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# Cranial neuralgias: from physiopathology to pharmacological treatment

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**Abstract** Cranial neuralgias are paroxysmal painful disorders of the head characterised by some shared features such as unilaterality of symptoms, transience and recurrence of attacks, superficial and "shock-like" quality of pain and the presence of triggering factors. Although rare, these disorders must be promptly recognised as they harbour a relatively high risk for underlying compressive or inflammatory disease. Nevertheless, misdiagnosis is frequent. Trigeminal and glossopharyngeal neuralgias are sustained in most cases by a neurovascular conflict in the posterior fossa resulting in a hyperexcitability state of the trigeminal circuitry. If the aetiology of trigeminal neuralgia (TN) and other typical neuralgias must be brought back to the peripheral injury, their pathogenesis could involve central allodynic mechanisms, which, in patients with inter-critical pain, also engage the nociceptive neurons at the thalamic-cortical level. Currently available medical treatments for TN and other cranial neuralgias are reviewed.

**Keywords** Cranial neuralgias · Trigeminal neuralgia · Glossopharyngeal neuralgia · Physiopathology · Treatment · Review

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## Introduction

Cranial neuralgias are paroxysmal painful disorders of the head, rarely seen in clinical practice. They are characterised by some shared features, such as unilaterality of symptoms, transience and recurrence of attacks, superficial and "shock-like" quality of pain, and the presence of triggering factors. Although trigeminal neuralgia (TN) and glossopharyngeal neuralgia are sustained in most cases by a neuro-vascular conflict in the posterior fossa, cranial neuralgias share a relatively high risk for a compressive underlying cause different from the neurovascular conflict.

## Classification, epidemiology and clinical aspects

The second edition of the International Classification of Headache Disorders (ICHD-II) [1] codes the cranial neuralgias in Chapter 13 and provides the diagnostic criteria for 18 different subtypes (Table 1) including a number of heterogeneous central causes of facial pain, which will not be discussed here.

### Trigeminal neuralgia

*Classification and epidemiology*

According to the ICHD-II the diagnosis of Classical Trigeminal Neuralgia has to fulfil the criteria listed in Table 2. These criteria must be also present in Symptomatic Trigeminal Neuralgia but in the latter form additional signs and symptoms such as a mild ache between attacks and the presence of sensorial defect in the affected territory are admitted. The boundary between classical and symptomatic forms of TN is therefore rather

**Table 1** ICHD-II classification of cranial neuralgias

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| 13. Cranial neuralgias and central causes of facial pain |
| 13.1 Trigeminal neuralgia |
| 13.1.1 Classical trigeminal neuralgia |
| 13.1.2 Symptomatic trigeminal neuralgia |
| 13.2 Glossopharyngeal neuralgia |
| 13.2.1 Classical glossopharyngeal neuralgia |
| 13.2.2 Symptomatic glossopharyngeal neuralgia |
| 13.3 Nervus intermedius neuralgia |
| 13.4 Superior laryngeal neuralgia |
| 13.5 Nasociliary neuralgia |
| 13.6 Supraorbital neuralgia |
| 13.7 Other terminal branch neuralgias |
| 13.8 Occipital neuralgia |
| 13.9 Neck-tongue syndrome |
| 13.10 External compression headache |
| 13.11 Cold-stimulus headache |
| 13.11.1 Headache attributed to external application of a cold stimulus |
| 13.11.2 Headache attributed to ingestion or inhalation of a cold stimulus |
| 13.12 Constant pain caused by compression, irritation or distortion of cranial nerves or upper cervical roots by structural lesions |
| 13.13 Optic neuritis |
| 13.14 Ocular diabetic neuropathy |
| 13.15 Head or facial pain attributed to herpes zoster |
| 13.15.1 Head or facial pain attributed to acute herpes zoster |
| 13.15.2 Post-herpetic neuralgia |
| 13.16 Tolosa-Hunt syndrome |
| 13.17 Ophthalmoplegic 'migraine' |
| 13.18 Central causes of facial pain |
| 13.18.1 Anaesthesia dolorosa |
| 13.18.2 Central post-stroke pain |
| 13.18.3 Facial pain attributed to multiple sclerosis |
| 13.18.4 Persistent idiopathic facial pain |
| 13.18.5 Burning mouth syndrome |
| 13.19 Other cranial neuralgia or other centrally mediated facial pain |

**Table 2** ICHD-II criteria for 13.1.1 Classic trigeminal neuralgia

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| 13.1.1 Classic trigeminal neuralgia |
| A. Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes, affecting one or more divisions of the trigeminal nerve |
| B. Pain has at least one of the following characteristics: |
| 1. Intense, sharp, superficial or stabbing |
| 2. Precipitated from trigger areas or by trigger factors |
| C. Attacks are stereotyped in the individual patient |
| D. There is no clinically evident neurological deficit |
| E. Not attributed to another disorder |

frail and neuroimaging investigations are highly recommended, especially in the cases of recent onset.

Although TN is the most common among the cranial neuralgias, with an incidence of 3–5 new cases for 100,000 subjects per year [2] and a prevalence of 15.5 cases per 100,000 [3], it is still to be considered a rare disease. TN can appear at any age, but the onset is after age 40 in 90% of the cases; women are more likely to be affected than men, with a gender ratio of 2:1. About 2% of the patients with multiple sclerosis (MS) can experience a pain disorder nearly identical to TN [4]; despite the evidence of a substantial clinical overlap [5], neuralgias related to MS are not classified among symptomatic forms, but in a specific subgroup of the same ICHD-II chapter (13.18.3. Facial Pain Attributed Multiple to Sclerosis).

*Clinical aspects*

The pain in TN usually occurs in brief paroxysmal attacks either isolated or in short clusters. Typically, it is felt superficially and is described as extremely severe and of burning or "shock-like" quality. Attacks tend to be stereotyped and are strictly confined to the territory of distribution of one or more branches of the trigeminal nerve of a single side. The maxillary and mandibular nerves, in combination or alone, are more often affected than the ophthalmic nerve, which is involved alone in less than 5% of cases [6]. The single attack lasts characteristically from less than a second to a few seconds, but it can be present in clusters up to 2 min in length; in many cases it is followed by a brief refractory period during which a new stimulation is not able to evoke the

pain. The location of the pain is typically unilateral, but it can be bilateral in patients with MS, although asynchronously. Interestingly, the right side is more often involved than the left. The disorders seldom affect more members of the same family [7, 8]. The attacks can occur spontaneously or they can be provoked by stimulation of specific trigger areas. These are often localised in the skin around the mouth and at the sides of the nose, due to its higher sensorial innervation, and can also involve the gums. In rare cases the attacks are evoked by extra-trigeminal triggers, such as olfactory or gustatory stimuli [9]. Characteristically, tactile stimuli can trigger an attack while painful stimuli usually do not. Furthermore, the provoking stimuli fall within a physiological range of intensity like those arising from normal daily activities: brushing teeth, shaving, chewing, yawning or swallowing. Quite often patients can experience a muscle spasm involving the mimic muscles occasionally associated with other involuntary movements. The presence of unintentional movements have led to the term "tic douloureux", often used to indicate this condition. Involvement of the autonomic nervous system is not usually present, but when the ophthalmic nerve is affected it is possible to observe a modest tearing discharge without conjunctival injection or any other autonomic sign. These cases create problems of differential diagnosis with the rare primary headache coded in the ICHD-II as sudden onset unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT). Differential diagnosis between TN and SUNCT depends on the different intensity and variety of autonomic symptoms involved [10].

*Clinical course*

The onset of a typical TN is quite often preceded by a painful condition affecting mandibular or maxillary areas. The pain can be variable but it usually resembles the pain of a sinus infection or toothache. This condition is named pretrigeminal neuralgia [11]. It can precede the onset of typical neuralgic symptoms by years and can present with episodes of long-lasting facial pain sometimes triggered by chewing or drinking warm or cold foods. Pretrigeminal neuralgia is responsive to the specific drug treatments for TN and represents a common cause of misdiagnosis in the early phases of disease. The clinical course of the definite disease is very often intermittent; spontaneous remissions of at least 6 months are described in 50% of cases and remissions of at least one year in about 25% of patients [12]. Nevertheless, the usual pattern is for a progressive worsening with increased severity and frequency of pain, prolonged duration of the active phases, lower response to drugs, possible development of constant soreness between attacks (inter-critical pain) and clinically evident defects of trigeminal sensory function.

*Diagnosis*

A clinical presentation with brief attacks of strict unilateral shock-like pain within trigeminal areas and the presence of typical trigger areas makes this condition easy to recognise. Nevertheless TN is often misdiagnosed in patients affected by cluster headache or sometimes by a side-locked migraine; conversely the correct diagnosis can be delayed until the failure of inappropriate odontostomatological treatments [11].

Like most typical neuralgias, TN is symptomatic in 5%–10% of symptomaticity cases [13]. The recent ICHD-II revision of the International Headache Society (IHS) classification considers the presence of inter-critical pain and sensory deficits as possible predictors of a structural cause; however inter-critical pain and sensory deficits have low specificity [14] and must be cautiously taken into account, especially in cases with a long duration of illness [15]. A possible structural cause must be considered in case of onset before 40 years, bilaterality of the symptoms, presence of neurological signs or atypical pain in terms of quality, affected area, intensity or duration. In these conditions extensive neuroimaging studies are highly recommended. Arterial hypertension is considered a possible risk factor [16]. Included among the possible causes of secondary TN are: MS; Charcot-Marie-Tooth disease [17], meningiomas, neurinomas and other slow-growing tumours of posterior cranial fossa; syringobulbia; arachnoiditis; basilar artery and internal carotids aneurysms; fractures of the cranial base; and herpes zoster.

Recent evidence [18] suggests that trigeminal reflexes studies by blink reflex and laser evoked potentials (LEPs) can differentiate symptomatic TN from classic TN more reliably than any other clinical data, including age of onset. Therefore such techniques could be performed to select those patients who need to be further investigated with neuroimaging.

## Glossopharyngeal neuralgia

Neuralgia of glossopharyngeal nerve (GFN) is a rare entity with an estimated incidence of 0.8 cases per 100,000 [2]. As a matter of fact, authors from the Mayo Clinic have reported only 217 cases in 55 years [19]. The prevalence, compared to NT, is of about 1 case of GFN for every 75 of TN [18]. As for other neuralgias, this form is separated into Classical and Symptomatic, which differ mostly by the presence of inter-critical pain and sensory deficit in the territories of distribution of the nerve. The ICHD-II diagnostic criteria for the Classic form of GFN are shown in Table 3. The term Classical, which is also used for TN, has been introduced to make the diagnosis compatible with the presence of neurovascular conflict in posterior fossa. Males and females are

**Table 3** ICHD-II criteria for 13.2.1 Classical glossopharyngeal neuralgia

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| 13.2.1 Classical glossopharyngeal neuralgia |
| A. Paroxysmal attacks of facial pain lasting from a fraction of a second to 2 minutes and fulfilling criteria B and C |
| B. Pain has all of the following characteristics: |
| 1. Unilateral location |
| 2. Distribution within the posterior part of the tongue, tonsillar fossa, pharynx or beneath the angle of the lower jaw and/or in the ear |
| 3. Sharp, stabbing and severe |
| 4. Precipitated by swallowing, chewing, talking, coughing and/or yawning |
| C. Attacks are stereotyped in the individual patient |
| D. There is no clinically evident neurological deficit |
| E. Not attributed to another disorder |

equally affected. Interestingly, the left nerve is more often involved than the right one [20].

From a clinical point of view GFN shares the same basic features of TN with a typical neuralgic pain occurring in a paroxysmal way. Pain is habitually located in the tonsillar region and in the back of the pharynx, with possible transmission to the lower portion of the jaw and to the ear. The painful attacks can be triggered by ordinary activity such as swallowing, chewing, speaking, coughing, sneezing, throat-clearing or by head rotation. The association with NT is not rare, accounting for about 10% of cases [6]. The clinical course is usually episodic, with active phases lasting weeks or months and off-pain periods of different length. Pain attacks are described to worsen in frequency or severity over time, whereas the remission phases tend to shorten.

The pain episodes usually last from less than a second up to 2 min but sometimes they can occur in rapid and continuous sequence (*status neuralgicus*). When the pain is triggered by swallowing, feeding can be impaired for long periods and it is not rare for these patients to undergo a striking weight loss. Unilaterality is a key sign and when the pain is bilateral a possible association with MS must be suspected. In about 2% of cases, patients can experience severe bradycardia with subsequent lost of consciousness [6]. Similarly to TN, the risk of an underlying cause is relatively high and it is always advisable to perform a wide diagnostic work-up in these patients.

Causes of symptomatic GFN are: tumours of the cerebellumpontine angle, nasopharyngeal carcinomas, aneurysms of the carotid, abscesses of tonsils, rare neurinomas of the IX nerve and MS. Worth noting is the syndrome of the stylohyoid apophysis (Eagle's syndrome) [21], in which the neuralgic symptoms are due to irritation of the glossopharyngeal nerve in its esocranial path when stylohyoid process is longer than normal (over 4.5 cm instead of 2.5 cm). Local anaesthesia (lidocaine 10%) of pharyngeal and tonsillar triggers areas has diagnostic value.

### Nervus intermedius neuralgia

Also known as *geniculate* or *Hunt's neuralgia*, this form is among the less frequent of the series. Typical clinical features are [22]: paroxysmal unilateral pain lasting from seconds to a few minutes localised deeply in the ear; radiation of pain to the external auditory meatus; occurrence of vegetative symptoms such as abnormal tearing and salivation, taste problems; relapsing course with active phases of disease and symptom-free periods; and higher prevalence in females. Geniculate neuralgia is often correlated with shingles of the external auditory duct.

### Occipital neuralgia

Occipital neuralgia is classically characterised by unilateral paroxysmal pain in the areas corresponding to location of lesser and greater occipital nerves. The pain can be associated to inter-critical pain and dysaesthesia [23]. The disease can occur after traumas of the occipital area, even if they are irrelevant, whereas it can be also sustained by numerous medical conditions such as Arnold-Chiari malformation, bone and joint diseases, herpetic neuropathies and masses that can compress the nerve along its path [24].

The pure form (Arnold neuralgia) is very rare compared to the countless syndromes affecting cervical spine, with which it shares some overlapping features. A selective tenderness after pressure on trigger points is also reported.

### Superior laryngeal nerve neuralgia

This is an extremely rare form. It is characterised by paroxysmal pain of the lateral part of throat, of the submandibular region, around the ear and along the neck; the paroxysms can be triggered by chewing, and head extension or rotation [25]. The superior laryngeal nerve is a branch of the vagus nerve and it is involved in the sensorial-motor innervation of the larynx and in the glottic reflex. It enters the larynx crossing the lateral aspect of the hyoid membrane. The pain, habitually unilateral, occurs in attacks of a few minutes that re-occur up to 10–30 times in 24 h with clustering of different length and tendency to the remission. The attacks can be associated to an uncontrollable cough and can be triggered by compression of the point of entry through the hyoid

membrane, sideways and immediately above the larynx. Benefits emerging from anaesthesia of these regions are of diagnostic value.

## Pathophysiology of the cranial neuralgias

Over the last decades cranial neuralgia pathophysiology has been partly clarified by important research contributions supporting the causative role of a chronic irritation of the affected nerve due to compressive or inflammatory causes. Nevertheless, evidence suggests that central factors can contribute to the development of these forms. The following considerations refer to TN, however it is supposed that also other typical painful diseases of the face, such as glossopharyngeal neuralgia, share similar mechanisms [6].

In 1976 Jannetta [26] published the first extensive case study of subjects with TN in all of which, after investigations of posterior cranial fossa, a causative factor was documented. Besides slow-growing tumours of the cerebellumpontine angle accounting for 6% of the patients, and MS found in another 6% of the cases, in 88% of the subjects a compression of the proximal tract of the root of the V nerve by one or more tortuous or ectasic blood vessels was recognised (Fig. 1). In the site of the neurovascular conflict a demyelination was constantly present. As placing a teflon pad between the two structures – so-called microvascular decompression (MVD) – immediately stopped the attacks, the focal demyelination of the nerve was proposed as the main causative factor. The observations of these Authors have inspired a great deal of research paving the way to important progress on TN mechanisms which led to including this condition, notwithstanding relevant dissimilarities, in the broader chapter of *neuropathic pain.*

Much evidence sustains the causative role of a proximal compression of the trigeminal nerve root including: high frequency of neuroimaging positive report documenting a neurovascular conflict [27]; the prompt resolution of symptoms and nerve conduction defects after MVD [28, 29]; and ultimately the gradual remission of sensory defects of clinical relevance after surgery [30].

### Mechanisms of the pain

It is noticeable that the conflict always involves the proximal portion of the trigeminal root, the so-called root entry zones (REZ). Myelin at this level is still of central type and this could impact the resistance of the nerve to mechanical stimuli [31]. The compression probably causes a mechanical twist of the fibres and their secondary demyelination, probably mediated by microvascular ischaemic damages [32]. These changes can significantly lower the excitability threshold and promote an inappropriate ephaptic propagation towards adjacent fibres [33]. Because of the cross-talk, the tactile signals coming from the fast myelinic fibres (A-beta) can directly activate the slow nociceptive fibres (A-delta) and produce repetitive high-frequency discharges responsible for the typical "lightening" pain triggered by tactile stimuli. After a few seconds or minutes the repetitive discharges spontaneously run out and are followed by a brief period of inactivity that explains the "refractory period" clinically evident in many cases [34]. The aetiological role of the focal

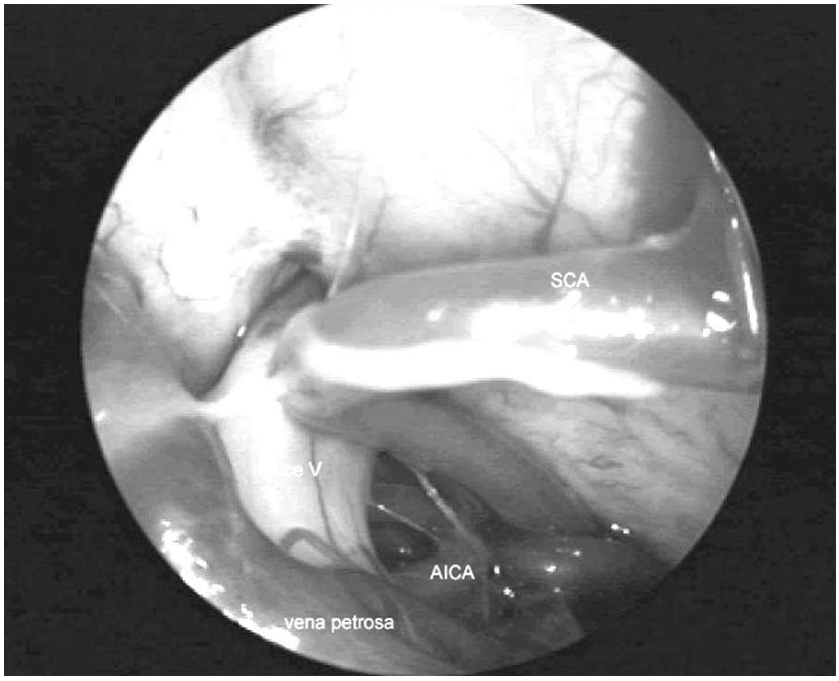


**Fig. 1** A triple neurovascular conflict (Courtesy of Prof. P. Cappabianca – Neurosurgery, University of Naples "Federico II", Naples, Italy)

demyelination of the REZ also explains the increased prevalence of NT in subjects with MS, in which demyelinated foci in the mid-pons and the REZ are usually demonstrated [35, 36]. Demyelination and remyelination processes observed in electronic microscopy studies [37] could also explain the typical periodicity of the syndrome.

Although these observations seem to point out that a demyelination of the REZ secondary to tumours, neurovascular conflict or MS is the causal element in all the cases of NT, different observations suggest that the hyperexcitability of the compressed nerve could represent a *necessary* condition, still not *sufficient* to cause the disease. Several autoptic case studies document a high prevalence of neurovascular conflicts at the proximal level in asymptomatic individuals [38–40]; a compression of REZ is not demonstrated in all the patients [41]; at least initially the pain is effectively treated by drugs such as baclofen, which is considered non-active on the peripheral fibres; familiar cases in which a neurovascular conflict is not detectable have been reported [8]. All these observations suggest a possible involvement of relevant central factors.

It has been suggested that a hypersensitivity of the tactile A-beta nerve fibres, initiated by the same nerve injury, leads to a sensitisation of the wide dynamic range neurons (WDRn) [42]. These peculiar nociceptive neurons are placed both in the V lamina of the dorsal horns and in the trigeminal nerve nuclei and are characterised by a progressive facilitation of excitability following repeated stimulation. Since these peculiar nociceptive II order neurons receive convergent information from both tactile A-beta and nociceptive A-delta and C fibres, their sensitisation can ultimately facilitate nociceptive input at the central level while promoting the perception of pain in response to tactile stimuli, a phenomenon called allodynia. The high prevalence of neurovascular conflicts in autoptic studies of asymptomatic subjects suggests that an individual predisposition to allodynic pain could be of great relevance in TN mechanisms. Noteworthy, allodynic sensitisation of thalamic nociceptive neurons has been recently documented in NT patients presenting with a continuous pain between attacks [14], a condition associated with a poor medical and surgical outcome [43]; interestingly, in this study the illness duration was not related to the presence of inter-critical pain, confirming its low specificity as a marker of symptomatic form or of protracted diseases.

Findings from recent studies on animal models point to dorsal root ganglia as a new site possibly involved in neuropathic pain and TN mechanisms [44]. At this level, a chemically mediated cross-talk between somata of both tactile A-type and nociceptive C-type sensory neurons has been recorded in physiologic conditions [45]. The mechanism results in a reciprocal excitability threshold modulation probably aimed to balance pain and tactile excitability in different physiologic conditions. In the presence of an injury-driven nerve sensitisation, the threshold for a cross-excitation between sensitised A and C fibres can be reached at the dorsal root ganglia level [46] and this may lead to pain generation in response to tactile stimuli. A possible involvement of Gasser ganglion in TN pathogenesis is supported by the finding of histological changes at this level both in Classic TN patients [47] and in subjects with TN associated to MS [48].

These observations link the pathophysiology of TN to a hyperexcitability of the trigeminal circuitry sustained by peripheral and central mechanisms. If the aetiology of TN and other typical neuralgias must be brought back to the peripheral injury, their pathogenesis could involve central allodynic mechanisms, which, in patients with inter-critical pain, also engage the nociceptive neurons at the thalamic-cortical level.

## Treatment

TN can be treated with drugs or surgical procedures; many patients end up with both treatments, although at different times. As a matter of fact, medical therapy works very well at the beginning and reaches almost complete control of symptoms in more than 80% of patients. As time passes, drugs progressively lose efficacy even if they are in multiple therapy. In these cases possible surgical options must be taken into account. Interestingly most of the drugs that are effective in TN have anti-epileptic activity or, in the case of baclofen, have effect on the central transmission of pain. This fact supports the hypothesis of the hypersensitivity of trigeminal circuitry following a nerve injury in the pathogenesis of TN. Historically phenytoin, used for the first time in 1942 by Berguignon, was the first drug to be reported to be effective in the treatment of TN. Only in 1962 with the introduction of carbamazepine did patients with TN begin to benefit from a truly effective treatment with a satisfying tolerability [6].

Despite the lack of randomised and controlled studies of large samples, due to the rarity of the disease and ethical difficulties in using placebo in such a devastating condition, the spectrum of available drugs has grown in time, adding several other anti-epileptic drugs (AED). Recently, medications that inhibit the transmission of the pain to the central II order neurons such as subcutaneous sumatriptan [49], or treatments with possible action against allodynia like the botulinum toxin [50, 51] have been found effective in pain control. Following is a list of the evidence on the efficacy of the main drugs used in clinical practice for the treatment of these forms.

### Anti-epileptic drugs

*Carbamazepine (CBZ)*

Carbamazepine is considered the mainstay for treating these disorders. It is also the only molecule for which

there is a great deal of evidence (1 systematic review and 4 RCT studies) [52]. Carbamazepine reduces sodium-channel conductivity, stabilising the membrane of pre- and post-synaptic neurons and making trigeminal mechanoceptors less prone to respond to peripheral input. About 80% of patients benefit from this treatment and in 94% of patients there is relief from symptoms in the first 48 h of treatment [53, 54]. As time passes however, the efficacy tends to be lower [55]. The recommended starting dose is 100 mg twice a day; this can be increased by 50–100 mg every 3–4 days up to a final dose of 400–1000 mg to continue until symptoms persist. The most common side effect is drowsiness, however this tends to decrease after a few days of treatment.

Other side effects are cerebellar symptoms, double vision, haematological changes, liver disease, skin rash, nausea and vomiting [56]. Intolerance is seen in 5%–19% of patients.

*Oxcarbazepine*

Oxcarbazepine is structurally a derivative of carbazepine, therefore it shares carbamazepine's mechanism of action. It can be used if intolerance to carbamazepine is present, or alternatively as the drug of choice [57]. Clinical trials on small groups of patients report that the drug is effective in 24 h and some report a greater efficacy and tolerability compared to carbamazepine [58]. The initial dose is 150 mg, which can be increased every 3 days of by 150–300 mg up to a therapeutic dose of 1200 mg three times a day.

*Phenytoin*

This is a drug of second or third choice and can added in case of intolerance or low efficacy to carbamazepine. The suggested mechanism of action is stabilisation of the CNS neuron' membrane, modulating sodium channels. Initially the drug is reported to be effective in 60% of patients, but after two years of treatment the efficacy is reduced to about 30%. The recommended starting dose is 200 mg, to be increased to a therapeutic dose of 300–500 mg twice a day. Injectable formulation, with a dose of 250 mg can be used for acute treatment of pain attacks and reaches a pain-free period of 4–72 h [59]. Side effects include double vision, ataxia, liver disease, gum hyperplasia, haematologic disturbance, hirsutism and memory defects.

*Gabapentin*

Gabapentin is widely used in the treatment of TN although its efficacy has been reported in few non-controlled studies. It has been empirically used because of its proven efficacy in pain control in post-herpetic and diabetic neuropathies [60]. It has been suggested that gabapentin acts by increasing GABA availability in the CNS and modulates the voltage-gated sodium channel, resulting in a reduced discharge of excitatory neurotransmitters. About 50% of patients respond to therapy after 3–4 days of treatment. A full remission from symptoms is achieved after about 2 weeks. The initial recommended dose is 300 mg, which can be doubled every 2–3 days to reach the maximum dose of 900–2400 mg/day. Adverse effects include drowsiness, weakness and abnormalities of kidney function. These effects are lesser and usually better tolerated in old patients compared to those observed with carbamazepine and phenytoin.

*Pregabalin*

Pregabalin shares the same activity of gabapentin, with better pharmacokinetics. Besides its efficacy in pain control in post-herpetic and diabetic neuropathies, recently pregabalin has been proven to be effective in an open pharmaceutical study showing that 74% of patients improve up to 50% and that efficacy reduction over a year is minor [61]. This study also highlights that patients with a concomitant chronic facial pain are less prone to benefit from treatment. Initially pregabalin can be administered at 75 mg and can be increased up to 600 mg in two separated daily doses. Drowsiness and dizziness are the most common side effects and they tend to recede after a few days of treatment. Higher doses can cause headache, peripheral oedema and dry mouth.

*Lamotrigine*

Lamotrigine is effective both alone and in combination with carbamazepine or phenytoin [62, 63] especially in elderly patients and in patients with MS with mild symptoms. The drug acts on sodium channels and it stabilises the plasma membrane, preventing neurotransmitter release, especially glutamate. Therapeutic dose is between 100 and 400 mg/day, which needs to be slowly achieved. Side effects are skin rashes, dizziness, constipation, nausea and drowsiness.

*Topiramate*

Topiramate has been proved effective in isolated clinical trials, in patients with MS and TN [64, 65]. It has a multiple mechanism of action including: blockage of sodium channels; and enhancement of GABA activity in the CNS via interaction with a specific site of action of the GABA A receptors, which is different from the benzodiazepine site of action. Topiramate also inhibits glutamergic excitatory activity through blockage of the AMPA/kainate receptor. Moreover, it inhibits specific carbonic anhydrase isoenzymes. The starting dose is 25 mg/day, which can be increased by 25 mg every week up to a dose of 100–400 mg/day. Side effects include dizziness, double vision, cognitive impairment, weight loss and high endocular pressure.

*Baclofen*

Baclofen deserves particular attention. It is not an anticonvulsant agent, rather it can be risky for targeting

epilepsy when abruptly stopped. Mechanism of action is at the central level and not on the peripheral nerve. Baclofen mimics GABA and acts on GABA receptors, slowing the influx of calcium ions, therefore decreasing the release of excitatory neurotransmitters. It is slightly less potent than carbamazepine and can be used as first choice or in combination with carbamazepine and phenytoin (synergism) [66].

Starting dose is 5–10 mg/day, which can be slowly increased until a satisfactory clinical response is achieved, which is usually 50–75 mg three times a day. Side effects are usually transient and appear at the beginning of treatment. They include postural hypotension, muscle weakness and gastroenteric discomfort. About 10% of patients show intolerance to the drug. Patients with MS also experience extra benefit from the anti-spastic effect of baclofen.

Other medications

*Subcutaneous sumatriptan*

Sumatriptan and zolmitriptan showed efficacy in controlling allodynic pain following nerve injury in an animal model for trigeminal neuropathic pain. Both medications have agonistic action on 5-HT$1_B$, which results in inhibition of neurons of the trigeminal nucleus localised in the medulla. Therefore these drugs are thought to act on the central nervous system [67]. These data were confirmed in another clinical single-blind study of subcutaneous sumatriptan vs. placebo. Results proved efficacy of sumatriptan on pain symptoms in patients with TN after 15 and 30 min compared to placebo. Benefits lasted for 7 h on average and this limits the clinical use of the drug. Potential side effects from subcutaneous injection of sumatriptan include increased blood pressure, nausea and weakness, which are not dangerous [49].

*Botulinum toxin*

BoNT-A has been used for a long time in the treatment of disorders characterised by pathologically increased muscle tone. Early observations in dystonia also demonstrated an analgesic effect of BoNT-A [68], which led to further investigation on its efficacy for painful conditions including neuropathic pain [50], low back pain [69] and headaches [70]. Evidence shows that BoNT-A reduces the local release of nociceptive neuropeptides such as substance P, glutamate and calcitonin gene-related peptide and inhibits peripheral sensitisation, which would result in decreased central sensitisation [51]. Hence it can be hypothesised that BoNT-A prevents peripheral sensitisation and subsequently central sensitisation. There are reports of isolated cases of NT responding to BoNT-A. In another open study, 13 patients showed significant relief from symptoms after treatment with BoNT-A [71].

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