Chapter 16
Trigeminal Neuralgia: Channels, Pathophysiology, and Therapeutic Challenges

Daniele Cazzato, Stine Maarbjerg, Lars Bendtsen, and Giuseppe Lauria

16.1 Introduction

Trigeminal neuralgia (TN) is defined by the International Classification of Headache Disorders-3 (ICHD-3) as a condition characterized by recurrent unilateral brief electric shock-like, shooting, stabbing, or sharp pain, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve, and triggered by innocuous stimuli. In ICHD-3 a new subclassification of TN into three subtypes was proposed: *idiopathic* TN with no neurovascular contact or neurovascular contact without morphological changes of the trigeminal nerve and without significant electrophysiological findings; *classical* TN with neurovascular compression with morphological changes of the trigeminal nerve; and *symptomatic* TN when there is another underlying neurological disease such as multiple sclerosis or a space-occupying lesion affecting the ipsilateral trigeminal nerve in the root entry zone [1].

D. Cazzato
Neurophysiology and Neuroalgology Units, Department of Clinical Neuroscience, IRCCS Foundation "Carlo Besta" Neurological Institute, Milan, Italy
e-mail: daniele.cazzato@istituto-besta.it

S. Maarbjerg · L. Bendtsen
Department of Neurology, Danish Headache Center, Rigshospitalet—Glostrup, University of Copenhagen, Copenhagen, Denmark
e-mail: stine.maarbjerg@regionh.dk; lars.bendtsen@regionh.dk

G. Lauria (✉)
Department of Biomedical and Clinical Sciences "Luigi Sacco", University of Milan, Milan, Italy

Neuroalgology Unit, Department of Clinical Neuroscience, IRCCS Foundation "Carlo Besta" Neurological Institute, Milan, Italy
e-mail: giuseppe.lauriapinter@istituto-besta.it; giuseppe.lauria@unimi.it

M. Leone, A. May (eds.), *Cluster Headache and other Trigeminal Autonomic Cephalgias*, Headache, https://doi.org/10.1007/978-3-030-12438-0_16

The clinical picture is characterized by painful paroxysms lasting from seconds to minutes, with highly variable frequency ranging from a few to hundreds of attacks per day. Long remission periods that can last years are seen in most patients. The pain is sharp and severe, and it can be triggered by trivial non-painful sensory stimuli in the area of trigeminal nerve distribution, such as light touch and cold wind, or by simple actions including chewing, talking, washing the face, or brushing the teeth. During the refractory period typically following a pain attack, patients can remain completely asymptomatic or experience background dull pain of variable intensity.

16.2 Pathophysiology

The finding of a neurovascular conflict at brain magnetic resonance imaging (MRI) in a high percentage of patients and the prolonged pain relief achieved by the microvascular decompression have suggested that nerve compression could have a primary role in the pathogenesis of TN [2, 3]. However, the presence of a neurovascular conflict does not necessarily induce TN, and not all the patients diagnosed with TN have a neurovascular conflict. Therefore, it is possible that individual susceptibility and/or specific conditions are needed to determine the development of TN. Moreover, how vascular compression can cause the clinical picture and explain its course remains speculative. Repetitive pulsatile microvascular compression has been proposed to cause nerve demyelination, as supported by neuropathology studies and the increased incidence of TN in multiple sclerosis patients with brainstem demyelinating lesions in the trigeminal root entry zone [4]. In TN patients with multiple sclerosis, one study found that both brainstem plaque and neurovascular compression were associated with the painful side thus suggesting a dual crush mechanism in this patient category [5].

The analysis of the pathophysiological mechanisms should consider the following crucial issues: (1) How do abnormal sensory impulses occur either spontaneously or triggered by non-painful stimuli and spread beyond the trigger area? (2) How do attacks abruptly stop and the triggering mechanism become temporary refractory?

Pathological findings confirming demyelination of trigeminal fibers and electrophysiological evidence of spontaneous discharge generation in focally demyelinated axons suggest that pulsatile compression of demyelinated axons may be responsible for initiating aberrant discharges in some patients. Nerve injury triggers the release of inflammatory mediators inducing alteration of primary afferent neurons. Changes in the expression of Na^+, K^+, and Ca^{2+} channels can increase nerve excitability, enhance ectopic and spontaneous activity, and reduce nociceptors threshold making them more responsive to low-intensity stimuli [6, 7]. Demyelinated nerve fibers can acquire the ability of producing after discharges, namely, bursts of spontaneous firing triggered by brief low-intensity stimulation lasting for tens of seconds after the stimulus removal. At the site of vascular compression, the close apposition of myelin-devoid axons is thought to facilitate the ephaptic transmission

of the impulses. The ephaptic cross-talk between nerve fibers conveying light touch and those conveying pain has been proposed as a possible explanation for the generation of excruciating attack in response to light mechanical triggering stimuli. The spreading of nerve impulses can cause the recruitment of nerve fibers conveying pain in a synchronous fashion, amplifying the neural response and inducing the spread of the lightening sensation.

The abrupt termination of the pain attack and the ensuing refractory period are thought to occur because of a prolonged hyperpolarization shift triggered by the repetitive firing of primary sensory neurons in the dorsal root ganglia (DRG). Ca^{2+} ions that enter the neuron during the burst activate calcium-activated potassium channels and increase the outflow of potassium ions which produce the neuronal hyperpolarization, firing termination, and refractoriness of the nerve fibers to further excitation. However, in experimental setting, the duration of the refractory period is much shorter than that experienced by the patients, suggesting that other unknown factors likely intervene.

16.3 Ion Channels and Trigeminal Neuralgia

The clinical evidence that carbamazepine and oxcarbazepine, which are sodium channel blockers, can provide fast and prolonged control in the majority of TN patients is used as an indirect clue in support of the role of sodium channel altered functioning in the pathophysiology of TN.

Most of the experimental studies suggesting that sodium channels could play key roles in the pathophysiology of TN have been performed applying the chronic constriction injury method to the infraorbital branch of the trigeminal nerve, providing a model to recapitulate human TN [8]. However, such model probably better mimics the nerve damage seen in painful posttraumatic trigeminal neuropathy.

Genetic mutations of sodium channel genes have been described in rare Mendelian disorders affecting pain perception, ranging from extremely painful conditions to complete insensitivity to pain. In particular, homozygous or compound heterozygous mutations inactivating *SCN9A* gene, which encode for $Na_v1.7$ α-subunit, and mutations of *SCN11A* encoding for $Na_v1.9$ α-subunit result in congenital insensitivity to pain [9–11]. Conversely, missense heterozygous gain-of-function mutations in *SCN9A* produce dominantly inherited pain syndromes such as inherited erythromelalgia and paroxysmal extreme pain disorder [12]. Further clinical studies have demonstrated the association between heterozygous gain-of-function mutations of *SCN9A*, *SCN10A*, and *SCN11A* genes, encoding for $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ α-subunits, respectively, and painful idiopathic small fiber neuropathy, a condition characterized by burning and paroxysmal pain, neuropathic pain, hyperalgesia, allodynia, and autonomic dysfunctions usually presenting with a length-dependent "gloves and stockings" distribution [13–15]. Gene mutations identified in the context of SFN are best described as variants, since some of them can have a minor allele frequency up to 3–7% and their penetrance is not yet known.

At electrophysiological testing, these mutations produce a range of dysfunctions including enhanced excitability of nociceptor membrane, hypoexcitability of sympathetic neurons, and altered channel functioning such as impaired slow inactivation or impaired fast and slow inactivation [16]. Overall, these sodium channel gene variants might be part of a complex genetic and molecular mosaic predisposing individuals to develop neuropathic pain.

Recently, sodium and calcium channel genes have been sequenced in a small series of patients with TN. A de novo missense mutation of *SCN8A* encoding for the $Na_v1.6$ α-subunit has been described in one patient with TN and neurovascular compression. The $Na_v1.6$ subunit is widely expressed in the central and peripheral nervous system and is crucial for the initial membrane depolarization that occurs during the generation of the action potential in excitable cells. Gain-of-function mutations in $Na_v1.6$ have previously been linked to epilepsy and cognitive impairment with or without ataxia. The electrophysiological characterization of the mutated $Na_v1.6$ revealed that the p.Met136Val substitution potentiates transient and resurgent sodium currents and leads to increased excitability of trigeminal ganglion neurons expressing the mutant channel, therefore suggesting a pathophysiological role of $Na_v1.6$ [17].

Other studies investigated the expression of three different sodium channels in TN patients. The quantification of mRNA extracted from homogenized gingival biopsies from patients and controls demonstrated the upregulation of $Na_v1.3$ and the downregulation of $Na_v1.7$, whereas no differences emerged in the expression of $Na_v1.8$ [18]. Interestingly, other works showed the upregulation of $Na_v1.3$ and the downregulation of $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ in the CION model [15]. Conversely, no changes in $Na_v1.3$, $Na_v1.8$, and $Na_v1.9$ expression have been found in DRG neurons after transection of the centrally projecting axons by dorsal rhizotomy.

Silencing of the $Na_v1.9$ subunit was found to prevent mice from developing CION-induced mechanical and thermal allodynia [19]. Intriguingly, mutations in this α-subunit can result in enhanced pain or complete loss of pain perception in man [11, 15]. However, this finding appears to be in contrast with other reports revealing only a minor role for this sodium channel subunit in other somatic neuropathic pain models, thus prompting possible distinct mechanisms of neuropathic pain [20, 21].

The emerging concept of “channelopathy” in several painful conditions prompted investigating further families of ion channels involved in the pathway of pain sensation. In particular, transient receptor potential (TRP), calcium, and potassium channels have been studied in a TN model.

TRP channels are a wide group of nonselective ion channels among which specific subtypes are involved in pain and thermal stimuli transduction. The capsaicin receptor transient receptor potential vanilloid 1 (TRPV1) activated by capsaicin, heat, and other painful stimuli has been the first identified [22]. In the CION model, TRPV1 was found to be overexpressed in trigeminal neurons and involved in heat hyperalgesia but not in mechanical allodynia. The antagonist capsazepine could abolish the heat hyperalgesia without changing the behavior related to mechanical stimuli. Cold allodynia is known to be associated with TRPM8 activation, which is

enhanced by the receptor agonist menthol and abolished by its antagonist capsazepine [23, 24]. TRPA1, also involved in painful cold sensation, has been studied in trigeminal neuropathic pain models. TRPA1 knockout mice do not develop non-evoked nociceptive, mechanical allodynia and cold hypersensitivity behaviors. Consistently, TRPA1 selective antagonists showed the rescue of the painful phenotype in CION mice. Conversely, loss of TRPA1 channel in knockout mice does not prevent heat hyperalgesia that therefore appears not to be related to this TRP channel subtype [25].

The painful phenotype of CION model has been also associated with a significant downregulation in trigeminal neurons of large-conductance, calcium-activated potassium channels (BKCa) both at mRNA and protein level. On the electrophysiological ground, it reflected into a decreased BKCa current and lower threshold intensity of action potential in neurons [26].

Second-line pharmacological treatments of TN include gabapentinoids. These compounds block the $\alpha_2\delta_1$calcium channels ($Ca_v\alpha_2\delta_1$) of nociceptors at presynaptic level, reducing the release of neurotransmitters at the dorsal horn where they exert the pharmacological action. $Ca_v\alpha_2\delta_1$ channels have been demonstrated to be upregulated in the trigeminal neurons of the CION model. The increased expression in the dorsal horns was associated with increased excitatory synaptogenesis and increased frequency of miniature excitatory postsynaptic currents in dorsal horn neurons that can be blocked by gabapentinoids [27]. This evidence provided further experimental support for their clinical use in TN.

The role of calcium channels has also been investigated in central processing of pain. Electroencephalogram and magnetoencephalogram studies revealed an increase of low-frequency thalamocortical oscillations in patients with neuropathic pain compared to healthy controls. This activity is thought to be mediated by T-type Ca^{2+} channels inducing thalamic burst firing which is a well-defined underlying mechanism for low-frequency oscillations. The CION model of $Ca_v3.1$ knockout mice has been used to investigate the role of T-type calcium channel in trigeminal neuropathic pain. Results revealed a decrease of trigeminal neuropathic pain associated with reduced low-frequency rhythms in mice lacking of $Ca_v3.1$ channel compared to wild type, therefore suggesting a possible role of $Ca_v3.1$ channels in pathophysiology of trigeminal neuropathic pain [28].

While disentangling the role of ion channels in TN can provide a better understanding of its pathophysiology, the identification of new molecular mechanisms represents the opportunity to identify new druggable target.

16.4 Treatment

Recommendations for medical treatment are generally the same in classical, idiopathic, and symptomatic TN [29]. Figure 16.1 outlines a proposed work-up and treatment algorithm. An MRI of the brain and brainstem, ECG, and laboratory testing should be part of early work-up.

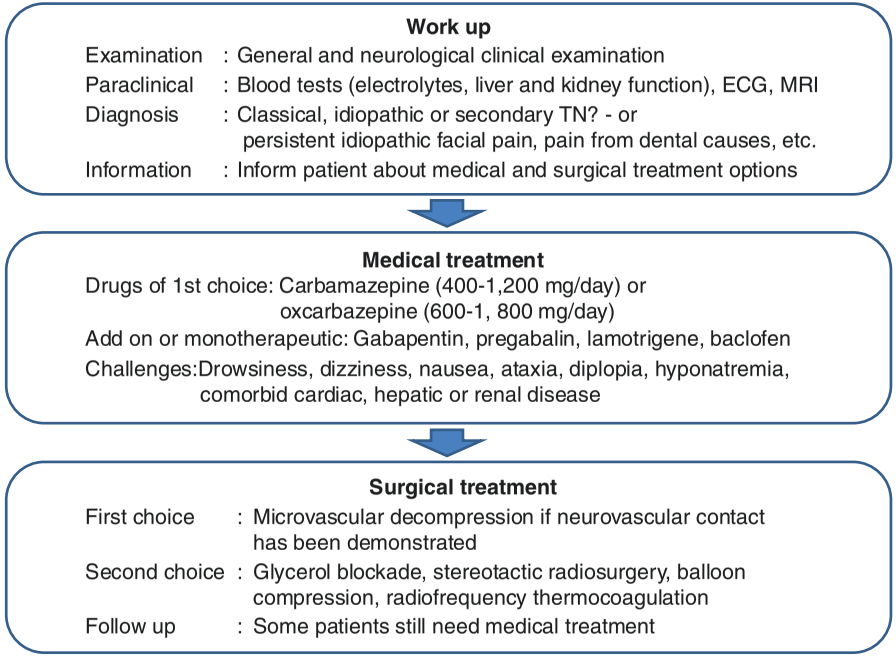

Fig. 16.1 Work-up and management of trigeminal neuralgia

First-line treatment is sodium channel blockers, either carbamazepine or oxcarbazepine [29]. Laboratory testing should be performed to ensure normal renal and liver function and normal sodium level prior to prescription of medication. ECG is warranted because carbamazepine and oxcarbazepine are contraindicated in patients with atrial ventricular block. They have the same mechanism of action, namely, the blockade of voltage-gated sodium channels in a frequency-dependent manner. It is thought that this stabilizes the hyperexcited neural membranes and inhibits repetitive firing. Sodium channel blockers are effective in most TN patients, and the numbers needed to treat for carbamazepine is 1.7 [30]. However, side effects including somnolence, drowsiness, dizziness, rash, and tremor are frequent [31], and the numbers needed to harm for carbamazepine are 3.4 for minor and 24 for severe side effects [30]. Furthermore, carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis have been described to be more frequent in Asiatic population carrying HLA-B*1502 allele [32]. Oxcarbazepine may be preferred because of a minor risk of drug interactions and better tolerability in comparison with carbamazepine [33]. Typical doses are 400–1200 mg/day for carbamazepine and 600–1800 for oxcarbazepine, but higher doses up to 2000 mg/day may be needed. They have a good effectiveness, and carbamazepine can provide up to 100% of pain relief in about 70% of patients, although over time response tends to wane, ensuring a sustained pain relief in fewer patients. Carbamazepine was reported to have a higher percentage of discontinuation due to all kinds of side effects, except for sodium depletion, for which discontinuation only occurred with oxcarbazepine [31]. It is possible that the efficacy of sodium channel blockers is lower in the subgroup of patients [34] with concomitant continuous pain [35]. It can be hypothesized that add-on therapy with gabapentin, pregabalin, or amitriptyline is particularly useful in this group of patients, but this has not been investigated.

Very often high dosages are necessary to achieve a satisfactory pain relief; thus patients can complain of disabling side effects, which are a major reason of drug withdrawal. In one study, worsening of pain with time and development of late resistance only occurred in a very small minority of patients [31]. A recent small open-label retrospective study indicated efficacy of eslicarbazepine, a third-generation antiepileptic drug [36].

According to the international guidelines, it is advised that “if any of these sodium-channel blockers is ineffective, referral for a surgical consultation would be a reasonable next step” [29]. Surgery should also be considered when drugs, although effective, cannot reach the therapeutic dosage due to adverse events. From a clinical perspective, it may be reasonable to try out both carbamazepine and oxcarbazepine sequentially. Furthermore, many TN patients benefit from add-on treatment combining carbamazepine or oxcarbazepine with gabapentin, pregabalin, lamotrigine, or baclofen. Combination treatment should be considered when carbamazepine or oxcarbazepine cannot reach full dosage because of side effects. Each of the before-mentioned drugs may also have efficacy as mono-therapeutic agents, although the available evidence is very weak.

Some recent studies have indicated that onabotulinumtoxinA (Botox) could be efficacious in TN [37]. However, injection paradigms and doses varied among the

studies making it difficult to draw conclusions. A phase 2 trial recently published has shown promising efficacy and safety profile of a selective sodium channel blocker in TN [38].

At severe exacerbations in-hospital treatment may be necessary for titration of antiepileptic drugs and rehydration. Exacerbation can be treated with intravenous loading of fosphenytoin, even though there is no evidence-based data in support.

Since medical treatment is generally recommended because of severe pain, there is only little information about the natural course of the disease. However, a retrospective study conducted over 40 years of observation reported that about 29% of patient experienced only one episode of facial pain, 19% two episodes, 24% three episodes, and 28% four to eleven episodes. Most of relapses occurred within 5 years from the first episodes, whereas in a quarter of patients, recurrence was reported after a pain-free period of more than 10 years [39].

In medically refractory patients with MRI evidence of neurovascular conflict, microvascular decompression (MVD) is first-choice treatment [29]. This procedure implies craniotomy and posterior fossa exploration for identification of the affected trigeminal nerve and the conflicting blood vessel. A recent study has demonstrated that the presence of neurovascular compression with morphological changes and male gender are both positive predictors of excellent outcome [40]. Microvascular decompression provides immediate pain relief in up to 90% and the longest duration of pain freedom in comparison with other surgical techniques as it provides significant pain relief in 73% of TN patients at a 5-year follow-up. Minor complications such as new aching or burning pain, sensory loss, and other mild or transient cranial nerve dysfunctions occur in 2–7%. Major complications such as major cranial nerve dysfunction (2%), stroke (0.3%), and death (0.2%) are rare, yet it is important to inform patients on the potential risks [41]. However, most studies did not provide the rate of surgical complications or efficacy as assessed by an independent examiner; therefore frequency of complications might be higher, and the rate of efficacy might be lower. The conventional opinion that multiple sclerosis is a contraindication to microvascular decompression has recently been confuted by a study showing that in multiple sclerosis patients with TN, a neurovascular conflict may act as a concurring mechanism in producing focal demyelination of the primary afferents at the root entry zone [5].

Second-choice neurosurgical treatments are lesioning peripheral procedures targeting the trigeminal ganglion by chemical glycerol blockade, balloon mechanic compression, or radiofrequency thermocoagulation. Stereotactic radiosurgery (Gamma Knife) targets the trigeminal root by convergent beams of radiation. Overall, these second-line procedures are efficacious in approximately 50% of the patients after 5 years. Complications such as sensory loss (12–50%), masticatory problems after balloon compression (up to 50%), and new burning or aching pain (12%) can occur [29].

The abovementioned treatment recommendations are mainly based on expert opinion. There is a lack of robust scientific evidence for effect and side effects of both medical and surgical treatment of TN.

References

1. Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ. 2014;348:g474. http://www.ncbi.nlm.nih.gov/pubmed/24534115
2. Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg. 1967;26(1part2):159–62. http://www.ncbi.nlm.nih.gov/pubmed/6018932
3. Jannetta PJ. Microsurgical approach to the trigeminal nerve for tic douloureux. Basel: Karger Publishers; 1976. p. 180–200. https://www.karger.com/Article/FullText/428328
4. Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. Brain. 2001;124(Pt 12):2347–60. https://www.ncbi.nlm.nih.gov/pubmed/11701590.
5. Truini A, Prosperini L, Calistri V, Fiorelli M, Pozzilli C, Millefiorini E, et al. A dual concurrent mechanism explains trigeminal neuralgia in patients with multiple sclerosis. Neurology. 2016;86(22):2094–9.
6. Woolf CJ, Ma Q. Nociceptors-noxious stimulus detectors. Neuron. 2007;55(3):353–64.
7. Waxman SG, Zamponi GW. Regulating excitability of peripheral afferents: emerging ion channel targets. Nat Neurosci. 2014;17(2):153–63.
8. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces. Pain. 1988;33:87–107. https://doi.org/10.1016/0304-3959(88)90209-6.
9. Ahmad S, Dahllund L, Eriksson AB, Hellgren D, Karlsson U, Lund PE, et al. A stop codon mutation in SCN9A causes lack of pain sensation. Hum Mol Genet. 2007;16(17):2114–21.
10. Yuan J, Matsuura E, Higuchi Y, Hashiguchi A, Nakamura T, Nozuma S, et al. Hereditary sensory and autonomic neuropathy type IID caused by an SCN9A mutation. Neurology. 2013;80(18):1641–9.
11. Leipold E, Liebmann L, Korenke GC, Heinrich T, Giesselmann S, Baets J, et al. A de novo gain-of-function mutation in SCN11A causes loss of pain perception. Nat Genet. 2013;45(11):1399–404. http://www.ncbi.nlm.nih.gov/pubmed/24036948
12. Bennett DLH, Woods CG. Painful and painless channelopathies. Lancet Neurol. 2014;13(6):587–99.
13. Faber CG, Hoeijmakers JGJ, Ahn HS, Cheng X, Han C, Choi JS, et al. Gain of function Na V1.7 mutations in idiopathic small fiber neuropathy. Ann Neurol. 2012;71(1):26–39.
14. Faber CG, Lauria G, Merkies ISJ, Cheng X, Han C, Ahn H-S, et al. Gain-of-function Nav1.8 mutations in painful neuropathy. Proc Natl Acad Sci U S A. 2012;109(47):19444–9. http://www.pnas.org/content/109/47/19444.long
15. Huang J, Han C, Estacion M, Vasylyev D, Hoeijmakers JGJ, Gerrits MM, et al. Gain-of-function mutations in sodium channel NaV1.9 in painful neuropathy. Brain. 2014;137(6):1627–42.
16. Waxman SG. Painful Na-channelopathies: an expanding universe. Trends Mol Med. 2013;19(7):406–9. https://doi.org/10.1016/j.molmed.2013.04.003.
17. Tanaka BS, Zhao P. A gain-of-function mutation in Nav1.6 in a case of trigeminal neuralgia. Mol Med. 2016;22(1):1. http://www.molmed.org/content/pdfstore/16_131_Tanaka.pdf
18. 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):573–7. https://doi.org/10.1016/j.neuroscience.2009.08.037.
19. Lulz AP, Kopach O, Santana-Varela S, Wood JN. The role of Nav1.9 channel in the development of neuropathic orofacial pain associated with trigeminal neuralgia. Mol Pain. 2015;11:1–7.
20. Leo S, D'Hooge R, Meert T. Exploring the role of nociceptor-specific sodium channels in pain transmission using Nav1.8 and Nav1.9 knockout mice. Behav Brain Res. 2010;208(1):149–57. https://doi.org/10.1016/j.bbr.2009.11.023.
21. Minett MS, Falk S, Santana-Varela S, Bogdanov YD, Nassar MA, Heegaard AM, et al. Pain without nociceptors? Nav1.7-independent pain mechanisms. Cell Rep. 2014;6(2):301–12. https://doi.org/10.1016/j.celrep.2013.12.033.

22. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature. 1997;389(6653):816–24. http://www.ncbi.nlm.nih.gov/pubmed/9349813
23. Urano H, Ara T, Fujinami Y, Yukihiro Hiraoka B. Aberrant TRPV1 expression in heat hyperalgesia associated with trigeminal neuropathic pain. Int J Med Sci. 2012;9(8):690–7.
24. Zuo X, Ling JX, Xu GY, Gu JG. Operant behavioral responses to orofacial cold stimuli in rats with chronic constrictive trigeminal nerve injury: effects of menthol and capsazepine. Mol Pain. 2013;9(1):28.
25. Trevisan G, Benemei S, Materazzi S, De Logu F, De Siena G, Fusi C, et al. TRPA1 mediates trigeminal neuropathic pain in mice downstream of monocytes/macrophages and oxidative stress. Brain. 2016;139(5):1361–77.
26. Liu C-Y, Lu Z-Y, Li N, Yu L-H, Zhao Y-F, Ma B. The role of large-conductance, calcium-activated potassium channels in a rat model of trigeminal neuropathic pain. Cephalalgia. 2015;35(1):16–35. http://journals.sagepub.com/doi/10.1177/0333102414534083
27. Li KW, Yu YP, Zhou C, Kim DS, Lin B, Sharp K, et al. Calcium channel α2δ1 proteins mediate trigeminal neuropathic pain states associated with aberrant excitatory synaptogenesis. J Biol Chem. 2014;289(10):7025–37.
28. Choi S, Yu E, Hwang E, Llinás RR. Pathophysiological implication of $Ca_V 3.1$ T-type Ca^{2+} channels in trigeminal neuropathic pain. Proc Natl Acad Sci U S A. 2016;113(8):2270–5. http://www.pnas.org/lookup/doi/10.1073/pnas.1600418113
29. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, et al. AAN-EFNS guidelines on trigeminal neuralgia management. Eur J Neurol. 2008;15(10):1013–28.
30. Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. Cochrane Database Syst Rev. 2011;(1):CD005451.
31. Di Stefano G, La Cesa S, Truini A, Cruccu G. Natural history and outcome of 200 outpatients with classical trigeminal neuralgia treated with carbamazepine or oxcarbazepine in a tertiary centre for neuropathic pain. J Headache Pain. 2014;15(1):1–5.
32. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol. 2013;149(9):1025–32. http://www.ncbi.nlm.nih.gov/pubmed/23884208
33. Beydoun A. Safety and efficacy of oxcarbazepine: results of randomized, double-blind trials. Pharmacotherapy. 2000;20(8):152S–8S. http://www.ncbi.nlm.nih.gov/pubmed/10937814
34. Vincent M, Wang S. Headache classification committee of the International Headache Society (IHS) the international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211. http://journals.sagepub.com/doi/10.1177/0333102417738202
35. Maarbjerg S, Wolfram F, Gozalov A, Olesen J, Bendtsen L. Significance of neurovascular contact in classical trigeminal neuralgia. Brain. 2015;138(2):311–9.
36. Sanchez-Larsen A, Sopelana D, Diaz-Maroto I, Perona-Moratalla AB, Gracia-Gil J, García-Muñozguren S, et al. Assessment of efficacy and safety of eslicarbazepine acetate for the treatment of trigeminal neuralgia. Eur J Pain. 2018;22(6):1080–7. http://www.ncbi.nlm.nih.gov/pubmed/29369456
37. Morra ME, Elgebaly A, Elmaraezy A, Khalil AM, Altibi AMA, TL-H V, 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. http://thejournalofheadacheandpain.springeropen.com/articles/10.1186/s10194-016-0651-8
38. Zakrzewska JM, Palmer J, Morisset V, Giblin GM, Obermann M, Ettlin DA, et al. Safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with trigeminal neuralgia: a double-blind, placebo-controlled, randomised withdrawal phase 2a trial. Lancet Neurol. 2017;16(4):291–300. https://doi.org/10.1016/S1474-4422(17)30005-4.

39. 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. http://www.ncbi.nlm.nih.gov/pubmed/2301931
40. Heinskou TB, Rochat P, Maarbjerg S, et al. Prognostic factors for outcome of microvascular decompression in trigeminal neuralgia. Cephalalgia. 2018;. in press
41. Barker FG, 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):1077–83. http://www.nejm.org/doi/abs/10.1056/NEJM199604253341701