Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Practice guidelines

# French guidelines for diagnosis and treatment of classical trigeminal neuralgia (French Headache Society and French Neurosurgical Society)

A. Donnet [a,b,*], E. Simon [c], E. Cuny [d], G. Demarquay [e], A. Ducros [f], S. De Gaalon [g], P. Giraud [h], E. Guégan Massardier [i], M. Lanteri-Minet [b,j], D. Leclercq [k], C. Lucas [l], M. Navez [m], C. Roos [n], D. Valade [n], P. Mertens [c]

[a] Centre d'évaluation et de traitement de la douleur, hôpital Timone–APH Marseille, 264, rue Saint-Pierre, 13005 Marseille, France
[b] Inserm/UdA, U1107, Neuro-Dol, 63100 Clermont-Ferrand, France
[c] Département de neurochirurgie, 69500 Lyon, France
[d] Service de neurochirurgie, 33000 Bordeaux, France
[e] Service de neurologie, hôpital de la Croix-Rousse, hospices civils de Lyon, 69004 Lyon, France
[f] Service de neurologie hôpital Gui-de-Chaulliac, 34000 Montpellier, France
[g] Service de neurologie, 44093 Nantes, France
[h] Centre d'évaluation et de traitement de la douleur, 74370 Annecy, France
[i] Service de neurologie, hôpital Charles-Nicolle, 76000 Rouen, France
[j] Département d'évaluation et de traitement de la douleur, hôpital Cimiez, 06000 Nice, France
[k] Service de neuroradiologie diagnostique et fonctionnelle, 75651 Paris, France
[l] Centre d'évaluation et de traitement de la douleur, hôpital Salengro, 59037 Lille, France
[m] Centre d'évaluation et de traitement de la douleur, hôpital Bellevue, CHU St.-Etienne, 42100 France
[n] Centre urgence céphalées, hôpital Lariboisière, 75010 Paris, France

INFO ARTICLE

*Article history:*
Received 19 June 2016
Accepted 19 December 2016
Available online 15 March 2017

*Keywords:*
Classical trigeminal neuralgia
Guidelines

*Mots clés :*
Névralgie trigéminale classique
Recommandations

* Corresponding author. Centre d'évaluation et de traitement de la douleur, hôpital Timone–APH Marseille, 264, rue Saint-Pierre, 13385 Marseille, France.
*E-mail address:* adonnet@ap-hm.fr (A. Donnet).
http://dx.doi.org/10.1016/j.neurol.2016.12.033

## 1. Preamble

### 1.1. Requesting body

These guidelines were elaborated at the request of the French Headache Society (SFEMC[1]) and the French Neurosurgical Society (SFNC[2]).

### 1.2. Subject of the guidelines

These guidelines concern the diagnosis and treatment of classical trigeminal neuralgia.

### 1.3. Patients concerned

These guidelines are for adult patients.

### 1.4. Professions concerned

These guidelines are intended for healthcare professionals participating in the treatment of patients with classical trigeminal neuralgia: general practitioners; neurologists; neurosurgeons; ENT specialists; ophthalmologists; stomatologists; dentists; radiologists.

### 1.5. Guideline grade and working methods

The proposed guidelines are classed as grade A, B or C in accordance with the following:

- a grade A guideline is founded on scientific evidence established by studies with a high level of proof such as randomized comparative trials with high statistical power and free of major bias and/or meta-analyses of randomized comparative trials, decision analysis based on well-conducted studies;
- a grade B guideline is founded on presumptive scientific evidence provided by studies with an intermediate level of proof, such as randomized comparative trials with low statistical power, well-conducted non-randomized comparative trials, cohort studies;
- a grade C guideline is founded on studies with a lower level of proof, such as case-control studies, series of cases.

Unless mentioned otherwise, the guidelines proposed are based on expert agreement among members of the working group.

The absence of a level of proof does not signify that an elaborated guideline is not pertinent or useful. The absence of proof should incite researchers to conduct complementary studies when possible.

These guidelines were established by the SFEMC and the SFNC in compliance with AGREE methodology. The working group divided the theme into specific topics:

- anatomy and pathophysiology of trigeminal neuralgia (Michel Lanteri-Minet);
- epidemiology, natural course, clinical spectrum of trigeminal neuralgia and positive clinical diagnosis (Anne Donnet and Dominique Valade);
- differential diagnosis of trigeminalneuralgia:
  - differential diagnosis with other primary headaches (Caroline Roos and Solène De Gaalon),
  - differential diagnosis with other essential neuralgias (Malou Navez and Geneviève Demarquay),
  - differential diagnosis with secondary facial neuralgias and trigeminal neuropathy (Pierric Giraud and Evelyne Guégan Massardier);
- imaging of trigeminal neuralgia (Christian Lucas and Delphine Leclercq);
- medical treatments (Anne Ducros and Anne Donnet);
- surgical treatments (Emmanuel Cuny and Emile Simon).

An editing committee was composed of SFEMC and SFNC members together with healthcare professionals working independently of the society.

## 2. Guidelines for the diagnosis and treatment of classical trigeminal neuralgia

### 2.1. Anatomy and pathophysiology of trigeminal neuralgia

The trigeminal nerve (V) is the most voluminous cranial nerve through which transits nearly all of the somatic sensory information coming from the anterior part of the cephalic segment (face, oral cavity and tongue, nasal and sinus cavities, supra-tentorial dura mater) via its three main branches: the ophthalmic nerve (VI), the maxillary nerve (V2) and the mandibular nerve (V3). These three branches harbor the trigeminal peripheral afferents and enter the cranium via the superior orbital fissure, the foramen rotundum and the foramen ovale respectively. The cell bodies of the peripheral afferents carried by these three branches are intracranial and are grouped together within Gasser's trigeminal ganglion situated in Meckel's cave. The central prolongations of these trigeminal peripheral afferents group together forming the trigeminal sensory root that penetrates into the brain stem via the pons then distributes to the trigeminal sensory complex constituting the first central sensory relay for orofacial and cranial somesthesic input. The trigeminal nerve is also a mixed nerve with motor function since it carries efferent fibers that innervate the masticator muscles via a branch of the mandibular nerve. Finally, while it does not have a specifically autonomous contingent, the trigeminal nerve is joined by parasympathetic fibers issuing from the facial nerve (VII) and the glossopharyngeal nerve (IX).

In order to better apprehend classical trigeminal neuralgia (CTN), the subject of these guidelines, it is essential to understand certain key anatomic and pathophysiological notions concerning the trigeminal nerve, including: i) the cutaneomucosal territories of the branches of the trigeminal nerve; ii) the somatotopic organization of fibers in the trigeminal ganglion; and iii) the role of neurovascular compression.

[1] SFEMC: *Société française d'étude des migraines et des céphalées.*
[2] SFNC: *Société française de neurochirurgie.*

#### 2.1.1. *Cutaneomucosal territories of the branches of the trigeminal nerve*

Knowledge of the cutaneomucosal territories of the branches of the trigeminal nerve [1] is essential to properly apprehend the topology of the pain described by patients suffering from CTN.

*2.1.1.1. Ophthalmic nerve.* The ophthalmic nerve innervates a territory of skin covering the anterior part of the temporal region, the forehead, the upper eyelid, and the dorsum nasi. Its mucosal territory concerns the frontal sinus, the sphenoid sinus and the nasal septum. Sensorial information from the bulbar and palpebral conjunctiva and from the cornea also passes through the ophthalmic nerve.

*2.1.1.2. Maxillary nerve.* The maxillary nerve innervates a territory of skin covering the middle part of the temporal region, the lower eyelid, the zygoma, the upper lip, the lateral part of the ala nasi, and the vestibule of the nasal fossa. Its mucosal territory concerns the soft and hard palate, the tubal orifice, the upper pole of the tonsil, the maxillary sinus, the gingiva, and the maxillary alveoli and teeth.

*2.1.1.3. Mandibular nerve.* The mandibular nerve innervates a territory of skin covering the posterior part of the temporal region, the anterior part of the earlobe, the anterior and superior walls of the external ear canal, the lower lip and the chin. Its mucosal territory concerns the anterior two-thirds of the tongue, the medial aspect of the cheek and the floor of the oral cavity, the gingiva, and the mandibular alveoli and teeth. As mentioned above, the mandibular nerve also carries trigeminal motor fibers that innervate the masticator muscles (masseter, temporal, internal and external pterygoid, mylohyoid, anterior body of the digastric and the tensor palati).

Regarding the cutaneous innervations of the anterior cephalic segment, it is important to recall that the concha auriculae and the angulomandibular region are not territories of the trigeminal nerve but are innervated by the intermediate facial nerve and the superior cervical plexus respectively. For the muscle innervations, the posterior third of the tongue is not innervated by the trigeminal nerve but by the glossopharyngeal nerve (Fig. 1).

#### 2.1.2. *Somatotopic organization of nerve fibers in the trigeminal ganglion*

Knowledge of the somatotopic organization of nerve fibers in the trigeminal ganglion [1] is essential because the efficacy of radiofrequency percutaneous thermorhizotomy depends on the accuracy of electrode positioning.

Gasser's trigeminal ganglion has a semi-lunar shape. Its concave posterior border continues posteriorly through a transition zone with the sensory root corresponding to the triangular plexus. Surgical ablation is performed within the triangular plexus where the mandibular afferent fibers are in an inferolateral position, the ophthalmic afferent fibers in a superomedian position and the maxillary afferent fibers in an intermediary position. This somatotopic organization is distinct immediately posterior to the trigeminal ganglion then disappears, taking on a functional organization. Thus in the justaprotuberential portion of the sensory root, the thermoalgic fibers are preferentially in an inferolateral position (in the pars major) while the epicritic and proprioceptive fibers are preferentially in a superomedian position (in the pars intermedia) (Fig. 2).

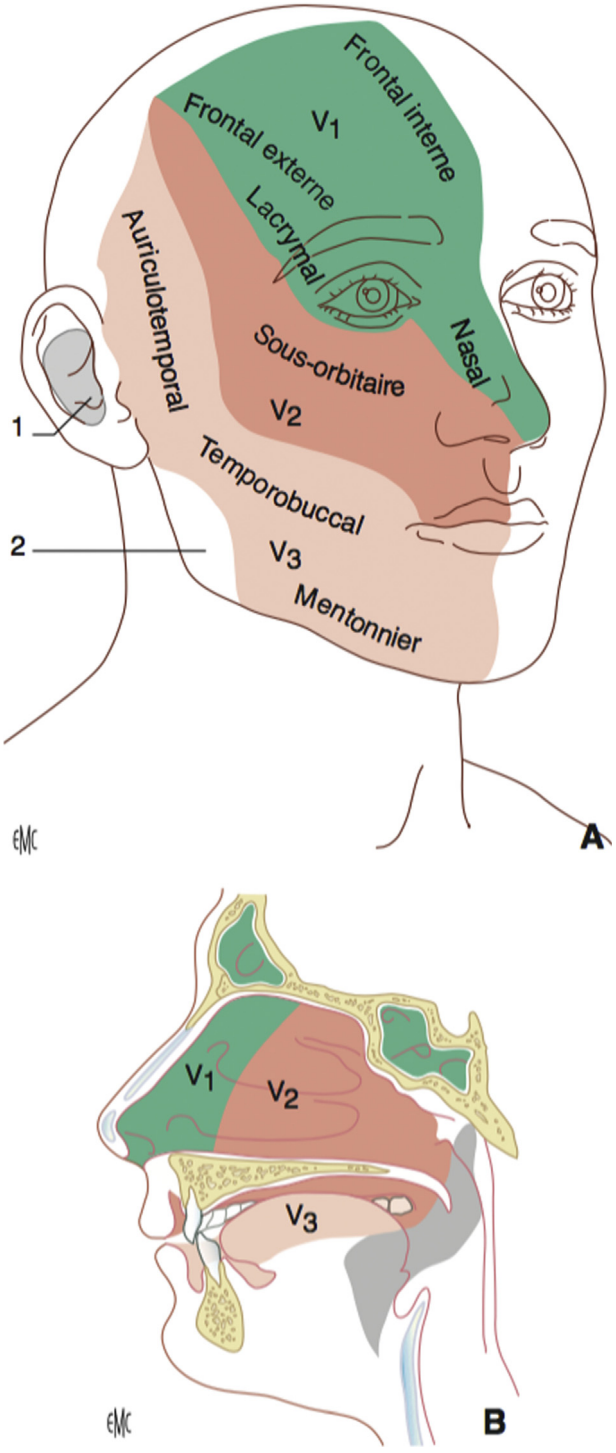


**Fig. 1 – Cutaneomucosal territories of the trigeminal divisions.**

#### 2.1.3. *Role of neurovascular compression*

Neurovascular compression is considered to be a major etiopathogenic factor of CTN [2] leading to the advent of

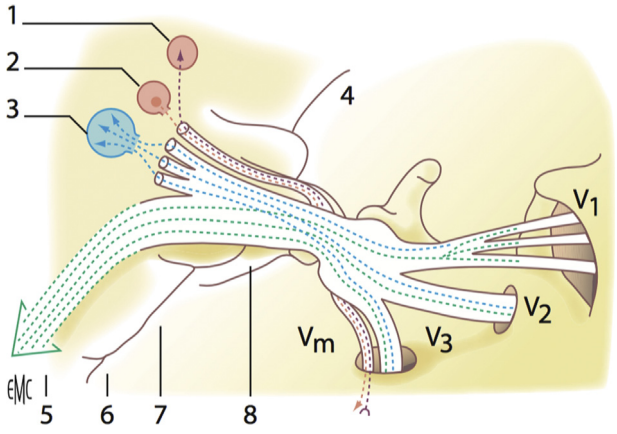


**Fig. 2 – Trigeminal somatotopia – schema of the sensory fibers.**

vascular decompression procedures first proposed by Gardner in 1959 then later developed by Jannetta [3] in the sixties. A recent Danish study of a retrospective series of 135 patients suffering from CTN who underwent 3 T magnetic resonance imaging (MRI) and radiographic evaluation assessed without knowledge of the pain lateralization confirmed the strong prevalence of neurovascular compression not only on the symptomatic side, but also on the asymptomatic side (89% versus 78%, $P = 0.014$; OR 2.4 [1.2–4.8]) together with significantly higher prevalence of severe neurovascular compression (in section 2.4.2.3) on the symptomatic side (53% versus 13%; $P < 0.001$; OR 11.6 [4.7–28.9]; $P < 0.001$) [4]. In the very large majority of cases, the compression is caused by a megadolicho artery within the prepontine cistern (generally the anterosuperior cerebellar artery). Anatomically, it has been shown that compression and pulsations of the impinged artery lead to demyelinization of the central portion of the trigeminal root and its transitional zone that, with the portion adjacent to the pons, constitutes the root entry zone (REZ) [5], the most fragile portions of the trigeminal nerve. This demyelinization would induce ectopic discharges and ephapses explaining the hyperexcitability of the trigeminal afferents [6]. As is the case for other types of pain, it is most likely that CTN is also supported by a secondary central hypersensitivization process involving the trigeminal system nuclei in the brainstem and supratrigeminal structures.

### 2.2. *Epidemiology, natural course, clinical spectrum of classical trigeminal neuralgia and positive clinical diagnosis*

The exact epidemiology of CTN is unknown. Few studies have examined the prevalence of this condition and since 1968 the estimations proposed by Penman have been restated [7]: prevalence = 10.7/100,000 in men and 20/100,000 in women; annual incidence 0.0046% in men and 0.0071% in women. These estimates are concordant with the results reported by El Tallawy et al. in 2013 who found an overall prevalence of 29.5/100,000 in the Egyptian population [8]. They are also in agreement with the results of a study by Katusic et al. who reported an annual incidence of 0.0047% in 1990 for the general North-American population [9]. These old figures confirm that CTN is a rare condition. The male-female ratio is about 3/2 with results being variable across studies: 7.1/4.7 for Penman [7]; 4.3/3.4 for Katusic et al. [9]; 5.2 for Rozen [10]; 3/2 for Maarbjerg et al. [11]; or even contradictory since male predominance has been reported in India [12].

Beyond the fact that this is a rare condition, the main epidemiological feature of CTN is its relation with patient age. Incidence increases with age, predominantly occurring in the second half of life. Thus when analyzing data by age group, the Rochester teams found an annual incidence of 0.0002% before the age of 40 years, 0.0037% in the 40–49 year group, 0.0089% in the 50–59 year group, and 0.026% beyond the age of 60 years [9]. Manzoni and Torelli (2005) found a higher incidence in older subjects: 17.5/100,000 for the 60–69 year group and 25.6/100,000 beyond the age of 70 years [13]. CTN was diagnosed in 19% of patients aged over 65 who were referred to a tertiary center for headache [14]. Juvenile forms are however known, but should be considered first as a potential symptomatic painful trigeminal neuralgia, especially related to a tumor or demyelinization [15].

The link between high blood pressure and CTN, suggested for many years [9], has been established, particularly through work by Pan et al. [16]. High blood pressure would give rise to tortuous arteries which in turn would lead to increased risk of CTN. Possible co-morbidity with Charcot-Marie-Tooth disease and with glossopharyngeal neuralgia has also been suggested [13].

**CTN is a rare cause of pain that most generally occurs in subjects over 60.**

The natural course of CTN is not well described. The study from Rochester demonstrated that painful episodes last a variable length of time from 1 to 1462 days, with a mean of 116 days and a median of 49 days [9]. This study that followed certain patients for forty years or more also showed that 29% of patients experienced only one acute episode, that 19% had only two, 24% three, and 28% from four to eleven. Spontaneous remission is also possible, reported for at least six months for more than 50% of patients and for more than one year for nearly 25% in the study by Ruhston and MacDonald [17]. Maarbjerg et al. also confirmed the interindividual variability in the duration of remission [11]. Though these data on the natural history of CTN are incomplete and come from old studies, they provide essential information to take into account when establishing a therapeutic strategy and evaluating medical or surgical treatments.

#### 2.2.1. *Clinical signs*

*2.2.1.1. Typical clinical presentation.* The clinical diagnosis is based on five classical elements [18]:

- time course and pain quality;
- pain topography;
- triggering circumstances of pain;
- refractory period between attacks;
- no neurological deficit after the pain attacks.

2.2.1.1.1. *Time course and quality of pain*. CTN is generally characterized by brief sudden-onset intense pain; patients describe as an electric shock-like pain or stabbing. Less often the pain is described as grinding or parting rarely a burning sensation. In all cases the pain is very intense, excruciating. The paroxysmal pain is very brief, lasting 3 to 20 s with abrupt onset and termination, sometimes occurring in salvos constituting an attack lasting one to two minutes. Attack duration is however quite variable, changing with time and tending to last longer when the pain is more intense. These attacks of severe pain can have a significant negative impact on quality of life and often are associated with weight loss. Between acute episodes, most patients are asymptomatic. Attacks may occur a few times a day in the more benign forms of CTN, or reach an *état-de-mal* status the more severe forms. Tertiary centers that undoubtedly have a recruitment screening for the more severe forms of the disease have reported that 40% of patients have more than 10 attacks daily [11]. The pain occurs generally during the day and does not affect sleep. When an attack occurs, the patient stops all movement taking on a specific attitude characteristic of a painful facial tic. This painful phase may be followed by a motor phase with localized contraction of specific muscles, sometimes followed by a clonic grimace affecting the entire hemiface. Finally, a vasomotor phase may ensue with congestion of the hemiface, conjunctival injection, lacrimation, and nasal or oral hypersecretion. These vasomotor signs are generally observed in the more severe and ''older'' forms [19]. When questioned systematically about involvement of the autonomous system, patients report signs in 31% of cases, mainly tearing or conjunctival injection [11]. Between attacks, the patient has no complaint, except anxiety about having another attack.

2.2.1.1.2. *Topography*. The pain is unilateral (bilateral pain is reported in 1–2% of cases but never simultaneously, the pain affecting one side then the other asynchronously).

Strictly located in the territory of the trigeminal nerve, and generally limited to one of its branches, the pain may remain confined to one branch but may also diffuse to other branches. Most often the mandibular branch (V2) is involved, the pain generally starting in the upper lip, the wing of nose and the maxillary gingiva. The inferior maxillary (V3) is the second most affected branch, with pain usually in the territory of the chiny nerve (tip of the chin, lower lip, mandibular teeth region). The ophthalmic branch (V1) is more rarely involved with pain in the supra-orbital territory. V1 neuralgia is often symptomatic, especially when strictly localized to this territory. Close surveillance is necessary. While the distribution figures vary across studies, the preferential localization of the pain is the V2 territory, followed by the V3, and finally an association of V2 and V3; these three localizations account for 69% of patients [11].

The vast majority of studies have found that CTN is observed more often on the right than the left side: 57.8% for Katusic et al. [9]; 56% for Maarbjerg et al. [11]; 64% for Bangash [20].

2.2.1.1.3. *Triggering circumstances*. Touching the trigger zone, a specific area of skin or mucosa, is the most common circumstance initiating CTN. An individual may have one or more trigger zones. They are generally situated in the nasolabial crease of the upper lip for V2 or the gingival-alveolar rim of the mandible for V3. In the case of an ''old'' CTN, trigger zones may overlap. More rarely, the trigger zone is situated outside the territory affected by the CTN: territory of another branch of the trigeminal nerve or a C2–C3 territory. There is a latency in the triggered pain that extends progressively around the painful territory and persists a certain time after interruption of the stimulus. Temporo-spatial summation phenomena have also been observed with increasingly intense and extensive pain in response to repeated stimulations.

Patients may attempt to prevent an attack by applying pressure on the trigger zone; they also attempt to avoid any low-intensity mechanical stimulation of the trigger zone that would normally not be painful (washing, shaving, make-up, brushing teeth). Painful attacks can also be triggered indirectly by low temperatures, wind, or everyday situations (talking, laughing, mastication, swallowing, shaving...) imposing avoidance behavior (stiff frozen face). Patients attempt to be perfectly immobile, avoiding speaking or hardly moving their lips and fearing everyday activities such as eating, face washing, tooth brushing become impossible.

2.2.1.1.4. *Refractory period*. Each painful attack is followed by a refractory period during which the pain cannot be triggered by a stimulus. Patients may use this refractory period to perform feared gestures.

2.2.1.1.5. *Neurological examination*. The physical examination performed outside a painful period is strictly normal. No sensitive, sensorial, or motor deficit can be found in the affected territory after an attack: facial and corneal sensitivity and the strength of the masseter and temporal muscles are unaffected.

Similarly, the examination of the other cranial nerves fails to detect any deficit and shows no evidence of any participation of the long pathways or cerebellar involvement. It must be noted however that the normality of the neurological examination has been questioned (see below ICDH3 criteria).

To these clinical criteria must be added a therapeutic criteria: very good response, at least initially, to carbamazepine.

2.2.1.2. *ICHD-3 criteria [21]*. The term *classical* trigeminal neuralgia (CTN) is preferred over other terms such as essential or idiopathic [21].

The third edition of the International Classification of Headache Disorders (ICHD-3) defines the diagnosis of *classical trigeminal neuralgia (code 13.1.1)* with the following criteria:

A. at least three attacks of unilateral facial pain fulfilling criteria B and C;
B. occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution;
C. pain has at least three of the following four characteristics:
   1. recurring in paroxysmal attacks lasting from a fraction of a second to 2 min,
   2. severe intensity,
   3. electric shock-like shooting, stabbing or sharp in quality,

4. precipitated by innocuous stimuli to the affected side of the face[3];

D. no clinically evident neurological deficit[4];
E. not better accounted for by another ICHD-3 diagnosis.

*2.2.1.2.1. The diagnosis of CTN is based on ICHD-3 criteria.* - The ICHD-3 distinguishes two subtypes of CTN [21]: Classical trigeminal neuralgia: purely paroxysmal (code 13.1.1.1); and Classical trigeminal neuralgia with concomitant persistent facial pain (code 13.1.1.2) that was long considered to be an ''atypical trigeminal neuralgia. These two subtypes are defined by the International Headache Society (IHS) by the following criteria.

*2.2.1.2.1.1Classical trigeminal neuralgia: purely paroxysmal (code 13.1.1.1).* Criteria of classical trigeminal neuralgia purely paroxysmal are:

A. recurrent attacks of unilateral facial pain fulfilling criteria for 13.1.1 Classical trigeminal neuralgia;
B. no persistent facial pain between attacks;
C. not better accounted for by another ICHD-3 diagnosis.

*2.2.1.2.1.2Classical trigeminal neuralgia with concomitant persistent facial pain.* Criteria of classical trigeminal neuralgia with concomitant persistent facial pain are:

A. recurrent attacks of unilateral facial pain fulfilling criteria for 13.1.1 Classical trigeminal neuralgia;
B. persistent facial pain of moderate intensity in the affected area;
C. not better accounted for by another ICDH-3 diagnosis.

Because of the lack of sensitivity of these ICHD-3 beta criteria, modifications have been suggested, mainly with a criterion D and including the possibility of sensory disorders without the presence of any clinical antecedent or imaging argument in favor of a structural, traumatic, or systemic etiology [22].

*2.2.1.3. Other clinical forms*

*2.2.1.3.1. Pre-trigeminal neuralgia.* Classical trigeminal neuralgia 13.1.1 may be preceded by a period of atypical continuous pain termed pre-trigeminal neuralgia in the literature [21].

*2.2.1.3.2. Advanced form or long term evolution of the symptoms.* As CTN is a discontinuous disease, painful periods become longer and longer with time, the periods of remission becoming shorter and shorter. It is also noted that the clinical presentation changes with time. Attacks occur more and more often so that the pain may appear to be continuous. There is also a permanent background of pain, described as a burning sensation or more rarely as a tension-type pain. Medical treatments become less and less effective such that therapeutic resistance begins to appear. Hypoesthesia may develop in the painful region that may extend to a neighboring root or even all three divisions of the trigeminal nerve.

*2.2.1.3.3. Associations with other primary headaches.* Facial neuralgia may be associated with primary headache, concomitantly during the same episode or alternatively: cluster-tic [23]; migraine-tic [24]; paroxysmal hemicrania-tic [25].

### 2.3. Differential diagnoses of CTN

#### 2.3.1. Painful trigeminal neuropathy

The first differential diagnosis of CTN is painful trigeminal neuropathy (PTN). In the IHS classification [21], PTN corresponds to the former trigeminal neuropathies and secondary trigeminal neuralgia. The concept of PTN is thus based on the presence of an etiology that can be suspected with history taking and/or appropriate complementary explorations. PTN is related to an irritation, compression, destruction or demyelinization of the trigeminal nerve at any point on its course, from its emergence from the brain stem to its nerve endings, that is not secondary to neurovascular compression. The IHS defined PTN (13.1.2) and its sub-entities (13.1.2.1 to 13.1.2.6) regarding to the etiology giving rise to the neuropathy: attributed to acute Herpes zoster; post-herpetic; post-traumatic; attributed to multiple sclerosis (MS) plaque; attributed to space occupying lesion; attributed to other disorder [21].

The clinical symptoms of PTN are close to those of CTN as shown by the ICHD-3 criteria [21]. Several reports illustrate the non-specific features of the clinical presentation, but emphasize the importance of a well-conducted physical and neurological examination.

PTN is often observed in patients under 40. Usually, the pain involves the ophthalmic branch, although the other divisions of the trigeminal nerve can also be affected. PTN can be uni- or bilateral. The pain is intense, paroxysmal without trigger zone. Sensory disorders are often present such as hypoesthesia or anesthesia. Interictal signs may nevertheless be absent in PTN, requiring the need for systematic radiographic exploration. A poor response to carbamazepine is often reported even if transient improvement can be observed. Involvement of areas outside the trigeminal territories may be reported: optic neuritis, skin involvement, oral cavity and/or nervous system lesions. The presence of fever, general signs or poor general health status, a neurological disease such as MS or a disease with neurological tropism such as sarcoidosis or Sjögren's syndrome are also suggestive of PTN and warrant complete exploration.

These red flags are summarized in box below [26].

Red flags suggesting PTN [26]:

- persistent sensory disorders;
- deafness or auditory disorders;
- poor response to carbamazepine;
- skin lesions or lesion affecting the oral cavity with possible extension to the nervous system;
- isolated involvement of the ophthalmic branch of the trigeminal nerve, uni- or bilaterally;

[3] Some attacks may be, or appear to be, spontaneous, but there must be at least three that are precipitated in this way to meet this criterion.

[4] Hypoesthesia or hypoalgesia in the affected trigeminal region always indicates axonal damage. When either is present, there is trigeminal neuropathy and an extensive diagnostic work-up is necessary to exclude symptomatic cases. There are some patients with hyperalgesia in the painful region, which should not necessarily lead to a diagnosis of trigeminal neuropathy because it may reflect the patients increased attention to the painful side.

- age at onset under 40 years;
- optic neuritis;
- personal history of MS.

### 2.3.2. *Non-trigeminal neuralgias and Raeder's syndrome*

Painful facial neuralgia can more rarely affect the sensory divisions of the glossopharyngeal nerve, the vagus nerve, and the facial nerve (nervus intermedius of Wrisberg). We have chosen to also include Raeder's syndrome affecting the trigeminal territory.

*2.3.2.1. Glossopharyngeal neuralgia.* Glossopharyngeal neuralgia is a rare disease, accounting for 0.2 to 1.3% of all facial pain syndromes [27]. The main manifestation is typical neuralgic pain (intense, paroxysmal, brief, stabbing or electric shock-like) localized in the sensory territory of the glossopharyngeal nerve (IX) (box below).

Diagnostic criteria of glossopharyngeal neuralgia (ICHD-3, 13.2) [21]:

A. at least three attacks of unilateral pain fulfilling criteria B and C;
B. pain is located in the posterior part of the tongue, tonsillar fossa, pharynx, beneath the angle of the lower jaw and/or in the ear;
C. pain has at least three of the following four characteristics:
   1. recurring in paroxysmal attacks lasting from a few seconds to 2 min,
   2. severe intensity,
   3. shooting, stabbing or sharp in quality,
   4. precipitated by swallowing, coughing, talking, or yawning;

D. no clinically evident neurological deficit;
E. not better accounted for by another ICHD-3 diagnosis.

The pain may also involve the sensory fibers of the vagus nerve (X), explaining the term vagoglossopharnygeal neuralgia [27,28]. The pain is localized in the oropharynx (pharynx, tonsillar fossa, base of the tongue) and/or the ear [21]. Oropharyngeal pain can radiate to the auricular region and vice versa [28]. The pain may be associated with vagal vegetative symptoms such as cough, sneezing, bradycardia, or even syncope and asystole. Exceptionally, patients present with syncope and no associated pain.

Glossopharyngeal neuralgia causes intense, brief, electric shock-like neuralgic pain affecting a territory different from CTN, i.e. the oropharynx (pharynx, tonsillar fossa, base of the tongue) and/or the ear. Oropharyngeal pain can radiate to the auricular region and vice versa. Glossopharyngeal neuralgia can be associated with vagal vegetative symptoms such as bradycardia, syncope or asystole.

The pain occurs spontaneously or after stimulation of a zone innervated by the IX (trigger zone) such as swallowing, mastication, coughing, yawning, sneezing, or laughing. Severe pain attacks may interfere with food intake and can be associated with substantial weight loss. Rarely, the pain may be provoked by ingestion of cold, hot, sweet, or acid food or by rotation of the head [28]. Paroxysmal attack may be followed by a brief refractory period, with possible periods of remission.

Painful attacks of IXth nerve neuralgia occur spontaneously or are triggered by swallowing, mastication, cough, yawning.

IXth nerve neuralgia can be secondary or idiopathic. Glossopharyngeal neuralgia may be due to lesions located on its trajectory, from its nucleus in the brain stem to its nerve endings: intracranial and ENT tumors; vascular compression; inflammation (MS); trauma; Arnold-Chiari malformation. A complete exploration of the head, the neck and the face is thus necessary in order to rule out symptomatic neuralgia. Glossopharyngeal neuralgia can also be idiopathic, related to neurovascular compression of the glossopharyngeal nerve that can be demonstrated by MRI.

Glossopharyngeal neuralgia can be secondary or idiopathic (neurovascular compression). A complete exploration of the head and neck (face, ENT) is required, notably in smokers.

*2.3.2.2. Nervus intermedius (facial nerve) neuralgia.* Nervus intermedius neuralgia causes pain affecting the sensory innervation of a small territory of skin over the auricular concha near the external orifice of the auditory canal [29]. This rare condition is characterized by neuralgic pain (brief, intense, paroxysmal, sharp, stabbing) located in the auditory canal (box below).

Diagnostic criteria of nevus intermedius neuralgia (ICHD-3, 13.3.1) [21]:

A. at least three attacks of unilateral pain fulfilling criteria B and C;
B. pain is located in the auditory canal, sometimes radiating to the parieto-occipital region;
C. pain has at least three of the following four characteristics:
   1. recurring in paroxysmal attacks lasting from a few seconds to minutes,
   2. severe intensity,
   3. shooting, stabbing or sharp in quality,
   4. precipitated by stimulation of a trigger area in the posterior wall of the auditory canal and/or periauricular region;

D. no clinically evident neurological deficit;
E. not better accounted for by another ICHD-3 diagnosis.

The pain may radiate to the parieto-occipital region. Disorders of lacrimation, salivation and/or taste may accompany the pain [29]. Attacks can be precipitated by stimulation of a trigger zone located in the posterior wall of the auditory canal, by contact with food on the tongue, or can occur spontaneously [30].

The neuralgia can be idiopathic or occur as a complication of herpes zoster (clinicians should search for a history of skin eruption in the territory of the nervus intermedius of Wrisberg).

Nervus intermedius neuralgia causes neuralgic pain in the external auditory canal. A symptomatic cause must be ruled out, e.g. herpes zoster neuralgia.

*2.3.2.3. Paratrigeminal oculosympathetic (Raeder's) syndrome (code 13.8 ICHD-3)* [21]. This syndrome associates trigeminal neuralgia, oculosympathetic signs such as ptosis and myosis, and sometimes involvement of other cranial nerves, facilitating the differential diagnosis with CTN [31–33]. This neuralgia is always secondary.

The diagnostic criteria are as follows:

A. constant, unilateral headache fulfilling criterion C;
B. imaging evidence of underlying disease of either the middle cranial fossa or of the ipsilateral carotid artery;
C. evidence of causation demonstrated by both of the following:
   1. headache has developed in temporal relation to the onset of the underlying disorder,
   2. headache has either or both of the following features:
      a) localized to the distribution of the ophthalmic division of the trigeminal nerve, with or without spread to the maxillary division;
      b) aggravated by eye movement;
D. ipsilateral Horner's syndrome;
E. not better accounted for by another ICHD-3 diagnosis.

*2.3.3. Primary headaches*

*2.3.3.1. SUNT and SUNA.* The ICHD-3 [21] distinguishes CTN from two rare trigeminal autonomic cephalalgias (TACs) (expert agreement): SUNCT (Short-lasting Unilateral Neuralgiform pain with Conjunctival injection and Tearing) and SUNA (Short-lasting Unilateral Neuralgiform headache Attacks with cranial autonomic feature). However, the clinical distinction may be difficult consistent with a continuum between these entities [34]. Thus, secondary SUNCT may be caused by lesions located in the posterior fossa compressing the Vth cranial nerve [35]. In some patients, trigeminal neuralgia progress toward SUNCT/SUNA [36,37]. In animal models, stimulation of the Vth cranial nerve triggers vegetative signs [38]. Finally common therapeutic may be effective in such patients.

Even though the diagnosis may be difficult, clinical signs that distinguish CTN from these entities are the involvement of V1 nerve, the predominance of dysautonomic signs, the high frequency of attacks, the absence of trigger zones, and the poor response to carbamazepine.

*2.3.3.2. Cluster headache.* Among the other trigeminal autonomic cephalalgias, cluster headache is characterized by long-lasting pain attacks (15–180 min), autonomic manifestations (mainly tearing), a circadian and circannual rhythm. These symptoms associated with the absence of neuralgic pain help to distinguish them from CTN [21]. Nevertheless, recognized associations known as cluster-tic have been reported (see III2.3.4).

*2.3.3.3. Stabbing headache.* Other primary headaches may have a presentation similar to CTN, notably stabbing headache, formerly known as ice-pick headache (ICHD-3 *code 4.7*) [21]. This headache with a stabbing quality develops spontaneously and lasts a few seconds, sometimes occurring in series. In 70% of cases, the pain location does not correspond to a trigeminal territory. Pain occurs in a fixed location in only one-third of patients, facilitating the differential diagnosis with CTN [21] (Table 1).

*2.3.3.4. Epicrania fugax.* CTN must be distinguished from epicrania fugax (EF), a primary headache individualized in 2008 and described in the Appendix of the ICHD-3 under code *A4.11* [21]. A few small cohorts have been described [39–41].

The diagnostic criteria proposed by the ICHD-3 are:

A. recurrent stabbing head pain attacks lasting 1–10 sec, fulfilling criterion B;
B. the pain is felt to move across the surface of one hemicranium in a linear or zig-zag trajectory, commencing and terminating in the territories of different nerves;
C. not better accounted for by another ICHD-3 diagnosis.

A structural lesion must be excluded by history taking, general and neurological examinations and complementary explorations as appropriate. Patients with *A4.11* epicrania fugax describe unilateral pain paroxysms as a brief (few seconds) unilateral pain that rapidly spreads along a trajectory between two distant points on the head surface. Such dynamic topography is a distinctive attribute that differentiates A4.11 Epicrania fugax from other epicranial headaches and neuralgias. The onset and termination points remain constant in each patient, although some patients have shifting sides. The pain usually starts in a focal area of the posterior scalp and spreads forward to the ipsilateral eye or nose, although backward radiation has been reported. Backward-moving pain starts in a frontal or periorbital area and spreads the occipital region.

Some attacks may be followed by ipsilateral autonomic signs such as lacrimation, conjunctival injection and/or rhinorrhoea. Most attacks are spontaneous, although they may occasionally be triggered by cutaneous stimulation of the point of onset, which may remain tender in between attacks.

## 2.4. *Imaging of trigeminal neuralgia*

Neuroimaging in patients with CTN aim to search for neurovascular compression even if CTN is obvious and to exclude a secondary etiology.

**Table 1 – Distinctive signs distinguishing CTN, SUNCT, SUNA, and stabbing headache.**

| | SUNCT | SUNA | CTN | Stabbing headache |
|---|---|---|---|---|
| Gender (M:F) | M >> F | M > F | F >> M | |
| Quality | Stabbing, sharp | Stabbing, sharp | Electric shock | Stabbing |
| Severity | Moderate to severe | Moderate to severe | Severe | |
| Duration | 1–600 s | 1–600 s | < 1 s to 2 min | A few seconds (usually 3 s) |
| Localization | Orbitotemporal | Orbitotemporal | V2 V3 > V1 | Generally territory other than V |
| Autonomic signs | Conjunctival injection and/or tearing (mandatory for SUNCT)<br>Nasal congestion and/or rhinorrhea<br>Palpebral edema<br>Facial sweating<br>Facial flushing<br>Sensation of ear fullness<br>Myosis and/or ptosis | | Possible tearing or conjunctival injection, though less frequent and less pronounced | No |
| Attack frequency | At least 1 attack/day for more than half of the active periods | Variable | Low | |

2.4.1. *Appropriate explorations*

Cerebral MRI at 3 Tesla (3 T) is the imaging modality of choice in patients with CTN. Several studies comparing the sensitivity and specificity of lesions imaged with 1.5 T and 3 T machines have demonstrated an undeniable superiority for 3 T imaging [42].

> Cerebral imaging with 3 T MRI using specific sequences (see below) is recommended for suspected classical or secondary trigeminal neuralgia (expert agreement).

2.4.2. *CTN and search for neurovascular compression*

2.4.2.1. *Appropriate MRI sequences*. High-resolution T2 images with thin slices (< 0.5 mm) in the plane of the Vth cranial nerve obtained with echo gradient sequences (CISS, Constructive Interference Stead-State for Siemens; or FIESTA, Fast Imaging Employing Stead-state for GE) or turbo spin echo sequences (DRIVE acquisition for Phillips) are used to 3D reconstructions in order to visualize possible neurovascular compression and the basal cisterns.

Native images acquired in the strict axial plan are reconstructed in double obliquity in the sagittal and coronal planes to obtain an axial oblique visualization of the cranial nerve in the cisterns. The high spatial resolution of the T2 sequence (CISS, DRIVE, FIESTA...) 3D image provides excellent contrast between the cerebrospinal fluid (hypersignal) and neurovascular structures (hyposignal) producing high-performance cisternography. The limitations are the lack of signal differentiation, not only between arteries and veins or between vessels and nerves, but also for the brain parenchyma.

Some MRI machines use a 3D T2 spin echo sequence on the posterior fossa (CUBE T2 for GE; SPACE T2 for Siemens, VISTA for Phillips). This approach aims to analyze the trigeminal nerve in the cisterns, the brain parenchyma, and the facial structures with a single sequence that can be an alternative substituting for the two T2 sequences cited above: axial T2 and 3D high-resolution T2 (CISS, DRIVE, FIESTA).

Search for neurovascular compression may require complementary sequences such as time of flight (TOF) magnetic resonance (MR) angiography to determine whether the vessel involved is an artery or a vein. TOF MR angiography provides good visualization of rapid blood flow, preferentially arterial flow, while the neighboring tissues produce a weaker signal. The visibility of the venous network can be removed by using a higher presaturation band. Reconstructions are made with maximum intensity projection (MIP), analysis of the vertebra-basilar system is visualized better after suppression of the carotid network.

> Combining the axial slices of three sequences (high-resolution 3D T2; 3D T1 with gadolinium injection; TOF MR angiography) is needed to obtain a good visualization of an underlying neurovascular compression).

2.4.2.2. *Localizing the compression*. The identification of a neurovascular compression needs to carefully study the REZ that is located 2–6 mm after the emergence of the trigeminal nerve. The REZ corresponds to the transition zone between the central myelin (oligodendrocytes) and the peripheral myelin (Schwann cells) involved in the pathophysiology of trigeminal neuralgia (Section 2.1.3).

2.4.2.3. *Criteria for the diagnosis of neurovascular compression*. Maarbjerg et al. [4] conducted a 3 T MRI study in 135 patients (mean age 53 years) with CTN in order to evaluate neurovascular contacts (graduating contact into three types: simple contact; nerve displacement; nerve atrophy) on the symptomatic and asymptomatic side since neurovascular contacts may exist without clinical expression in 10–71% of cases [42]. In their study, the prevalence of neurovascular contact was 89% on the symptomatic side and 78% on the asymptomatic side ($P = 0.0014$, OR = 2.4, IC 95%: 1.2–4.8). When considering the item 'neurovascular contact' on the symptomatic *versus* asymptomatic side, the sensitivity was 89% but the specificity only 22%.

Severe neurovascular contacts, defined as the displacement or atrophy of the trigeminal nerve, were highly prevalent on the symptomatic side (53% versus 13%; $P < 0.001$; OR = 11.6; 95Ùci 4.7–28.9). Severe neurovascular contacts were arterial in 99% of cases. The sensitivity of ''severe neurovascular contact'' on the symptomatic *versus* asymptomatic side was 53% and the specificity was 87%.

In 2015, Antonini et al. conducted a double–blind study performed in 24 patients and a meta-analysis of the literature published from January 1970 through June 2013 on neurovascular contacts in CTN [43]. In their study, contact with the REZ ($P = 0.027$), nerve dislocation ($P = 0.05$), or nerve atrophy ($P = 0.035$) were correlated independently with CTN. The sensitivity of each item considered alone was low, but with high specificity. Regarding contact with the REZ and co-existing atrophy, the sensitivity and specificity were almost 100%. In the meta-analysis, neurovascular contact with the REZ was detected in 76% on the symptomatic side and in 17% on the asymptomatic side ($P < 0.001$) while anatomic alterations were detected in 52% on the symptomatic side and in 9% on the asymptomatic side ($P < 0.001$).

Thus the causality of CTN is attributed to neurovascular compression, when the MRI visualizes right angle crossing with direct contact between the artery and the nerve in the REZ and with nerve displacement and/or deformation or atrophy.

> The diagnosis of neurovascular compression can be retained when the following criteria are fulfilled: right angle crossing with direct vessel-nerve contact in the REZ, nerve displacement/deformation or atrophy and concordant clinical and radiographic presentations.

#### 2.4.3. *PTN and imaging*

*2.4.3.1. MRI sequences.* MRI should include specific sequences to optimize the exclusion for a secondary etiology.

The 3TMRI exploration should start with sagittal T1 acquisition to identify the Vth cranial nerve, visualize the brain stem (intra-axial cause?), and the junction (Chiari malformation?). The trigeminal nerve is identified on the 1st slice outside the brain stem. Axial T2 sequences (or FLAIR sequences) aim to visualize the brain stem, the cavernous sinus, and the facial structures.

Coronal T2 acquisition of 2 mm slices centered on the cavernous sinus can be used to demonstrate and characterize a small sized lesion in this region.

*2.4.3.2. Etiologies.* The main etiologies are summarized in Table 2.

#### 2.4.4. *Imaging perspectives*

Tensor diffusion imaging may be shown to be an interesting non-invasive tool for evaluated nerve damage at a site of neurovascular contact but complementary studies are needed [44].

### 2.5. *Medical treatments for trigeminal neuralgia*

#### 2.5.1. *General aspects*

It is difficult to evaluate treatments for trigeminal neuralgia because of the rarity of the disease and the small number of clinical trials conducted with a robust methodology and including a sufficient number of patients [45–47]. American and European guidelines were published in 2008 and 2010 [45,48]. All of the randomized controlled trials were conducted for CTN. Only open studies have been reported for PTN. Studies have mainly involved anti-epileptic agents. Despite the difficulty encountered, it would be indispensable to conduct methodologically robust clinical trials for CTN in order to validate and stratify the different therapeutic approaches [49]. It is to be noted that the IHS has not yet published guidelines for controlled trials of drugs in trigeminal neuralgia (www.ihs-headache.org).

#### 2.5.2. *Medicines evaluated for classical trigeminal neuralgia*

*2.5.2.1. Carbamazepine.* Carbamazepine, a sodium channel blocker, was developed in the 1960s specifically for the treatment of trigeminal neuralgia before being rapidly

**Table 2 – Etiologies of secondary trigeminal neuralgias.**

| Anatomic localization | Etiology |
|---|---|
| Intra-axial (brain stem) | Multiple sclerosis |
| | Syringobulbia |
| | Laterobulbar infarction (Wallenberg syndrome) |
| | Intra-axial tumor |
| Sub-arachnoid space (neighboring the cerebellopontine angle) | Meningoradiculitis |
| | Carcinomatous meningitis |
| | Infectious meningitis involving the cranial nerves |
| | Tumor in the cerebellopontine angle (VIII Neurinoma, meningioma, cyst, cholesteatoma) |
| | Trigeminal nerve cavernoma |
| | compression by vascular malformation or aneurysm of the basilar artery |
| Gasser's trigeminal ganglion | Local tumor |
| | Infection (herpes zoster) |
| Nerve divisions (skull base and cavernous sinus, facial structures) | Tumors of the skull base (extension of a Cavum cancer, meningioma especially in the cavernous sinus, perineural extension, etc. |
| | Fractures (skull base or sinus, facial structures) |
| | Thrombosis in the cavernous sinus |
| | Vth nerve mononeuropathies (diabetes, Sjögren's syndrome, etc.) |

recognized as an anti-epileptic agent. It remains the reference treatment for trigeminal neuralgia [45,48]. Four randomized controlled trials with a double-blinded design demonstrated the superiority of carbamazepine over placebo [47]. It must however be noted that the methodological quality of these old trials was considered to be weak by a recent Cochrane review [47], especially the report by Rockcliff and Davis (1966) that concerned only nine patients. In the crossover trial by Killian (1968), 19 of the 27 patients experienced complete or excellent response with carbamazepine (increased from 400 to 1000 mg/d) versus none with placebo after five days of treatment. In the crossover trial by Nicol (1969), 15 of the 20 patients experienced good or excellent response with carbamazepine (increased from 100 to 2400 mg/d) versus six with placebo after 14 days of treatment. The Cochrane meta-analysis of these two trials concluded that carbamazepine was superior to placebo (RR = 6.02, 95%CI: 2.82–12.85) [47]. The trial by Campbell (1966) that was not included in the Cochrane meta-analysis [47] because it did not report overall pain response showed a mean 58% decrease in maximal pain intensity with 400–800 mg/d carbamazepine versus 26% with placebo.

According to these four trials versus placebo (grade A), carbamazepine is an effective treatment for trigeminal neuralgia and provides complete initial relief in at least 70% of treated patients [50] with a number needed to treat (NNT) below 2 [46,47]. Carbamazepine reduces the frequency and intensity of neuralgic attacks and exhibits equal efficacy for spontaneous or provoked episodes [46].

Carbamazepine has also been investigated in several other randomized controlled trials in comparison with other agents and has been found to be equivalent to tocainide [51] and oxcarbazepine [52] and inferior to pimozide [53].

Its efficacy should be balanced against its frequent adverse effects. In the randomized controlled trials, the number of subjects to treat to induce an adverse effect (NNH: number needed to harm) was 3.4 for minor adverse effects and 24 for serious adverse effects [47,54]. In a retrospective study of 95 patients treated with carbamazepine, 98% were responders at a median dose of 600 mg (200–1200 mg) and the adverse effects led to treatment interruption in 27% of responders with an 8.6-month median duration of treatment [55]. The most common adverse effects involve the central nervous system (CNS) with vertigo, ataxia, somnolence, fatigue, and less often diplopia, accommodation disorders, confusion, or agitation. These CNS effects affect up to 40–60% of patients, particularly older subjects [56]. Blood tests may show hyponatremia. Serious adverse effects are rare, but can lead to death by hematological disorders, including anemic aplasia [56], skin rash with Lyell or Stevens-Johnson syndrome, or systemic hypersensitivity reaction [57,58]. Carbamazepine is also an enzymatic inducer strongly inhibiting the action of several drugs including anticoagulants (anti-vitamin K and new anticoagulants), anti-retroviral agents, statins, certain anti-hypertensive agents, and oral contraceptives [59].

Carbamazepine has been labeled in France for the treatment of trigeminal neuralgia and glossopharyngeal neuralgia. Available formulations include scored tablets (200 mg; 200 mg and 400 mg extended release tablets that should not be chewed or crushed) and oral solution (20 mg/1 mL). The initial dose is 200–400 mg/d d.i.d. or t.i.d. It is recommended to increase the dose progressively until pain relief is obtained, then to taper off to the lowest effective dose (see product labeling) [60]. The maximal recommended daily dose is 1600 mg. It may be useful to separate the dose for intake three times a day, 30 to 40 minutes before meals and facial and dental hygiene. The conventional formulation is preferred, the extended release formulation producing lower serum levels and requiring higher doses [61]. The extended release formulation may however be useful at bedtime.

Contraindications for carbamazepine include atrioventricular block, known hypersensitivity to the active compound or its excipients, history of medullary hypoplasia, history of hepatic porphyria, and treatment with telaprevir and voriconazole. Many drug interactions with this enzyme inducer are described and require systematic examination of the labeling documents [60].

It is recommended to obtain a blood cell count and liver tests before starting treatment, once a week during the first month, then as appropriate for the clinical context. An electrocardiogram would be useful for older patients before starting treatment to rule out rhythm disorders.

Carbamazepine should be withdrawn in the event of allergic skin reactions, altered liver function, or clear change in blood cell counts suggesting possible agranulocytosis or medullary aplasia (rare). A strong association between HLA-B-1502 and carbamazepine-induced Stevens-Johnson syndrome and epidermal toxic necrosis has been described in Asian populations, but not in European populations; a link with HLA-A*3101 has been recently described in the European population [62].

> Carbamazepine is effective to treat trigeminal neuralgia and provides complete initial relief in at least 70% of treated patients. Carbamazepine has marketing approval in France for the treatment of CTN. In the absence of contraindications, it is the first-line pharmacological treatment. This treatment can give rise to severe adverse events and requires biological surveillance.

*2.5.2.2. Oxcarbazepine.* This derivative of carbamazepine was developed with the goal of limiting the central side effects of carbamazepine. It is the other treatment of choice for trigeminal neuralgia [46,49]. The efficacy of oxcarbazepine was demonstrated in four randomized controlled double-blind trials versus carbamazepine, including one published *in extenso* in German [63] and the others in abstract form and included in a meta-analysis with a total of 130 patients [53] (grade B). Its efficacy at the dose of 600–1800 mg/d is similar to that of carbamazepine. A > 50% reduction in the frequency of painful attacks was obtained in 88% of patients with better tolerance and less drug interaction.

Oxcarbazepine was found to be effective in one open study of 35 patients who were unresponsive to carbamazepine [64]. In a retrospective study of 83 patients treated with oxcarbazepine, 94% were responders at the median dose of 1200 mg (600–1800 mg); adverse effects led to treatment withdrawal in 18% of responders after a median 13-month treatment [56].

The most common adverse effects are CNS effects with somnolence, instability and vertigo, but they are 3-fold less frequent than with carbamazepine. Serious skin reactions (Lyell or Stevens-Johnson syndrome) are very rare, as are serious adverse hematological reactions (aplastic anemia). Conversely, hyponatremia below 125 mmol/L, which is generally asymptomatic and does not require therapeutic adjustment, has been reported in 2.7% of patients treated with oxcarbazepine for different indications (see labeling documents) [60]. In the study by Di Stefano et al. [56] five of the 83 patients treated for trigeminal neuralgia stopped treatment for hyponatremia. The experience acquired during clinical trials showed that the serum sodium level returns to normal after reducing the dose, withdrawing treatment, or with symptomatic treatment such as restricted fluid intake (labeling document) [60]. Finally, oxcarbazepine is a weak enzyme inducer and can inhibit the efficacy of oral contraceptives.

Oxcarbazepin is used off-label in France for the treatment of trigeminal neuralgia. It is available in tablets dosed 150, 300 and 600 mg. The initial dose is often 600 mg/d d.i.d., then increased by 300 mg by intervals of a few days up to 900–1800 mg/d. The only contraindication is hypersensitivity reaction.

It is recommended to check serum sodium level before starting treatment in patients with a pre-existing kidney condition associated with low natremia or in patients receiving sodium-lowering drugs concomitantly (e.g. diuretics, desmopressin) or non-steroidal anti-inflammatory drugs (e.g. indometacin). Serum sodium should be checked about two weeks later, then every month for the first three months of treatment or as needed. The same protocol can apply for the elderly subject.

> Oxcarbazepine is probably an effective treatment for CTN. It can be used after non-response or intolerance to carbamazepine. This treatment is off-label.

2.5.2.3. *Lamotrigine*. We have not found a randomized trial versus placebo for lamotrigine in a single-drug regimen for the treatment of CTN.

Lamotrigine has been investigated in two open trials showing its efficacy [65,66].

Furthermore, lamotrigine has been investigated in a randomized double-blind crossover trial versus placebo in 14 patients treated with carbamazepine and/or phenytoin for 14 days [67]. Lamotrigine, increased to 50–400 mg/d in four days was slightly more effective (using a composite index of efficacy) than placebo in this low–power study (RR non-significant). Ten patients were improved with lamotrigine versus eight with placebo [68] (grade C).

In one last non-randomized crossover and open comparative trial performed in 21 patients, relief was obtained in 13 patients with lamotrigine versus 19 patients with carbamazepine [69].

Lamotrigine is used off-label in France for trigeminal neuralgia. It is available in tablets dosed 25, 50, 100, and 200 mg. Due to the risk of allergic reactions, the initial dose should be 25 mg/d in adults for the first two weeks. The dose is then increased to 50 mg/d in one dose for the next two weeks, then by 50 to 100 mg/d every 1 to 2 weeks. This rate of dose escalation should not be exceeded and the rapid escalating protocol presented by Zakrzewska is not recommended [67]. Even with these recommended precautions, the incidence of serious skin reactions among adults recruited for lamotrigine trials for the treatment of epilepsy was about 1/500 epileptic patients with 50% having Stevens-Johnson syndrome (1/1000) (labeling documents) [60].

> Lamotrigine is possibly effective for the treatment of trigeminal neuralgia but appears to be less effective than carbamazepine. It can be proposed in the event of non-response or intolerance to carbamazepine or oxcarbazepine. Lamotrigine does not have marketing approval for this indication in France and there is a risk of allergic skin reaction.

2.5.2.4. *Phenytoin*. Phenytoin was the first drug treatment proposed for trigeminal neuralgia. A positive effect was noted in open studies [70–72], but there has been no any randomized controlled trial. This treatment has a less favorable benefit/risk ratio than carbamazepine.

> While oral phenytoin has marketing approval in France for trigeminal neuralgia, it appears to be less effective than carbamazepine and causes numerous adverse effects, such that it is not recommended.

2.5.2.5. *Other anti-epileptic agents*. Individual cases suggest that gabapentin is effective [46]. In a small-randomized trial with three treatment arms, gabapentin associated with repeated injections of ropivacaine in trigger zones led to improvement in pain and quality of life compared with gabapentin alone, the treatment arm with ropivicaine injections alone being discontinued for inefficacy [73].

Two open prospective studies including a total of 118 patients suggested the efficacy of pregabalin [74,75].

In a randomized double-blind crossover pilot study versus placebo conducted in three patients, topiramate was effective in the initial phase, but with treatment escape after prolonged treatment [76]. In a small open study, three of eight patients achieved complete remission, three moderate improvement, and two no improvement with 50–100 mg/d topiramate [77]. In a meta-analysis of six randomized controlled trials all conducted in China and published in Chinese, with a total of 354 patients and a low-quality methodology, topiramate appeared to be more effective than carbamazepine [78]. There was no difference between these two compounds for the efficacy rate at one-month treatment, the rate of remission at two months, and the rate of adverse effects. The authors of the meat-analysis concluded that further international trials should be conducted [78].

In a small open study, four of ten patients treated with levetiracetam were responders; levetiracetam was used a high dose (4000 mg/d) [79]. Levetiracetam added to other ongoing treatments was effective in an open study of 25 patients with classical or secondary trigeminal neuralgia [80].

Other small open studies suggest that other antiepileptic agents (clonazepam, valproate) have a therapeutic effect, but the proportion of patients exhibiting improvement was lower than observed with carbamazepine [46].

2.5.2.6. *Baclofen*. Non-antiepileptic agents have been used since the 1970s for the treatment of trigeminal neuralgia and have been the topic of a Cochrane review in 2013 [81]. This Cochrane review did not include the study by Fromm et al. [82] because this baclofen trial included too few subjects. In this unique randomized crossover trial, seven of ten patients had a reduction in the number of neuralgic attacks with baclofen (40–80 mg/d) versus none with placebo after seven days of treatment [82]. This study also had an open phase with 50 patients, 70% of whom reported long-term efficacy with baclofen, alone or in combination with carbamazepine when this latter drug was ineffective alone or not tolerated at the effective dose [82].

This antispastic agent does not have marketing approval in France for trigeminal neuralgia (grade C). It is available in scored tablets had is started at low dose, 5–15 mg/d t.i.d., before increasing the dose every 3–4 days to the optimal dose of 30–80 mg. It must not be withdrawn suddenly due to the risk of a potentially fatal weaning syndrome, analogous to that observed in patients treated for spasticity with intratecal injections (see labeling documents). The only contraindication is hypersensitivity reaction. The most common adverse effects are sedation early in treatment, somnolence, and nausea.

> Baclofen is possibly effective for the treatment of trigeminal neuralgia, but does not have marketing approval. It can be used only in the event of intolerance to carbamazepine or oxcarbazepine, or in combination with one of these compounds in the event of incomplete efficacy (expert agreement).

2.5.2.7. *Other non-anti-epileptic agents*. Simple analgesics, codeine, aspirin, and non-steroidal anti-inflammatory drugs are not used because clinical experience has shown they are not useful [81].

A randomized crossover double-blind study by Lindstrom and Lindblom [51] compared carbamazepine with an anti-arrhythmic analog of lidocaine, tocainide, in 12 patients. The authors found no difference between the treatments but did not report results for the first period of treatment. Tocainide was withdrawn from the market due to the risk of fatal agranulocytosis.

Lechin et al. [54] reported a randomized double-blind crossover comparison ofcarbamazepine (300–1200 mg/d) with the antipsychotic neuroleptic pimozide (4–12 mg/d) for eight weeks in 68 patients. Pimozide was superior to carbamazepine. In the first period of the trial, six weeks after treatment onset, there was a 78.4% reduction in the overall score of neuralgic severity with pimozide versus 49.7% with carbamazepine (mean difference 27.70% [95%CI 20.88–36.52%]). Combining the two periods of treatment, 48 of the 68 patients were improved with pimozide versus 27 with carbamazepine. Adverse effects were reported in 86% of patients taking pimozide (sedation, tremor, extrapyramidal syndrome).

Pimozide is possibly effective for the treatment of trigeminal neuralgia (grade C). It does not have marketing approval for the treatment of trigeminal neuralgia and is not recommended due to its adverse effects (expert agreement). Pimozide is available in France in 1 and 4 mg tablets (Orap®, no available generic). Its contraindications and adverse effects are those observed with neuroleptics (see labeling documents) [60].

Tizanidin is an antispastic agent unavailable in France. In a randomized double–blind trial in parallel groups by Viming et al. (1986) with 12 patients, tizanidine was inferior to carbamazepine, with no statistically significant difference [83]. In another randomized double-blind crossover study with small sample size including patients with refractory CTN, tizanidine was superior to placebo, eight of the ten patients treated exhibiting a reduction in the frequency of neuralgia attacks with tizanidine, but the six patients who chose to continue tizanidine all experienced recurrent neuralgia within one to three months [84].

2.5.2.8. *Local anesthetic blocks*. In a small randomized trial with three treatment arms, gabapentin associated with repeated injections of ropivacaine in trigger zones led to improvement in pain and quality-of-life compared with gabapentin alone, the treatment arm with ropivicaine injections alone being discontinued for inefficacy [73].

In a randomized study versus placebo with 45 patients, ropivicaine injections in each trigger zone (2 mL of a 2 mg/mL solution) once a week for one month combined with carbamazepine (400–1000 mg/d) was equivalent to saline solution for the reduction of neuralgia attack frequency and intensity at one month, but enabled a significant reduction in daily dose of carbamazepine at one and six months [85].

In France, recommendations established by expert agreement in 2013 concerning locoregional analgesic techniques for the treatment of pain stipulated that peripheral blocks of the terminal divisions of the cranial nerves V1, V2 and V3 had a low level of proof. Observational data report 85% transient improvement for local anesthetic blocks or neurolytic blocks [86]. In light of current knowledge, this therapeutic approach cannot be recommended.

2.5.2.9. *Botulinum toxin*. In an open study, injections of botulinum toxin were effective in 13 of 13 treated patients [87].

Nine studies have studied the effect of botulinum toxin type A in CTN; there were four randomized double-blind studies [81,88–90] and five case studies. The efficacy of botulinum toxin in this indication is to date highly controversial, a systematic review concluded that evidence is insufficient to conclude that it is effective in this indication [91]. Indeed, many points remain to be clarified using clinical trials with rigorous methodology: precise number and localization of the injection points; optimal dose; relation with the presence of trigger zones; sufficient follow-up to

confirm treatment efficacy. In light of current knowledge, this treatment cannot be recommended.

#### 2.5.3. *Different drugs evaluated in CTN*

There is no randomized double-blind study versus placebo in CTN. Most of the open studies concern neuralgia secondary to MS and have had small sample sizes.

Lamotrigine has been found to be more effective than carbamazepine in 18 patients [92]. Three studies with a total of 19 patients demonstrated a positive effect of gabapentin alone or combined with carbamazepine [93–95]. Topiramate was effective in two small studies and in one case, i.e. 10 patients in all [96–98]. Misoprostol (a prostaglandin E1 analog indicated in France for the treatment of ulcers and the prevention of gastroduodenal ulcers related to use of non-steroidal anti-inflammatory drugs) was effective in two open studies with a total of 25 patients with MS [99,100].

> Due to the low level of proof, treatment cannot be recommended for symptomatic trigeminal neuralgia. It is proposed to use carbamazepine or oxcarbazepine for the first-line treatment.

#### 2.5.4. *Different compounds evaluated for neuralgia exacerbations*

There is no randomized double-blind study versus placebo for the treatment of CTN or PTN exacerbations in patients who already receive a prophylaxis.

A few publications suggest that intravenous infusion of phenytoin or sodium fosphenytoin at lower doses that for status epilepticus can be useful to control at least temporarily acute exacerbations of refractory trigeminal neuralgias [101,102]. Parenteral phenytoin affects ventricular automatism. Use of fosphenytoin is thus contraindication in patients with sinusal bracycardia, second or third degree atrio-ventricular block, and Stoke-Adams syndrome. Administration requires rigorous cardiovascular surveillance with continuous monitoring.

> While oral phenytoin has marketing approval for the treatment of trigeminal neuralgia, intravenous fosphytoin does not have marketing approval for this indication. It is proposed to limit its use for neuralgia exacerbation to specialized hospital units with continuous cardiovascular monitoring.

Intravenous lidocaine has been reported in rare cases [103]. Lidocaine does not have marketing approval for this indication. As for fosphenytoin, it requires teams experienced in the use of these substances and cardiovascular surveillance with continuous monitoring. These treatments are often punctual treatments designed to enable adaptation of medical treatment or to organize surgical treatment of severe forms of CTN or PTN. One case suggests the efficacy of intravenous magnesium sulfate [104].

### 2.6. *Surgical treatments*

Neurosurgical management of trigeminal neuralgia can involve the use of three major types of surgery: non-destructive 'etiological' techniques (corresponding to microsurgical vascular decompression) consisting in the decompression of the trigeminal nerve in the cerebellopontine angle where a neurovascular compression is frequently found giving rise to pain; percutaneous 'lesion' techniques designed to alter the transmission of the nociception message; and radiosurgical techniques.

These different surgical techniques will be presented in this chapter together with their indications and strategies for surgical treatment.

#### 2.6.1. *Surgical techniques*

2.6.1.1. *Microsurgical vascular decompression*. Proposed by Dandy as early as 1934 [105] following observations made during surgical procedures of sectioning the trigeminal nerve in patients with trigeminal neuralgia, the theory of trigeminal nerve compression by a blood vessel in the cerebellopontine angle as the cause of CTN was later revisited and formalized by Gardner [106] and Jannetta [107] (Section 2.1). Progress in imaging techniques (Section 2.4) also largely contributed to the development of this technique.

The purpose of the intervention is to release the trigeminal nerve from the vascular compression by a microsurgical procedure in the cerebellopontine angle. This is achieved under general anesthesia with the patient in lateral or supine position depending on the surgeon preferences, using a 2-cm retromastoid incision. The procedure consists in an exploration of the integrity of the trigeminal nerve, from Meckel's trigeminal cave anteriorly to the entry of the nerve into the brainstem posteriorly. This assessment checks for the presence of any nerve compression, even if vessel impingement appears to be obvious since multiple zones of compression can lead to postoperative failure.

Decompression is achieved by displacing the artery compressing the nerve or by coagulation and dividing the vein in the rare cases of venous compression. Recurrent compression is prevented using implanted material (Teflon fragments, sling, slip, felt) that ideally should not touch the trigeminal nerve in order to ensure the best postoperative results [108,109].

Microsurgical decompression provides immediate relief in 80–98% of patients (mean 91.8%) with drug-free pain relief for 62–89% (mean 76.6%) at term follow-up (5–11 years across studies, mean 7 years). In the series reported by Sindou et al. [110,111], 81.2% of patients were free of pain without medical treatment at one year, 73.4% at 15 years. Analyzing the severity of the vascular compression on the trigeminal nerve noted intraoperatively, the same authors [110] reported that results were better when the compression was more severe (85% of patients with grade II on a scale of III, signifying "marked indentation of the nerve", were pain-free without medication at 15 years follow-up), which would appear to confirm the theory of neurovascular compression in trigeminal neuralgia.

Microsurgical vascular decompression is an open surgical procedure that has its risks; mortality is reported at 0% to 1.2%

across series [3]. This mortality is generally due to vascular phenomena diffusing into the posterior cranial fossa (edema, ischemia, hemorrhage). Neurological complications are generally related to the manipulation of neighboring cranial nerves: more or less severe hypoacousia and/or balance disorders (0.8–4.5%); facial palsy (0–1%); diplopia involving the IVth (0.5–1%); trigeminal hypoesthesia (2–10%). Finally, this intra-dural surgery via a retromastoid approach can be complicated by late wound healing, otorrhea or rhinorrhea, or infection notably meningitis (2–17% across series). An American study found that centers and surgeons with a higher activity level for trigeminal neuralgia procedures had lower morbidity-mortality figures and better results than centers treating a few cases per year [112].

This surgery is indicated for patients in good general health who have been informed and are aware of the benefit/risk balance.

*2.6.1.2. Percutaneous radiofrequency "Thermocoagulation" or retrogasserian percutaneous thermorhizotomy*. This percutaneous technique consists in achieving thermoalgic anesthesia of the painful territory by applying heat on the trigeminal nerve sensory axons by positioning the tip of a transjugal trans-foramen ovale electrode behind Gasser's trigeminal ganglion in the triangular plexus, situated in Meckel's trigeminal cave. The currently accepted mechanism of action considers that the Aδ and C thermoalgic fibers (respectively weakly myelinated or amyelin fibers) are thermo-sensitive.

The procedure is performed under local anesthesia, and thus can be proposed for patients with a contraindication for general anesthesia. Complementary sedation (usually a rapidly eliminated propofol formulation) is administered during the painful phases of the procedure. Using Hartel's technique, a beveled cannula, isolated at the tip, guides an electrode via a transjugal route to Meckel's cave (trigeminal cavum) [113,114]. Radiographic control checks the proper position of the electrode. Electrical stimulation is then applied to the electrode, evoking paresthesia in the territory of the trigeminal fibers lying close to the electrode tip. The electrode can be repositioned to better cover the painful territory, including the trigger zone. High intensity stimulations are delivered producing masseter muscle contractions, especially when close to the motor root of the trigeminal. Low-intensity stimulations cause small contractions of the face muscles resulting from activation of the trigemino-facial reflexes. Once the desired position has been obtained, the patient is slightly sedated and an electrical current is applied in order to increase the temperature of the tip of the electrode to 60–85 °C for about 30 s for a thermocoagulation test [113]. The corneal reflex is monitored during the test and throughout the remainder of the procedure to ensure the absence of corneal anesthesia. The patient is then awakened for a pin prick test to determine the topography of the thermoalgic hypoesthesia. The procedure is repeated as many times as necessary to obtain the desired level of analgesia.

The review of the literature reporting results of this procedure identified ten series from a total of 7483 patients with 3–26 years follow-up (mean 9 yr) [115–117] who experienced immediate relief for 94% (81–99%) with long-term efficacy for 60.4% (20–93%). Patients should be clearly informed that pain relief is obtained at the "cost" of trigeminal hypoesthesia, which ideally is purely thermoalgic but also includes an almost inevitable tactile hypoesthesia or facial numbness. Tactile hypoesthesia has been reported in 5–98% of cases, apparently with better efficacy over time in patients with trigeminal hypoesthesia [115]. This trigeminal hypoesthesia/anesthesia obtained by facial deafferentation can lead to keratitis in 1–8% of cases especially when the painful territory concerns V1, and/or intolerable dysesthesia or painful anesthesia (0.8–7%). Deficiency of masseter muscles has been reported in 4–24% of cases due to injury of the trigeminal motor root. Reported mortality is 1‰, particularly by carotid puncture.

*2.6.1.3. Percutaneous balloon compression of the trigeminal ganglion*. The principle of this technique is that compression of the retrogasserian fibers of the trigeminal ganglion in Meckel's cave injures in priority small amyelin and weakly myelinated nociceptive fibers. This is a trans-foramen ovale percutaneous procedure using an approach similar to the thermocoagulation method described above. A Fogarty balloon catheter is inserted via a cannula. The balloon is inflated progressively with contrast agent under radiographic control, usually for 60 s. On the intraoperative radiography, the balloon takes on a pear shape if Meckel's cave is small, the tail of the pear lying on the triangular plexus. If the cave is large, the balloon looks like a tomacula, a sign of insufficient compression and failure. The balloon takes on a barbell form if part of it passes into the posterior cranial fossa, creating a risk of oculomotor deficiency. The inflation pressure and the duration of the compression are adapted to each patient and type of balloon deformation. This technique usually generates postoperative hypoesthesia of the entire hemiface that regresses in 4–8 weeks. In rare cases, the hypoesthesia does not resolve, rarely with the development of facial deafferentations.

The advantages of this technique are: it appears to produce less definitive trigeminal hypoesthesia than thermocoagulation, so it can be useful in cases with V1 neuralgia or a risk of keratitis. Performed under general anesthesia, it does not require the patient's collaboration (as is necessary for thermocoagulation). This may be an advantage for older populations with cognitive or behavioral disorders or if there is a language barrier contraindicating thermocoagulation. There is no stimulation phase (as in thermocoagulation) that might reactivate the pain. The main drawback is the need for general anesthesia because the compression is painful and because trigemino-cardiac reflexes may trigger severe (but transient) bradycardia implying careful coordination with the anesthetist. This general anesthesia rules out testing during the procedure to determine the appropriate dose (as used for thermocoagulation).

The results of this technique (10 series including 1404 patients with 1–6 years follow-up (mean 4 yr) [115,118,119] show relief in 82–100% of patients (mean 96%) with sustained long–term efficacy in 54.5–91.3% of cases (mean 67%). Regarding adverse effects and neurological complications, trigeminal hypoesthesia is reported in 4–77% over the series and more or less transient masticator paresia in 50–66% of cases. Mortality by carotid puncture is about 2‰.

*2.6.1.4. Percutaneous glycerol injection into the trigeminal cistern.* This technique is much less used in France compared with the preceding techniques. It is based on the neurotoxic effect of glycerol coming into contact with the post-gasserian fibers of the trigeminal nerve [120]. A percutaneous transjugal route is used to puncture Meckel's cave as described above. The patient is in a sitting position under local anesthesia, head turned to the side. A sample of cerebrospinal fluid is drawn before injecting a small quantity of contrast medium to obtain a cisternography and verify the proper position of the needle in Meckel's trigeminal cave. The contrast medium is withdrawn and 0.2–0.4 mL glycerol is injected by small doses to achieve the desired level of hypoesthesia in the painful territories. The main advantage of this technique is the low cost. The main drawback is potential diffusion of glycerol into the basal cisterns where it would have a significant neurotoxic effect.

A review of the literature including 1310 cases with 1–10 years follow-up (mean 6.5 years) showed 42–84% efficacy that is sustained in the long-term for 18–59% (mean 38.5%) [121]. The main complications are: hypoesthesia with dysesthesia in 30% of cases, refractory keratitis in 5%, herpes zoster eruptions in 50% (such eruptions are also noted as complications in the other percutaneous techniques).

*2.6.1.5. Stereotaxic radiosurgery.* Invented by Lars Leksel [122], the minimally invasive technique consists in a single high-dose radiation of the trigeminal nerve using stereotaxic techniques. A stereotaxic apparatus is positioned under local anesthesia followed by CT and MRI to obtain a 3D localization of the target zone.

The retrogasserian target technique developed in Marseille [123,124] is the most widely used. It consists in targeting the retrogasserian portion of the trigeminal nerve along is cisternal trajectory 7.5 mm from its emergence from the brain stem. An 80–90 Gy dose is delivered to a single 4-mm isocenter. It is recommended to not exceed a dose of 15 Gy on the brain stem. A latency period of a few days to a few weeks is generally necessary to obtain a pain relief. With the retrogasserian technique, control was obtained at three months in 92% of patients and 45% of patients were free of acute episodes without medication at 10 years follow-up [124].

Facial hypoesthesia is the only complication after radiosurgery described in the literature. With the retrogasserian technique, it is reported in 20% of cases (5-years actuarial rate). The probability of hypoesthesia described as ''intolerable'' is 0.6% [124].

Several series have reported a slightly higher long-term rate of relief in patients with trigeminal hypoesthesia [125], but this does not appear to be mandatory for successful radiosurgery [124], since certain patients are relieved without hypoesthesia.

*2.6.1.6. Evaluation of neurosurgical techniques.* There is no randomized controlled study in the literature comparing the different surgical techniques or surgical treatment versus medical treatment. A Cochrane review [126] has been published on the only randomized controlled studies available, i.e. three articles focusing on technical points: radiosurgery using one versus two isodoses targeting the trigeminal nerve [127]; use of a navigation system versus C-arm amplifier to target thermocoagulation [128]; pulsed versus standard thermocoagulation [129]. This review emphasized the lack of evaluation by independent observers assessing the treatment outcomes in the prospective series, as well as the difficulty in scoring post-operative relief, even with recognized scoring systems such as the Barrow Neurological Institute scale [130].

Finally, the authors concluded that all neurosurgical procedures provide some relief, with or without medications, and that there is some evidence that percutaneous techniques provide a certain degree of hypoesthesia. There has not been any randomized controlled study on microsurgical vascular decompression, which according to observational series, generates a longer pain-free postoperative period.

In one large meta-analysis reported in the literature [131], The American Academy of Neurology and the European Federation of Neurology Societies indicate:

- that patients treated with microsurgical vascular decompression have a longer pain-free postoperative period than those treated with other surgical techniques, but at the cost of non-negligible morbidity that is lower in teams with a high activity level [132];
- that the radiosurgery technique has the lowest rate of complications, but that there is no randomized controlled study assessing the different surgical techniques such that formal recommendations cannot be established for surgical treatment.

*2.6.2. When should patients suffering from trigeminal neuralgia be referral to neurosurgery?*

The question of referral to neurosurgery depends on three elements.

First, the diagnosis of CTN must be confirmed (Section 2.2), which is relatively easy when the clinical presentation is typical [21]. CTN must also be distinguished from atypical trigeminal neuralgia (e.g. forms with a permanently painful background or with trigeminal sensory or motor deficit). In this later situation, careful history taking should search for the characteristic onset features of the classical form since it is known that with time and medications the pain may be modified becoming atypical.

For all patients, but especially for those with an atypical presentation, careful examination is necessary to search for CTN (Section 2.3). Good quality MRI, with sequences dedicated to study the neurovascular anatomy and the pontocerebellar angle (Section 2.4), should be ordered. Neurovascular compression is a common finding, leading to propose the most adapted neurosurgical technique.

Finally, surgery is proposed for patients with invalidating trigeminal neuralgia that fails to respond to medications or only at the cost of poorly tolerated side effects altering their quality-of-life.

No firm agreement has been reached on the definition of refractory CTN, but the following indications can be proposed:

- failure of well-conducted medical treatment, defined by non-response to medical treatment given at optimal doses and/or non-sustained therapeutic effect, and/or presence of adverse effects and/or a notion of contraindication for treatment;

- failure of three agents (at effective doses) including carbamazepine.

These propositions are to be confirmed once the refractory nature of the CTN is clearly established as a certain number of experts suggest that early surgery should be proposed after carbamazepine failure.

*2.6.3. Strategy for surgical treatment*

The objective of the neurosurgery consultation is to check the three elements noted above (is this a trigeminal neuralgia? is it a classical form? is it unresponsive to medical treatment?) and to present the different surgical options to the patient, emphasizing the risk-benefit ratio, with a final proposition adapted to the patient's particular situation.

The final decision is of course made by the patient, after receiving clear objective information, often explicitly written on the preoperative consent form.

For PTN, treatment will depend on the cause of the neuralgia and its resistance to treatments. For example, for refractory trigeminal neuralgia in a patient with a demyelinating condition, lesion procedures or radiosurgery are generally the first-line proposition, more rarely microsurgical vascular decompression (sometimes nevertheless proposed first for young patients in good general health clearly suffering from neurovascular compression demonstrated on the MRI). In the absence of evidence from controlled clinical trials, local preferences prevail.

For CTN, several situations can be described:

- for a patient in good general health who can tolerate general anesthesia with good MRI evidence of neurovascular compression, it would appear logical to discuss microsurgical vascular decompression as the first-line proposition because this reference technique treats the cause of the CTN and has a good probability of a satisfactory long-term outcome (BNI 1 no pain, no medications). Radiosurgery can also be an alternative proposition, especially since it has a very low rate of hypoesthesia compared with the percutaneous techniques;
- for a patient with an altered general status, or after failure of a microsurgical vascular decompression procedure (and if the postoperative MRI does not show any residual neurovascular compression), a lesion procedure could be proposed depending on local preferences, but also depending on the nerve division concerned by the pain (V1 would be an argument for micro-balloon decompression) and on the anatomic characteristics (a large Meckel's cave would suggest thermocoagulation), or patient cooperation (especially if thermocoagulation is proposed). Depending on the technique chosen, the patient should be informed that relief from neuralgia will often be at the cost of more or less marked hypoesthesia;
- all types of situations between these two are possible. The choice of which surgical procedure to propose will depend on the operator's experience with the different techniques. Current data do not enable an evidence-based decision. For example, with the improved sensitivity and specificity of current imaging techniques, what should be proposed for patients for whom the MRI offers no evidence of neurovascular compression?

The decision for the type of surgical procedure proposed will be made in agreement with the patient after delivery of clear objective information about the predictable benefits and risks of this type of procedure.

## Disclosure of interest

In the last five years, Anne Donnet have received honoraria in clinical trials, contribution to advisory boards, or oral presentations from Amgen, Astellas, Grunenthal, Lilly, Menarini, Novartis, Pfizer, Zambon. In the last five years, Anne Ducros have received honoraria in clinical trials, contribution to advisory boards, or oral presentations from Lilly and Novartis. E Simon, E Cuny, G Demarquay, S De Gaalon, E Guegan Massardier, P Giraud, C Lucas, D Leclercq, M Navez, C Roos, D Valade, P Mertens have no conflict of interest. In the last five years, Michel Lanteri-Minet have received honoraria in clinical trials, contribution to advisory boards, or oral presentations from Allergan, Amgen, Astellas, ATI, BMS, Boehringer, Boston Scientific, CoLucid, Convergence, GlaxoSmithKline, Grunenthal, Lilly, Medtronic, Menarini, MSD, Novartis, Pfizer, ReckittBenckiser, Saint-Jude, Sanofi-Aventis, UCB, Zambon.

## Acknowledgments

We thank the physicians who participated in the reading group: Dr Haiel Alchaar (neurology), Dr Jean-Pierre Alibeu (anesthesia), Dr Delphine Baudoin (neurology), Pr Gilles Brassier (neurosurgery), Dr Hugo Andrés Coca (neurosurgery), Dr Christelle Creac'h (neurology), Pr Evelyne Emery (neurosurgery), Dr Glwadys Fontaine (general medicine), Dr Colette Goujon (neurology), Pr Claire Le Jeune (internal medicine), Dr Mirela Muresan (neurology), Dr Virginie Piano (algology), Pr Jean Regis (neurosurgery) Pr Alain Serrie (anesthesia).

## REFERENCES

[1] Leston JM. Functional anatomy of the trigeminal nerve. Neurochirurgie 2009;55:99–102.
[2] Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. Clin J Pain 2002;18:4–13.
[3] Sindou M, Keravel Y, Simon E, Mertens P. Névralgie du trijumeau et neurochirurgie. EMC (Elsevier Mason SAS, Paris), Neurochirurgie; 2012 [17-023-A-85].
[4] Maarbjerg S, Wolfram F, Gozalov A, Olesen J, Bendtsen L. Significance of neurovascular contact in classical trigeminal neuralgia. Brain 2015;138:311–9.
[5] 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;68:182–6.
[6] Rappaport ZH, Devor M. Trigeminal neuralgia: the role of self-sustaining discharge in the trigeminal ganglion. Pain 1994;56:127–38.
[7] Penman J. Trigeminal neuralgia. In: Vinken PJ, Bruyn GW, editors. Handbook of clinical Neurology, vol. 5. Amsterdam: NorthHoland; 1968. p. 296–322.

[8] El-Tallawy HN, Farghaly WM, Rageh TA, Shehata GA, Abdel Hakeem MN, Badry R, et al. Prevalence of trigeminal neuralgia in Al-Quseir city (Red sea Governorate), Egypt. Clin Neurol Neurosurg 2013;115(9):1792–4.
[9] Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. Ann Neurol 1990;27(1):89–95.
[10] Rozen TD. Trigeminal neuralgia and glossopharyngeal neuralgia. Neurol Clin 2004;22(1):185–206.
[11] Maarbjerg S, Gozalov A, Olesen J, Bendtsen L. Trigeminal neuralgia-a prospective systematic study of clinical characteristics in 158 patients. Headache 2014;54(10):1574–82.
[12] Kalyanaraman S, Ramamurthi B. Trigeminal neuralgia-a review of 331 cases. Neurol India 1970;18(Suppl. 1):100–8.
[13] Manzoni GC, Torelli P. Epidemiology of typical and atypical craniofacial neuralgias. Neurol Sci 2005;26(Suppl. 2):s65–7.
[14] Pascual J, Berciano J. Experience in the diagnosis of headaches that start in elderly people. JNNP 1994;57:1255–7.
[15] Bahgat D, Ray DK, Raslan AM, McCartney S, Burchiel KJ. Trigeminal neuralgia in young adults. J Neurosurg 2011;114(5):1306–11.
[16] Pan SL, Yen MF, Chiu YH, Chen LS, Chen HH. Increased risk of trigeminal neuralgia after hypertension: a population-base study. Neurology 2011;77(17):1605–10.
[17] Rushton JG, MacDonald HN. Trigeminal neuralgia; special considerations of nonsurgical treatment. J Am Med Assoc 1957;165(5):437–40.
[18] Laurent B, Keravel Y, Sindou M. Clinical aspects of trigeminal neuralgia. Neurochirurgie 2009;55(2):181–4.
[19] Navez M, Créac'h C, Koenig M, Cathébras P, Laurent B. Primary and atypical facial pain: diagnosis and treatment. Rev Med Interne 2005;26(9):703–16.
[20] Bangash TH, Trigeminal Neuralgia:. Frequency of occurence in different nerve branches. Anesth Pain 2011;1(2):70–2.
[21] Headache Classification Committee of the International Headache. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629–808.
[22] Maarbjerg S, Sørensen MT, Gozalov A, Bendtsen L, Olesen J. Field-testing of the ICHD-3 beta diagnostic criteria for classical trigeminal neuralgia. Cephalalgia 2015;35(4):291–300.
[23] Mulleners WM, Verhagen WI. Cluster–tic syndrome. Neurology 1996;47(1):302.
[24] Levin M, Ward TN, Larson E. Migraine-tic syndrome: a case report of a new headache type. Cephalalgia 2004;24(1):72–3.
[25] Boes CJ, Matharu MS, Goadsby PJ. The paroxysmal hemicrania-tic syndrome. Cephalalgia 2003;23(1):24–8.
[26] Zakrzewska JM, Linskey ME. Trigeminal neuralgia. BMJ 2015;12:350.
[27] Chen J, Sindou M. Vago-glossopharyngeal neuralgia: a literature review of neurosurgical experience. Acta Neurochir 2015;157:311–21.
[28] Blumenfeld A, Nikolskaya G. Glossopharyngeal neuralgia. Curr Pain Headache Rep 2013;17:343.
[29] Bruyn GW. Nervus intermedius neuralgia (Hunt). Cephalalgia 1984;4:71–8.
[30] Smith JH, Robertson CE, Garza I, Cutrer FM. Triggerless neuralgic otalgia: a case series and systematic literature review. Cephalalgia 2013;33:914–23.
[31] Shoja MM, Tubbs RS, Ghabili K, Loukas M, Oakes WJ, Cohen-Gadol AA. Johan Georg Raeder (1889-1959) and paratrigeminal sympathetic paresis. Childs Nerv Syst 2010;26:373–6.
[32] Seymour S. Reader Syndrome. Arch Neurol 2001;58(4):661–2.
[33] Goadsby P. J. Raeder's syndrome: paratrigeminal paralysis of the oculopupillary sympathetic system. JNNP 2002;72:297–9.
[34] Lambru G, Matharu MS. SUNCT, SUNA and trigeminal neuralgia: different disorders or variants of the same disorder? Curr Opin Neurol 2014;27(3):325–31.
[35] Bussone G, Leone M, Dalla Volta G, Strada L, Gasparotti R, Di Monda V. Short-lasting unilateral neuralgiform headache attacks with tearing and conjunctival injection: the first "symptomatic" case? Cephalalgia 1991;11(3):123–7.
[36] Bouhassira D, Attal N, Estève M, Chauvin M. SUNCT syndrome. A case of transformation from trigeminal neuralgia? Cephalalgia 1994;14(2):168–70.
[37] Sesso RM. SUNCT syndrome or trigeminal neuralgia with lacrimation and conjunctival injection? Cephalalgia 2001;21(2):151–3.
[38] May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metab 1999;19(2):115–27.
[39] Cuadrado M-L, Ordás CM, Sánchez-Lizcano M, Casas-Limón J, Matías-Guiu JA, García-García ME, et al. Epicrania fuax: 19 cases of an emerging headache. Headache 2013;53:764–74.
[40] Guerrero AL, Cuadrado ML, Porta-Etessam J, García-Ramos R, Gómez-Vicente L, Herrero S, et al. Epicrania Fugax: ten new cases ant therapeutic results. Headache 2010;50:451–8.
[41] Pareja JA, Cuadrado ML, Fernández-de-las-Peñas C, Caminero AB, Nieto C, Sánchez C, et al. Epicrania fugax: an ultrabrief paroxysmal epicranial pain. Cephalalgia 2008;28:257–63.
[42] Peker S, Dinçer A, Necmettin Pamir M. Vascular compression of the trigeminal nerve is a frequent finding in asymptomatic individuals: 3-T MR imaging of 200 trigeminal nerves using 3D CISS sequences. Acta Neurochir 2009;151(9):1081–8.
[43] Antonini G, Di Pasquale A, Cruccu G, Truini A, Morino S, Saltelli G, et al. Magnetic resonance imaging contribution for diagnosing neurovascular contact in classical trigeminal neuralgia: a blinded case-control study and meta-analysis. Pain 2014;155(8):1464–71.
[44] DeSouza DD, Hodaie M, Davis KD. Diffusion imaging in trigeminal neuralgia reveals abnormal trigeminal nerve and brain white matter. Pain 2014;155(9):1905–6.
[45] 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;15:1013–28.
[46] Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, 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;71:1183–90.
[47] Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2014;4:CD005451. http://dx.doi.org/10.1002/14651858.CD005451.pub3.
[48] Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, et al. European Federation of Neurological Societies, EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17(9):1113–23.

[49] Zakrzewska JM. Robust randomised control trials needed for drug treatments for trigeminal neuralgia. Evid Based Dent 2006;7(4):107.
[50] Zakrzewska JM, Linskey ME. Trigeminal neuralgia. Trigeminal neuralgia 2014;348:g474. http://dx.doi.org/10.1136/bmj.g474.
[51] Lindstrom P, Lindblom U. The analgesic effect of tocainide in trigeminal neuralgia. Pain 1987;28:45–50.
[52] Beydoun A. Clinical use of tricyclic anticonvulsants in painful neuropathies and bipolar disorders. Epilepsy Behav 2002;3:S18–22.
[53] Lechin F, van der Dijs B, Lechin ME, Amat J, Lechin AE, Cabrera A, et al. Pimozide therapy for trigeminal neuralgia. Arch Neurol 1989;46:960–3.
[54] McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ 1995;311(7012):1047–52.
[55] 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;15:34.
[56] Sweetman S, editor. Martindale: The Complete Drug Reference. 4th ed. London: Pharmaceutical Press; 2005. p. 353–8 [ISBN 0 85369 550 4].
[57] Chung WH, Hung SI, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin Drug Saf 2010;9:15–21.
[58] Kulkantrakorn K, Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Prabmechai N, Vannaprasaht S, et al. HLA-B*1502 strongly predicts carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Thai patients with neuropathic pain. Pain Practice 2012;12(3):202–8.
[59] Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? Epilepsia 2013;54(1):11–27.
[60] VIDAL. https://vidal.fr [Copyright 2017].
[61] Mc Kee PJW, BlacllawJ, Butler E, Gilham RA, Brodie MJ. Monotherapy with conventional and controlled-release carbamazepine: a double-blind double-dummy comparison in epileptic patients. Br J Clin Pharmacol 1991;32:99–104.
[62] Genin E, Chen DP, Hung SI, Sekula P, Schumacher M, Chang PY, et al. Roujeau JC.HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. Pharmacogenomics J 2014;14(3):281–8.
[63] Liebel JT, Menger N, Langohr H. Oxcarbazepine in der Behandlung der Trigeminusneuralgie. Nervenheilkunde 2001;20:461–5.
[64] Gomez-Arguelles JM, Dorado R, Sepulveda JM, Herrera A, Arrojo FG, Aragón E, et al. Oxcarbazepine monotherapy in carbamazepine-unresponsive trigeminal neuralgia. J Clin Neurosci 2008;15(5):516–9.
[65] Lunardi G, Leandri M, Albano C, et al. Clinical effectiveness of lamotrigine and plasma levels in essential and symptomatic trigeminal neuralgia. Neurology 1997;48:1714–7.
[66] Canavero S, Bonicalzi V. Lamotrigine control of trigeminal neuralgia: an expanded study. J Neurol 1997;244:527–32.
[67] Zakrzewska JM1, Chaudhry Z, Nurmikko TJ, Patton DW, Mullens EL. Lamotrigine (lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. Pain 1997;73(2):223–30.
[68] Wiffen PJ, Derry S, Moore RA. Lamotrigine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev 2013;Issue 12. http://dx.doi.org/10.1002/14651858.CD006044.pub4 [Art. No.: CD006044].
[69] Shaikh S, Yaacob HB, Abd Rahman RB. Lamotrigine for trigeminal neuralgia: efficacy and safety in comparison with carbamazepine. J Chin Med Assoc 2011;74(6):243–9.
[70] Iannone A, Baker AB, Morrell F. Dilantin in the treatment of trigeminal neuralgia. Neurology 1958;8:126–8.
[71] Braham J, Saia A. Phenytoin in the treatment of trigeminal and other neuralgias. Lancet 1960;2:892–3.
[72] Sindrup SH1, Jensen TS. Pharmacotherapy of trigeminal neuralgia. Clin J Pain 2002;18(1):22–7.
[73] Lemos L, Flores S, Oliveira P, Almeida A. Gabapentin supplemented with ropivacain block of trigger points improves pain control and quality of life in trigeminal neuralgia patients when compared with gabapentin alone. Clin J Pain 2008;24:64–75.
[74] Obermann M, Yoon MS, Sensen K, Maschke M, Diener HC, Katsarava Z. Efficacy of pregabalin in the treatment of trigeminal neuralgia. Cephalalgia 2008;28:174–81.
[75] Pérez C, Navarro A, Saldaña MT, Martínez S, Rejas J. Patient-reported outcomes in subjects with painful trigeminal neuralgia receiving pregabalin: evidence from medical practice in primary care settings. Cephalalgia 2009;29(7):781–90.
[76] Gilron I, Booher SL, Rowan JS, Max MB. Topiramate in trigeminal neuralgia: a randomized, placebo-controlled multiple crossover pilot study. Clin Neuropharmacol 2001;24(2):109–12.
[77] Domingues RB, Kuster GW, Aquino CC. Treatment of trigeminal neuralgia with low doses of topiramate. Arq Neuropsiquiatr 2007;65(3B):792–4.
[78] Wang QP1, Bai M. Topiramate versus carbamazepine for the treatment of classical trigeminal neuralgia: a meta-analysis. CNS Drugs 2011;25(10):847–57.
[79] Jorns TP, Johnston A, Zakrzewska JM. Pilot study to evaluate the efficacy and tolerability of levetiracetam (Keppra) in treatment of patients with trigeminal neuralgia. Eur J Neurol 2009;16(6):740–4.
[80] Mitsikostas DD, Pantes GV, Avramidis TG, Karageorgiou KE, Gatzonis SD, Stathis PG, et al. An observational trial to investigate the efficacy and tolerability of levetiracetam in trigeminal neuralgia. Headache 2010;50(8):1371–7.
[81] Zhang J, Yang M, Zhou M, He L, Chen N, Zakrzewska JM. Non-antiepileptic drugs for trigeminal neuralgia. Cochrane Database Syst Rev 2013;Issue 12. http://dx.doi.org/10.1002/14651858.CD004029.pub4 [Art. No.: CD004029].
[82] Fromm GH, Terrence CF, Chattha AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. Ann Neurol 1984;15:240–4.
[83] Vilming ST, Lyberg T, Lataste X. Tizanidine in the management of trigeminal neuralgia. Cephalalgia 1986;6(3):181–2.
[84] Fromm GH, Aumentado D, Terrence CF. A clinical and experimental investigation of the effects of tizanidine in trigeminal neuralgia. Pain 1993;53(3):265–71.
[85] Lemos L, Fontes R, Flores S, Oliveira P, Almeida A. Effectiveness of the association between carbamazepine and peripheral analgesic block with ropivacaine for the treatment of trigeminal neuralgia. J Pain Res 2010;3:201–12. http://dx.doi.org/10.2147/JPR.S13154.
[86] Beloeil H, Viel E, Navez ML, Fletcher D, Peronnet D. Guidelines for regional anesthetic and analgesic techniques in the treatment of chronic pain syndromes. Recommandation formalisée d'experts. Ann Fr Anesth Reanim 2013;32(4):275–84.
[87] Piovesan EJ, Teive HG, Kowacs PA, Della Coletta MV, Werneck LC, Silberstein SD. An open study of botulinum-A toxin treatment of trigeminal neuralgia. Neurology 2005;65(8):1306–8.

[88] Wu CJ, Lian YJ, Zheng YK, Zhang HF, Chen Y, Xie NC, et al. Botulinum toxin type A for the treatment of trigeminal neuralgia: results from a randomized, double-blind, placebo-controlled trial. Cephalalgia 2012;32(6):443–50.
[89] Zúñiga C, Piedimonte F, Díaz S, Micheli F. Acute treatment of trigeminal neuralgia with onabotulinum toxin A. Clin Neuropharmacol 2013;36(5):146–50.
[90] Sirois D, Epler M, Toufani M, Blitzer A. Botulinum toxin-A in trigeminal neuralgia: outcome of placebo-controlled RCT. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:e130.
[91] Linde M, Hagen K, Stovner LJ. Botulinum toxin treatment of secondary headaches and cranial neuralgias: a review of evidence. Acta Neurol Scand Suppl 2011;50–5.
[92] Leandri M, Lundardi G, Inglese M, Messmer-Uccelli M, Mancardi GL, Gottlieb A, et al. Lamotrigine in trigeminal neuralgia secondary to multiple sclerosis. J Neurol 2000;247(7):556–8.
[93] Khan OA. Gabapentin relieves trigeminal neuralgia in multiple sclerosis patients. Neurology 1998;51(2):611–4.
[94] Solaro C, Lunardi GL, Capello E, Inglese M, Messmer Uccelli M, Uccelli A, et al. An open-label trial of gabapentin treatment of paroxysmal symptoms in multiple sclerosis patients. Neurology 1998;51(2):609–11.
[95] Solaro C, Messmer Uccelli M, Uccelli A, Leandri M, Mancardi GL. Low-dose gabapentin combined with either lamotrigine or carbamazepine can be useful therapies for trigeminal neuralgia in multiple sclerosis. Eur Neurol 2000;44(1):45–8.
[96] Zvartau-Hind M, Din MU, Gilani A, Lisak RP, Khan OA. Topiramate relieves refractory trigeminal neuralgia in MS patients. Neurology 2000;55(10):1587–8.
[97] Solaro C, Uccelli MM, Brichetto G, Gaspperini C, Mancardi G. Topiramate relieves idiopathic and symptomatic trigeminal neuralgia. J Pain Symptom Manage 2001;21(5):367–8.
[98] Siniscalchi A, Gallelli L, Scornaienghi D, Mancuso F, De Sarro G. Topiramate therapy for symptomatic trigeminal neuralgia. Clin Drug Investig 2006;26(2):113–5.
[99] Reder AT, Arnason BG. Trigeminal neuralgia in multiple sclerosis relieved by a prostaglandin E analogue. Neurology 1995;45(6):1097–100.
[100] DMKG., study group. Misoprostol in the treatment of trigeminal neuralgia associated with multiple sclerosis. J Neurol 2003;250(5):542–5.
[101] Tate R, Rubin LM, Krajewski KC. Treatment of refractory trigeminal neuralgia with intravenous phenytoin. Am J Health Syst Pharm 2011;68(21):2059–61.
[102] Cheshire WP. Fosphenytoin: an intravenous option for the management of acute trigeminal neuralgia crisis. J Pain Symptom Manage 2001;21(6):506–10.
[103] Chaudhry P, Friedman DI. Intravenous lidocaine treatment in classical trigeminal neuralgia with concomitant persistent facial pain. Headache 2014;54(8):1376–9.
[104] Soleimanpour H, Aghamohammadi D, Ghaffarzad A, Golzari SE, Safari S, Soleimanpour M. Novel treatment in refractory tic douloureux. J Clin Anesth 2014;26(6):495–6.
[105] Dandy WE. Concerning the cause of trigeminal neuralgia. Am J Surg 1934;24(2):447–55.
[106] Gardner WJ, Miklos MV. Response of trigeminal neuralgia to decompression of sensory root; discussion of cause of trigeminal neuralgia. J Am Med Assoc 1959;170(15):1773–6.
[107] Jannetta PJ. Microsurgical approach to the trigeminal nerve for tic douloureux. Prog Neurol Surg 1976;7:180–200.
[108] Sindou M, Amrani F, Mertens P. Does microsurgical vascular decompression for trigeminal neuralgia work through a neo-compressive mechanism? Anatomical-surgical evidence for a decompressive effect. Acta Neurochir Suppl (Wien) 1991;52:127–9.
[109] Sindou M, Leston JM, Decullier E, Chapuis F. Microvascular decompression for trigeminal neuralgia: the importance of a noncompressive technique–Kaplan-Meier analysis in a consecutive series of 330 patients. Neurosurgery 2008;63(4 Suppl. 22):341–50 [discussion 50-1].
[110] Sindou M, Leston J, Decullier E, Chapuis F. Microvascular decompression for primary trigeminal neuralgia: long-term effectiveness and prognostic factors in a series of 362 consecutive patients with clear-cut neurovascular conflicts who underwent pure decompression. J Neurosurg 2007;107(6):1144–53.
[111] 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):1235–45 [discussion 45].
[112] Kalkanis SN, Eskandar EN, Carter BS, Barker FG 2nd. Microvascular decompression surgery in the United States, 1996 to 2000: mortality rates, morbidity rates, and the effects of hospital and surgeon volumes. Neurosurgery 2003;52(6):1251–61.
[113] Alvernia J, Wydh E, Simon E, Sindou M, Mertens P. Microsurgical anatomy of the transoval percutaneous route to the trigeminal cave and the trigeminal ganglion. Neurochirurgie 2009;55(2):87–91.
[114] Härtel F. Uber die intracranielle Injektions behandlung der trigeminusneuralgie. Med Klin 1914;10:582.
[115] Tatli M, Satici O, Kanpolat Y, Sindou M. Various surgical modalities for trigeminal neuralgia: literature study of respective long-term outcomes. Acta Neurochir (Wien) 2008;150(3):243–55.
[116] Kanpolat Y, Savas A, Bekar A, Berk C. Percutaneous controlled radiofrequency trigeminal rhizotomy for the treatment of idiopathic trigeminal neuralgia: 25-year experience with 1,600 patients. Neurosurgery 2001;48(3):524–32 [discussion 32-4].
[117] Sindou M, Tatli M. Treatment of trigeminal neuralgia with thermorhizotomy. Neurochirurgie 2009;55(2):203–10.
[118] Keravel Y, Gaston A, Ciampi de Andrade D, Mencattini G, Le Guerinel C. Balloon compression for the treatment of trigeminal neuralgia. Neurochirurgie 2009;55(2):197–202.
[119] Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. J Neurosurg 1983;59(6):1007–12.
[120] Hakanson S. Trigeminal neuralgia treated by the injection of glycerol into the trigeminal cistern. Neurosurgery 1981;9(6):638–46.
[121] Sindou M, Tatli M. Treatment of trigeminal neuralgia with glycerol injection at the gasserian ganglion. Neurochirurgie 2009;55(2):211–2.
[122] Leksell L. Sterotaxic radiosurgery in trigeminal neuralgia. Acta Chir Scand 1971;137(4):311–4.
[123] Regis J, Metellus P, Hayashi M, Roussel P, Donnet A, Bille-Turc F:. Prospective controlled trial of gamma knife surgery for essential trigeminal neuralgia. J Neurosurg 2006;104:913–24.
[124] Regis J, Tuleasca C, Resseguier N, Carron R, Donnet A, Gaudart J, et al. Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. J Neurosurg 2016;124:1079–987.
[125] Regis J, Arkha Y, Yomo S, Murata N, Roussel P, Donnet A, et al. Radiosurgery in trigeminal neuralgia: long-term results and influence of operative nuances. Neurochirurgie 2009;55(2):213–22.

[126] Zakrzewska JM, Akram H. Neurosurgical interventions for the treatment of classical trigeminal neuralgia. Cochrane Database Syst Rev 2011;9:CD007312.
[127] Flickinger JC, Pollock BE, Kondziolka D, Phuong LK, Foote RL, Stafford SL, et al. Does increased nerve length within the treatment volume improve trigeminal neuralgia radiosurgery? A prospective double-blind, randomized study. Int J Radiat Oncology Biol Phys 2001;51(2):449–54.
[128] Xu SJ, Zhang WH, Chen T, Wu CY, Zhou MD. Neuronavigator-guided percutaneous radiofrequency thermocoagulation in the treatment of intractable trigeminal neuralgia. Chin Med J (Engl) 2006;119(18): 1528–35.
[129] Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional radiofrequency in the treatment of idiopathic trigeminal neuralgia. Eur J Pain 2007;11(3):309–13.
[130] Rogers CL, Shetter AG, Fiedler JA, Smith KA, Han PP, Speiser BL. Gamma knife radiosurgery for trigeminal neuralgia: the initial experience of The Barrow Neurological Institute. Int J Radiat Oncology Biol Phys 2000;47(4):1013–9.
[131] Gronseth G, Cruccu G, Alksne J, Argoff C, Brainin M, Burchiel K, 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;71:1183–90.
[132] Kalkanis SN, Eskandar EN, Carter BS, Barker FG 2nd. Microvascular decompression surgery in the United States, 1996 to 2000: mortality rates, morbidity rates, and the effects of hospital and surgeon volumes. Neurosurgery 2003;52(6):1251–61.