveness and safety of CBZ in different pain conditions concluded that 40% to 60% of the patients would exhibit adverse events, mainly impaired cognition, somnolence, dizziness, gastrointestinal symptoms, headaches, dry mouth or taste change, and mood changes. Severe side effects had a very low incidence and included upper gastrointestinal bleeding and cutaneous rashes, which may be considered serious because of association with CBZ-induced Stevens–Johnson syndrome.[134] These observations were corroborated by a recent study evaluating the side effects of antiepileptic drugs in TN. It was reported that impact on memory and cognition were the most common complaints. OXC showed a less negative impact on memory and induced less fatigue. Additionally, at low doses, OXC seemed to be better tolerated than CBZ, but an increase in OXC dosage was less tolerated and correlated with higher side effect scores.[135] Table 1 summarizes the mechanism of action and pharmacokinetic profile of CBZ and OXC.

## Pharmacological alternatives to CBZ

CBZ and OXC represent the only first-line recommendation for long-term treatment of TN. However, when

**Table 1.** Comparison of mechanism of action and pharmacokinetic profile between carbamazepine and oxcarbazepine.

| Drug | Mechanisms of action | Metabolism | Half-life | Therapeutic indication |
|---|---|---|---|---|
| Carbamazepine | VGSC blocker, L-type VGCC blocker | Cytochrome P450 | 0.5 h | Epilepsy, trigeminal neuralgia |
| Oxcarbazepine | VGSC blocker; N-P- and R-type VGCC blocker | Cytosolic enzymes | 9 h | Epilepsy |

VGSC: voltage-gated sodium channel; VGCC: voltage-gated calcium channel.

necessary (i.e., due to failure or toxicity) other drugs may be combined with either one of them or used instead. The alternatives include other anticonvulsants (e.g., pregabalin, gabapentin, lamotrigine, and phenytoin), baclofen, and botulinum toxin type A (BoNT-A). So far, the quality of evidence for their use in TN management is low to very low.[79]

Gabapentinoids (gabapentin and pregabalin) have become the mainstay of treatment for various pain syndromes, including fibromyalgia, diabetic neuropathy, and postherpetic neuralgia.[136] These anticonvulsants have been consistently shown to induce analgesia by targeting the $\alpha 2\delta$ auxiliary subunit of VGCCs,[137–139] which results in impaired trafficking of VGCCs to the plasma membrane and subsequent reduction of neurotransmitter release and neuronal excitability.[140,141] This mechanism may account for their analgesic activity in TN, but in addition, they have been shown to suppress subthreshold oscillations and peripheral ectopia.[142,143] It has been suggested that the membrane stabilizing action is due to a selective effect on the slow component of $Na^+$ conductance,[143] but it remains to be clarified whether this is a direct effect on $Na^+$ channels or indirect via $\alpha 2\delta$ binding. In any case, this effect may contribute to its analgesic effect in TN. Several other mechanisms have been proposed to underlie gabapentinoid analgesia, such as suppression of spinal N-methyl-d-aspartic acid receptors via a coagonist binding site, activation of potassium channels leading to neuronal hyperpolarization and inhibition of descending serotonergic facilitation of nociceptive processing, and finally, activation of descending inhibitory noradrenergic input to the dorsal horn[105] (for review, see Alles and Smith[144] and Kremer et al.[145]). Since most of these effects, if not all, are related to gabapentinoid interaction with multifunctional $\alpha 2\delta$ proteins, it would be relevant to determine whether TN patients present changes in $\alpha 2\delta$ protein expression. Indeed, an upregulation has already been reported in certain experimental conditions[146] and may predict a better response to these drugs.

Lamotrigine and phenytoin are effective in pain states by virtue of the same selective blocking properties of high-frequency action potential firing that account for their antiseizure activity.[147] Their main mechanism of action is comparable to CBZ, as they induce voltage-dependent and frequency-dependent blockade of VGSCs. In fact, phenytoin was the first drug introduced for the treatment of TN in 1942,[148] and in the following decades evidence accumulated regarding its effectiveness in TN pain management (for review, see Keppel Hesselink and Schatman[149]). Its use, as well of its prodrug fosphenytoin, is still recommended in the treatment of refractory TN or in acute exacerbations of pain.[79,150] Phenytoin is considered a weak blocker of VGSCs at hyperpolarized membrane potentials, but its inhibitory action is greatly enhanced by sustained membrane depolarization and during high-frequency channel activity. Compared with CBZ, it has three-fold higher affinity for depolarized channels, but CBZ binds to them at a five-fold faster rate (for review, see Mantegazza et al.[151]).

It has been suggested that all three anticonvulsants (i.e., CBZ, phenytoin, and lamotrigine) bind at a common site in the inner pore of the sodium channel causing its occlusion.[152,153] However, in contrast to CBZ and phenytoin, several additional mechanisms have been proposed for lamotrigine, including inhibition of N-type and P-type high-voltage-activated calcium channels and enhancement of potassium repolarizing currents.[154–156] These mechanisms may account for the differential effect of lamotrigine in epileptic states, as it is the only anticonvulsant among the three to be effective in absence seizures (for review, see Mantegazza et al.[151]). There is currently a weak recommendation for lamotrigine as add-on or monotherapy for TN pain management, but unlike phenytoin, it is not recommended for acute pain exacerbations, since doses must be escalated slowly in order to avoid rashes.[79] It is noteworthy that both phenytoin and lamotrigine may interact with CBZ when used as add-on therapies. Phenytoin is reported to reduce plasma CBZ concentrations to a clinically significant extent probably by stimulating CYP3A4, while lamotrigine metabolism is accelerated by CBZ due to its ability to induce the same isoform of cytochrome P enzyme.[157]

Preclinical observations suggest that baclofen resembles CBZ and phenytoin in its ability to depress excitatory transmission and facilitate segmental inhibition in the trigeminal nucleus.[158,159] These data are corroborated by clinical evidence that baclofen is effective as monotherapy or combined with CBZ in the management of TN pain.[160–165] Baclofen is a $GABA_B$ receptor agonist acting on the $\beta$ subunit of receptors expressed on neurons at the spinal cord level and brain. It has long been a mainstay in the management of spasticity of several

origins.[166] The off-label use includes treatment of alcoholic liver disease, maintenance of alcohol abstinence by decreasing alcohol cravings, alcohol-related anxiety, gastroesophageal reflux disease, hiccups, and TN. It induces analgesia possibly by presynaptic inhibition of neurotransmitter release from the central endings of primary nociceptors in the spinal cord and by stimulating inhibitory neuronal signals in the postsynaptic neurons.[167] Moreover, it has been demonstrated to have affinity for VGSCs, with a potential to eliminate both persistent sodium currents and, indirectly, sodium-activated potassium currents.[168] The relevance of this finding to baclofen-induced analgesia remains to be investigated. Oral use of baclofen is limited by adverse effects, which affect between 25% and 75% of patients and include mainly muscle weakness, nausea, somnolence, and paraesthesia. As baclofen does not easily penetrate the blood-barrier, its intrathecal use has been indicated to control spasticity in refractory patients or those who experience intolerable side effects with oral use.[166] To our knowledge, there is no evidence whether this alternative would benefit TN patients.

There is growing evidence that BoNT-A may represent a safe and effective alternative for TN management.[150,169–171] However, based on the low quality of evidence, the recommendation given for BoNT-A is weak and restricted to an add-on therapy for medium-term treatment of TN.[79] It is now widely accepted that BoNT-A may induced analgesia independently of muscle relaxation but still involves its interaction with the SNAP receptor complex and consequent blockade of synaptic vesicle fusion.[172] Through this mechanism, it has been shown to inhibit the release of various pain-modulating neurotransmitters, such as glutamate, substance P, and calcitonin gene-related peptide (CGRP), as well as to reduce the expression of Transient Receptor Potential V1 (TRPV1) channels by inhibiting the exocytosis of TRPV1-harboring vesicles, leading to the proteosomal degradation of TRPV1.[172–175] The mechanisms that contribute to the analgesic effects of BoNT-A in TN patients remain unclear, but data from preclinical studies have pointed out that axonal transport of BoNT-A from the periphery to the spinal trigeminal nucleus is a determinant for BoNT-A-mediated analgesia.[176,177] Table 2 summarizes the mechanisms of action and therapeutic indications for alternative drugs to CBZ.

Surgical procedures are indicated for patients with incapacitating symptoms of TN, refractory or recurrent TN or in case of intolerable adverse effects related to medication. These procedures include microvascular decompression, gamma knife radiosurgery, and percutaneous techniques, such as glycerol rhizotomy, radiofrequency thermocoagulation, and percutaneous balloon compression.[83] Among these procedures, microvascular decompression is the most invasive, requiring retrosigmoid craniotomy and microsurgical exploration in the posterior fossa, but it offers the higher success rate in pain relief.[127,178] Indications and details on the surgical procedures employed for TN treatment have been reviewed by others and are outside the scope of this review.[127,179–182] Despite these avenues, there remains a critical need for new therapies, and this requires an in-depth understanding of the underlying pathways and molecular mechanisms of TN.

## Additional pharmacological perspectives

Advances in the pharmacological treatment of TN include the assessment of an extended-release formulation of OXC (termed eslicarbazepine) and evaluation of a new selective Nav1.7 channel blocker (BIIB074 or Vixotrigine), which are currently in progress (ClinicalTrials.gov, Identifiers # NCT03374709 and NCT03637387, respectively).

Eslicarbazepine is the active metabolite of OXC and was approved in Europe in 2009 and in 2013 by the FDA and Health Canada as an adjunctive therapy in adults with partial-onset seizures.[91] Efficacy and safety of eslicarbazepine in TN patients was first assessed in 2018.[183] The results of this open-label study that included 15 patients suggested that eslicarbazepine is an effective, safe, and well-tolerated treatment for TN. It is noteworthy that around 60% of the patients presented adverse events, mainly lightheadedness, severe dizziness, and hyponatremia and 4 of the 15 patients discontinued treatment for this reason.[183] Although the adverse events induced by eslicarbazepine are similar to CBZ

**Table 2.** Mechanism of action of other therapeutic treatments used for trigeminal neuralgia.

| Drug | Mechanisms of action | Therapeutic indication |
|---|---|---|
| Gabapentinoids | Cav$\alpha 2\delta$ subunit | Epilepsy, pain |
| Lamotrigine | VGSC blocker, N-P-type VGCC blocker | Epilepsy |
| Phenytoin | VGSC blocker | Epilepsy |
| Baclofen | $GABA_B$ receptor agonist | Spasticity |
| BoNT-A | SNARE complex | Spasticity |

VGSC: voltage-gated sodium channel; VGCC: voltage-gated calcium channel; GABA: gamma-aminobutyric acid; BoNT-A: botulinum toxin type A; SNARE: SNAP receptor.

and OXC, they are considered less frequent.[184,185] Eslicarbazepine is contraindicated in patients with hypersensitivity reactions to CBZ (European Medicines Agency, London, UK), but some studies have suggested that severe skin reactions occur less frequently with eslicarbazepine compared to other anticonvulsants, leading to treatment discontinuation in only 0.1% of the cases.[186] As data are scarce and contradictory,[187–189] further studies are clearly needed before definitive conclusions may be drawn.

Eslicarbazepine has been shown to interact selectively with the inactive state of VGSCs through altered slow inactivation, as opposed to the effects on fast inactivation associated with CBZ and OXC. In addition, eslicarbazepine effectively inhibited Cav3.2 calcium channels with greater affinity than CBZ.[91] Eslicarbazepine also failed to cause a paradoxical upregulation of sodium currents, as described for CBZ, indicating a potential to more effectively decrease neuronal firing.[91,118] Thus, the pharmacodynamic profile makes eslicarbazepine an interesting alternative to be evaluated for TN pain control. Other advantages of eslicarbazepine include better safety profile, a reduced potential to act on cytochrome P450 enzymes and a longer elimination half-life of 20 to 24 h, which allows single daily dosing.[190] However, current evidence is considered insufficient to recommend eslicarbazepine for the treatment of neuropathic pain and cranial neuralgias, since available data come from open observational studies with no control group and a small number of patients.[191] Therefore, randomized clinical trials with greater numbers of patients are clearly warranted to support this recommendation.

Vixotrigine was first discovered in 2006 and the target indications included depression, bipolar mood disorder, and substance disorders. It was formerly named raxatrigine and was considered a selective Nav1.3 channel blocker. Subsequently, the compound was stated to be a selective Nav1.7 channel blocker and a lead neuropathic pain candidate with two main indications: TN and lumbar radiculopathy (for review, see Keppel Hesselink[192]). Vixotrigine has been considered a state- and use-dependent Nav1.7 channel blocker, but its selectivity lacks validation and available data are controversial. In a clinical paper that discusses the experimental design to assess vixotrigine efficacy in TN patients, its preclinical profile is described as the compound having selectivity for Nav1.7 channels over the other Nav isoforms for both the resting and depolarized states.[193] In sharp contrast, in a model of Nav1.7-mediated pain, Deuis et al. showed that vixotrigine inhibited Nav channels state dependently but nonselectively.[194] In addition, vixotrigine showed analgesic effects when delivered systemically,[194] which is in line with more recent data showing that oral administration of vixotrigine fully reversed paw mechanical allodynia in a mouse model of postsurgical pain.[195] Despite the controversy regarding the selectivity of vixotrigine, it is plausible that blockade of Nav1.7 channels contributes to its analgesic effect, since data from electrophysiology studies indicated that vixotrigine is able to cause a dramatic hyperpolarizing shift of channel inactivation (without effects on activation) in HEK293 cells transfected with Nav1.7 channels. This enhanced ability of a sodium channel blocker to discriminate between the resting and inactivated channels compared to CBZ may provide a better safety profile and tolerability during systematic administration.[196]

Results from a phase 2a study indicated that vixotrigine can be administered at therapeutic doses without titration and has shown good tolerability.[197] The study first enrolled 67 patients which received vixotrigine (150 mg, three times per day, orally) for 21 days. During this open-label phase, 23 patients withdrew mainly due to lack of efficacy (18 patients). Thus, 44 patients were eligible for the open-label phase which showed that treatment failure was not significantly different between placebo- and vixotrigine-treated groups, but significant treatment differences were found in time to treatment failure, number of paroxysms, average daily pain score, and assessments of overall function and quality of life. The drug was well tolerated, headache, and dizziness being the most frequent adverse events.[197] There was a suspicion that vixotrigine might lead to an increase in blood pressure, but a clinical study in healthy patients receiving vixotrigine 300 to 400 mg twice daily for 36 days failed to show a clinically important increase in blood pressure.[198]

The conclusion regarding efficacy is limited by challenges in the realization of TN clinical studies,[199] but the results encourage moving forward to a phase 3 study, which is currently in progress (ClinicalTrials.gov, Identifier # NCT03070132). The drug has been also evaluated in individuals with IEM, the first Nav1.7 channelopathy identified, as well as in small fiber neuropathy (ClinicalTrials.gov), and it failed phase II trial in patients with in painful lumbosacral radiculopathy.[200]

It is noteworthy that other small molecules and peptide-derived Nav channels blockers are under development by different pharmaceutical companies and may represent perspectives for TN pain control. However, there are several challenges for advancing in this area, including high structural similarity of the Nav subtypes and species-specific differences in the levels of expression and/or biophysical properties of Nav channels (for review, see Kingwell[200] and Dib-Hajj and Waxman[201]).

Another potential target to be explored in TN is the Kv7.2 channel. A study conducted in the rat model of infraorbital nerve constriction showed that Kv7.2 channels were expressed on cold-sensing trigeminal ganglion neurons and that retigabine treatment reduced the

**Table 3.** Mechanism of action and half-life profile for new pharmacological approaches to trigeminal neuralgia.

| Drug | Mechanisms of action | Half-life | Therapeutic indication |
|---|---|---|---|
| Eslicarbazepine | VGSC blocker, T-type VGCC blocker | 20–24 h | Epilepsy, pain |
| Vixotrigine | VGSC blocker | 9 h | Depression, bipolar disorder, pain |
| – | CGRP antagonists | – | Antimigraine |
| Flupirtine | Potassium channel opener | – | Acute pain |

VGSC: voltage-gated sodium channel; VGCC: voltage-gated calcium channel; CGRP: calcitonin gene-related peptide.

excitability of nociceptive cold-sensing neurons and alleviated cold allodynia and hyperalgesia.[61,62] Retigabine is a selective Kv7.2 channel opener, which shifts the voltage dependence of Kv7.2 channels to more hyperpolarized potentials, thereby decreasing neuronal hyperexcitability.[63] Since the 1980s, an analog of retigabine (i.e., flupirtine) has been used in Europe for treatment of acute and chronic pain. Small clinical studies suggest that flupirtine effectively reduces chronic musculoskeletal pain, migraine and neuralgias, among other types of pain, but, to our knowledge, its efficacy in TN patients has never been investigated.[202]

Finally, it is tempting to speculate whether CGRP antagonists would provide pain control in TN. This assumption is based mainly in preclinical data showing that CGRP plays a role in trigeminal afferent sensitization and CGRP receptor blockade results in antinociceptive effects in different models of trigeminal neuropathic pain.[203–205] Interestingly, blockade of CGRP receptors significantly reduced mechanical allodynia in a model of trigeminal neuropathic pain (i.e., infraorbital nerve constriction) but not in a model of spinal nerve injury (i.e., sciatic nerve ligation).[206] In humans, seminal work by Goadsby et al. showed that CGRP is released in the extracerebral circulation during activation of the trigeminovascular system, which was further corroborated by the observation that CGRP was the only neuropeptide released during the headache phase of migraine attacks.[207,208] This evidence has contributed to the development of antimigraine therapies that target multiple components of CGRP transmission (for review, see Edvinsson et al.[209]). Likewise, there are some reports indicating elevated CGRP levels in blood, cerebrospinal fluid, and plasma of TN patients.[210,211] These observations allude to the fact that an antibody toward the CGRP receptor is clinically available (for review, see Edvinsson et al.[209]) and may encourage studies assessing this therapeutic intervention in TN patients. A summary of pharmacological profiles and therapeutic indications of the drugs mentioned earlier are presented in Table 3.

## Concluding remarks

Although TN is considered a rare condition, it dramatically reduces the quality of life of affected individuals not only due to pain attacks but also to other disease-associated comorbidities, such as anxiety and depression. In fact, it is probable that the prevalence of TN in the general populations is underestimated, as studies in this condition are very challenging and population aging is increasing. Likewise, the two main TN-related comorbidities, that is, anxiety and depression, are often underdiagnosed and undertreated and just recently have gained attention. Thus, a better understanding of the pathophysiology is necessary for the improvement of current therapies or development of innovative pharmacological treatments.

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