

## Neuropathic Orofacial Pain

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Neuropathic pain is initiated by a primary lesion or dysfunction of the nervous system (Table 1) [1]. Neuropathic pain may be triggered by local trauma or systemic disorders, such as diabetes, that affect structures along the neuraxis from the central nervous system to peripheral structures. Based on symptomatology, neuropathic orofacial pain may be divided into two broad categories: episodic and continuous [2]. Episodic neuropathies are characterized by short electrical or sharp pain that may be paroxysmal, as in trigeminal neuralgia. Continuous burning pain is characteristic of posttraumatic neuropathy or inflammation in nerve structures (neuritis). Depending on the location of the initiating event, neuropathic pain may also be classified as peripheral or central. However, persistent peripheral neuropathies eventually involve maladaptive responses of the central nervous system.

### Clinical approach to neuropathic pain

Occurrence of neuropathic pain may be spontaneous (stimulus-independent) or touch-evoked (stimulus-dependent), and these episodes may be superimposed on a background of constant pain. Typically neuropathies include positive (eg, hyperalgesia; see Table 1) or negative (eg, numbness) signs. Some sensory signs and symptoms, particularly thermal or mechanical allodynia, are frequently associated with neuropathic pain. Assessment of sensory changes is best performed by quantitative sensory testing (QST), usually using sophisticated equipment. However, when

advanced QST equipment is unavailable, a simple pin, blunt instrument, warmed and cooled implements, and cotton wool may be used. This information may be complemented by mapping of areas with sensory changes; these should be documented with sketches or photographs and should be part of the patient evaluation and follow-up (Fig. 1A).

### Quantitative sensory testing

QST uses noninvasive assessment and quantification of normal and abnormal responses of the nervous system to various stimuli. External stimuli are usually mechanical, thermal, or electrical; each selectively activates different sensory nerve fibers (eg, heat activates C-fibers and cold stimuli and punctuate mechanical stimuli activate A-delta-fibers and electrical stimuli A-beta fibers).

### Clinical relevance

Extensive mechanical nerve damage is characterized by myelinated and unmyelinated nerve fiber hyposensitivity, clinically characterized by elevated detection thresholds to heat, electrical, and mechanical stimulation [3]. Partial damage may be followed by either hypo- or hypersensitivity [3]. In contrast, other specific nociceptive processes may provide a different, identifiable sensory signature. For example, neuritis (perineural inflammation) is characterized, particularly during its early phase, by a reduced detection threshold (hypersensitivity) in large myelinated A-beta nerve fibers [4,5]. Additionally, a measurable reduction in the interval between detection and pain thresholds has been shown to characterize centrally mediated pain conditions. Thus, data

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Table 1  
Definition of commonly used terms

Term	Definition
Allodynia	Pain caused by a stimulus which does not normally cause pain
Analgesia	Absence of pain in response to normally painful stimuli
Anesthesia dolorosa	Pain in an area or region that is anesthetic
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Hyperalgesia	An increased response (more pain) to a normally painful stimulus
Hypoalgesia	Diminished pain in response to a normally painful stimulus
Hypoesthesia	Decreased sensitivity to sensory stimulation (excludes the special senses)
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system
Paresthesia	An abnormal sensation, whether spontaneous or evoked

Data from Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms. 2nd edition. Seattle: IASP Press; 1994.

obtained from QST may provide vital information for treatment decisions, such as in which cases to perform microsurgical repair and when to use centrally acting drugs.

### Clinical syndromes

#### Trigeminal neuralgia

Trigeminal neuralgia (TN) is an excruciating, short-lasting, unilateral facial pain (Table 2). Two subsets of TN are recognized: classical and symptomatic. Symptomatic TN is related to various clear pathologies, including tumors, cysts, viral infection, trauma, and systemic disease [6]. Most patients (>85%) who have TN are diagnosed as having classical TN. Atypical TN cases that present with most but not all diagnostic criteria are unrecognized by any current classification.

#### Clinical features

Onset of TN may be abrupt or through a rarer preceding syndrome termed *pre-TN*. TN is a unilateral facial pain syndrome [6], but bilateral pain has been reported in 1% to 4% of patients [7,8]. Pain location is usually described according to the major branches of the trigeminal nerve. In 16% to 18% of patients, the singly affected branch will be the maxillary or mandibular branch, whereas the ophthalmic is affected singly in only approximately 2% of cases [8]. Most commonly the maxillary and mandibular branches are affected together (35%), and all three branches are involved in 14% of patients [8]. The jaws are therefore involved in most cases, explaining why patients who have classical TN often seek help from dentists. Although the features of TN vary across patients, they are highly consistent (stereotyped) within individuals.

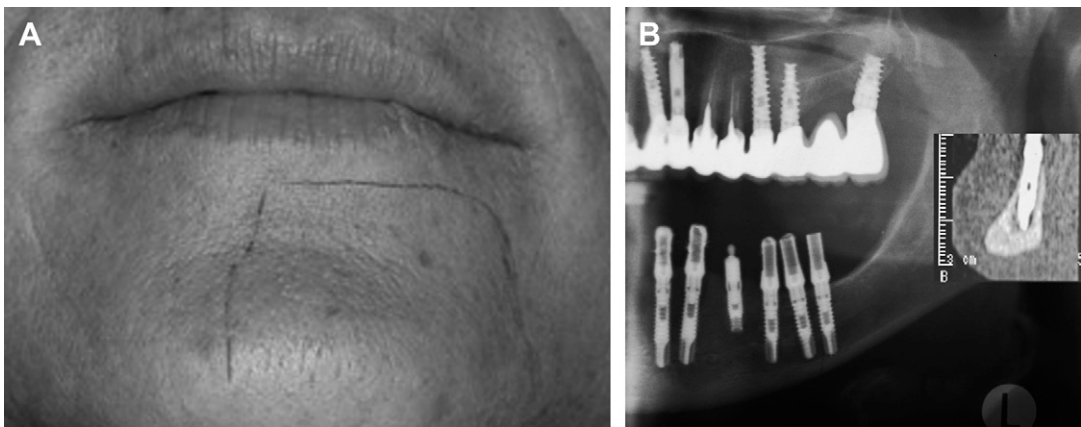


Fig. 1. Pain and neurosensory deficit after dental implants. (A) Mapped area of pain and disturbed sensation. (B) Implant placement. Insert is a CT section of an implant causing damage to the inferior alveolar nerve.

Table 2  
Classical trigeminal neuralgia

Feature	Notes
Paroxysmal attacks of pain lasting from a fraction of a second to 2 minutes	Usually no pain is experienced between attacks, but some atypical cases have low-grade background pain or longer-lasting attacks Periods of remission from days to years may occur
May affect one or more divisions of the trigeminal nerve	Pain is mostly unilateral and does not cross the midline Pain is very rarely bilateral (1%–4%) Bilateral pain may indicate disease (eg, multiple sclerosis) Most patients experience pain in the distribution of the second or third division or both
Pain characteristics are electrical, intense, sharp, or stabbing; precipitated from trigger areas by innocuous stimuli; and precipitated by trigger factors	Pain may be accompanied by spasm of the facial muscles After an attack a refractory period occurs when pain cannot be triggered Innocuous stimuli include touch, wind, and shaving but may also be temperature, noise, lights, and taste Trigger points may however change location within the same patient A short gap between trigger and pain may be observed (latency)
Stereotyped attacks	Attack duration, distribution, and so forth may vary among patients but are highly consistent within cases
Usually no neurologic deficit is clinically evident	Particularly in longstanding cases sensory testing may show mild deficits in the distribution of the trigeminal nerve
Pathology that may mimic trigeminal neuralgia (TN) must be ruled out through history, physical examination, and special investigations. All patients who have TN should undergo brain imaging. Compression of the nerve root by a vascular malformation (tortuous or aberrant vessels) is considered classical.	

*Data from Okeson JP. Orofacial pain: guidelines for assessment, classification, and management. The American Academy of Orofacial Pain. Hanover Park (IL): Quintessence Publishing Co., Inc.; 1996; and Olesen J, Bousser MG, Diener HC, et al. The international classification of headache disorders: 2nd edition. Cephalalgia 2004;24(suppl 1): 24–150.*

Pain associated with TN is most often described as paroxysmal, shooting, sharp, piercing, stabbing, or electrical [9,10]. Pain severity is extreme, rating 9 to 10 on a 10-cm visual analog scale (VAS) [10,11]. Some patients may experience a dull background pain of varying duration, described as dull, throbbing, and burning [7,12]. Findings suggest that patients who have prominent background pain usually have detectable sensory loss, suggesting nerve damage [13].

The clinical characteristics of TN include the presence of trigger zones, and innocuous stimuli in these areas lead to pain. A short gap between the stimulation of a trigger zone and pain onset may be observed and is termed *latency*. However, TN attacks are often spontaneous and triggers are not always present or identifiable [14]. Triggers are usually in the distribution of the affected trigeminal branch, particularly around the lips but may be extratrigeminal and multiple, and even change location [11]. Triggering stimuli include talking, chewing, touch, temperature, wind, and shaving [11].

Pain in TN is characterized by a rapid onset and peak, lasting from 10 seconds to 2 minutes [11], followed by a refractory period during which pain is impossible or extremely difficult to trigger.

Attacks occur mostly during the day, but nocturnal TN has been reported [12]. Contraction of the facial expression muscles typically accompanies the pain of TN, hence the terms *tic douloureux/tic convulsif*. Sensory disturbances such as hypoesthesia are rare and more readily detected when using sophisticated QST techniques [15].

A thorough history and clinical evaluation with adequate radiographs of oral structures are essential to rule out pathology. All patients who have TN should undergo imaging (CT or MRI) at least once during diagnosis and therapy [16]. Imaging techniques such as magnetic resonance tomographic angiography (MRTA or MRA) may indicate vascular compression of the nerve root. More sophisticated techniques, such as three-dimensional MRI with constructive interference in steady state sequence, are superior to MRTA/MRA in detecting venular compressions [17].

#### *Prognosis*

Long-term followup of patients who have TN shows that well-defined periods of pain attacks are variably followed by periods of remission [7,12]. However, TN bears a poor prognosis; approximately 90% of patients who have TN report

increased attack frequency and severity accompanied by a progressive and increasing resistance to pharmacologic and surgical treatment [11,18].

#### *Atypical trigeminal neuralgia*

Up to 30% of patients who have TN report atypical features, such as longer attacks and constant background pain [13,14], often associated with increased resistance to therapy. For example, only 47% of atypical TN cases reported absolute pain relief after microvascular decompression compared with 80% in classical TN. Additionally, a higher rate of recurrence was seen in atypical cases [19].

*Pretrigeminal neuralgia.* An early form of TN, termed *pretrigeminal neuralgia* (PTN), has been described in 18% of patients who have TN [20,21]. PTN is characterized by a dull continuous pain in one of the jaws that lasts from days to years before becoming typical [21]. Thermal stimuli may cause triggering at a higher rate, and a throbbing quality to PTN pain is sometimes present mimicking dental pathology [21]. These features and the success of regional anesthesia have led to misdiagnosis of PTN as pain of dental origin. The lack of clear and consistent diagnostic criteria makes this a problematic entity to recognize; it is usually diagnosed when all other possibilities are exhausted or in retrospect when classical TN develops [2].

#### *Differential diagnosis*

The differential diagnosis of TN includes dental pain, short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing [9], an atypical (shorter) cluster-tic syndrome, and symptomatic TN. TN often mimics dental pain and a quarter of cases will initially consult a dentist [12,22,23]. Unfortunately, TN is often misdiagnosed and 33% to 65% of patients undergo unwarranted dental interventions; up to 12% eventually may be rendered edentulous [11,23].

#### *Symptomatic trigeminal neuralgia*

Multiple sclerosis (MS) is a common disabling disease affecting individuals between ages 20 and 40 years. MS-related demyelination of the trigeminal nerve leads to an increased risk for developing TN by a factor of 20 [7]. Clinical signs predictive of MS in patients who have TN are bilateral pain (14% in MS) and young age [24]. Very rarely (0.3%) is TN the presenting sign of MS onset; it usually (1.5%–4.9%) develops in patients diagnosed with MS [25,26].

Trigeminal nerve dysfunction has been observed in 33% of patients who have middle and posterior cranial fossa tumors, but in only 13% were these presenting symptoms [27]. Approximately 10% of cases with intracranial tumors report TN-like symptomatology, which are mostly posterior fossa tumors and meningiomas [28,29]. Cerebellopontine angle tumors may also cause TN, and this diagnosis is more likely when the patient is young and experiences pain in more than one trigeminal branch [16]. In patients younger than 29 years who have TN, the prevalence of intracranial tumor is extremely high (approximately 100%) but subsequently decreases with increasing age [16]. Overall, 10% to 13.4% of patients who have TN may have intracranial tumors and MRI is the most sensitive imaging modality [29,30].

#### *Epidemiology*

TN is a rare condition with a lifetime prevalence of approximately 70 TN cases per 100,000 population [31]. The crude annual incidence of TN is 4.3 to 8 per 100,000 and is higher in women (5.7) than men (2.5). However, among individuals older than 80 years, men have a very high incidence of 45/100,000 [31,32]. Peak incidence begins at 50 to 60 years and increases with age [7]. TN is extremely rare in children.

#### *Pathophysiology*

Several lines of evidence point to arterial or venous compression of the trigeminal root at or near the dorsal root entry zone as a major causative or contributing factor [13,33]. Imaging, surgical observations, and cadaver studies confirm a high rate of vascular compression of the nerve in patients who have TN [34–37]. Subsequent neuronal damage is suggested in biopsy specimens from patients who have TN, showing axonal loss and demyelination of trigeminal roots [33,38]. Degenerative hypermyelination and microneuromata in the trigeminal ganglion have also been shown [39].

Initiation of pain through an innocuous trigger is an intriguing feature of TN partly explained by the ignition hypothesis [40]. According to this hypothesis, injury renders axons and axotomized somata hyperexcitable, resulting in synchronized afterdischarge activity, cross excitation of nociceptors, and pain paroxysms [41,42]. Central nervous system neuroplasticity will undoubtedly occur in the presence of these changes and will ultimately affect the clinical phenotype and response to therapy.

Surgical and cadaver studies show that vascular contact is not invariably found in patients who have

TN [36,43], suggesting that additional pathophysiologic mechanisms are involved.

### Treatment

**Pharmacologic.** A simple and useful way of expressing the efficiency of a drug relative to placebo is using the number needed to treat (NNT). Efficiency is most often measured as at least a 50% reduction in the patients' level of pain. For example, an NNT of three indicates that every third patient will obtain this reduction. Carbamazepine is highly efficacious in TN, with an NNT of 2.6 for significant pain relief, and is usually the first drug tested [44,45]. Its success in TN is often extrapolated to a diagnostic test, but up to 30% of patients may be initially resistant and up to 50% become refractory to carbamazepine therapy [14,46]. Oxcarbazepine, a carbamazepine derivative, is efficacious in TN with fewer side effects [18]. Baclofen has been successfully used in TN and, because of its low side-effect profile, may be titrated to high doses (80 mg/d) with an NNT of 1.4, but this recommendation is based on only one trial [47]. Moreover, few patients are actually able to tolerate high doses. A strong synergistic effect with carbamazepine is reported, also making baclofen suitable for combined therapy. The newer anticonvulsants have fewer side effects and may be effective for some patients either as mono- or add-on therapy. Lamotrigine is effective and has been rigorously tested as add-on therapy with an NNT of 2.1 [48]. Gabapentin has not been rigorously tested in TN but may be useful in selected patients who have TN.

Based on current evidence, the authors initiate therapy with carbamazepine and rapidly transfer

patients to the controlled-release formulation that has fewer side effects. If carbamazepine continues to cause troublesome side effects, they reduce the dose and add baclofen, or may try oxcarbazepine. In refractory cases, add-on therapy with lamotrigine or baclofen should be tried before changing drugs. Gabapentin is probably the most promising alternative, but pregabalin, topiramate, or even the older anticonvulsants valproate and phenytoin may be tried in recalcitrant cases [49] (Table 3). All patients taking anticonvulsants need baseline and follow-up tests of hematologic, electrolyte, and liver function. Even in patients who undergo successful treatment, exacerbations (ie, breakthrough pain) may occur and require temporary dose adjustment.

**Surgical.** The decision to choose surgery is partly based on results obtained from medical treatment, the patient's age, and medical status. The choice of neurosurgical procedures is often limited by the surgical facilities and expertise available. Quality of life in patients treated medically is significantly lower than in patients after microvascular decompression, and successful surgery often relieves anxiety and depression associated with TN [10]. Therefore, patients who have typical classical TN who are physically able are prime candidates for surgery.

**Peripheral procedures.** Nerve blocks provide temporary but absolute pain relief in TN. Reported success rates for neurectomy conflict (50%–64%) and involve small series with short-term follow-up [50]. In any event, pain in TN invariably recurs after neurectomy within a mean period of 2 years [51]. Cryotherapy of peripheral branches may provide

Table 3

Antiepileptic drugs and dose schedules commonly used in the treatment of trigeminal neuralgia and other painful trigeminal neuropathies

Drug	Initial dose (mg)	Target or maximal dose (mg) <sup>a</sup>	Dose increase (titration) <sup>a</sup>	Schedule
Carbamazepine	100–200	1200	100–200 mg every 2 days	3–4 times per day
Carbamazepine CR	200–400	1200	Usually transfer from regular format at equivalent dose	2 times per day
Oxcarbazepine	300	1200–2400	300–600 mg/wk	3 times per day
Baclofen	5–15	30–60	5 mg every 3 days	3 times per day
Gabapentin	300	900–2400	300 mg every 1–2 days	3 times per day
Pregabalin	150	300–600	50 mg every 2–3 days	2–3 times per day
Lamotrigine*	25	400–600	25–50 mg/wk	1–2 times per day

*Abbreviation:* CR, controlled release.

<sup>a</sup> Titrate according to response and side effects.

\* Lamotrigine has been tested as add-on therapy in trigeminal neuralgia.

pain relief for 6 months and may be repeated with good results [52]. Alcohol injections may be effective for about 1 year but are painful, and fibrosis makes repeat injections technically difficult [53]. Complications may include full-thickness skin or mucosal ulceration, cranial nerve palsies, herpes zoster reactivation, and bony necrosis [50]. A 60% success rate at 24 months after peripheral glycerol injection has been reported, but others report pain relapse by 7 months [53,54]. However, single reinjection is possible, with good results reported [54]. Peripheral procedures all have the goal of inducing nerve damage and therefore carry the attendant risk for patients to develop dysesthesias. Neurectomy, cryotherapy, and alcohol block have all resulted in neuropathic pain (sometimes termed *anesthesia dolorosa*; see Table 1). Peripheral procedures should be reserved for emergency use or patients who have significant medical problems that make other procedures unsafe [50].

Based on the theory that neuralgia-inducing cavitation osteonecrosis (NICO) may cause some cases of TN, curettage and packing of affected jaw areas have been described [55]. The concepts underlying the pathophysiology have developed over the years from an infective process to an inflammatory reaction and a disorder based on coagulation defects that may induce avascular necrosis [56,57]. However, rigorous scientific investigation has not established a cause-and-effect relationship [57]; NICO data are sparse compared with the rich laboratory, imaging, surgical, and cadaver studies underlying the etiologic hypothesis for TN. Moreover, imaging often shows no evidence for cavitation and diagnosis is based on nonspecific criteria, such as the presence of pain and its elimination with local anesthesia. Pathologic review of excised tissue often shows nonspecific findings. Therefore, the authors and many prominent oral and maxillofacial surgeons cannot currently endorse this mode of treatment [57–59].

**Central procedures. Percutaneous trigeminal rhizotomy.** These procedures are directed at the trigeminal ganglion and include radiofrequency rhizolysis, glycerol injection, or balloon compression. The three modalities provide approximately equal initial pain relief (around 90%) but are each associated with different rates of recurrence and complications [35,60]. Overall, radiofrequency rhizolysis consistently provides the highest rates of sustained pain relief but is associated with high frequencies of facial and corneal numbness.

**Microvascular decompression.** Microvascular decompression is based on the premise that TN is

caused by vascular compression of the nerve root, and surgically separating them may offer a permanent cure. Surgical morbidity for this procedure has decreased to approximately 0.3% to 3% [61], making it a more attractive option than in the past. Complication rates are lowest in high-volume hospitals and when the surgeon performs a large number of these procedures yearly [61]. Initial success rates for microvascular decompression are very high (approximately 90%), but long-term follow-up shows that after 10 years 30% to 40% of patients will experience a relapse [62,63]. Notwithstanding, patient satisfaction with microvascular decompression is very high, particularly if it is the first intervention for TN [64]. Data suggest that the best results for microvascular decompression are obtained when performed within 7 years of TN onset [65] in patients who have no (or minimal) sensory loss [19].

**Gamma knife.** Gamma knife stereotactic radiosurgery (GK-SRS) is a minimally invasive technique that precisely delivers radiosurgical doses of 70 to 90 Gy to the trigeminal nerve root at the point of vascular compression as mapped using MRI. GK-SRS may be indicated in patients who are poor candidates for microvascular decompression, and provides good to excellent (60%–90%) initial pain relief [66,67]. Although posterior fossa surgery was shown to be superior to GK-SRS over a mean follow-up duration of approximately 2 years [68], some reports have shown that GK-SRS results may be improved through modifying the dose and delivery mode [69]. Additionally data suggest that GK-SRS may be the preferred procedure for recurrent classical TN [70]. This modality thus requires further investigation and review.

#### *Trigeminal neuralgia: oral and maxillofacial surgery perspective*

The numbers of TN cases with extensive and misguided dental interventions suggest a lack of awareness of many dentists to the features of classical TN or the existence of PTN. Oral and maxillofacial surgeons are often consulted for patients who have unexplained pain, which may be TN. Alternatively, patients experiencing TN pain may be referred to oral and maxillofacial surgeons for extractions. Invasive dental treatment must not be performed when it is not indicated by positive anamnestic, clinical, and radiographic signs. Additionally, oral and maxillofacial surgeons may be asked to help manage medically complex, elderly patients who have TN who are unsuitable for central

procedures. Several peripheral procedures are available that may offer temporary relief.

### *Glossopharyngeal neuralgia*

Glossopharyngeal neuralgia (GN) is characterized by a milder natural history than that of TN. However, because of its location, clinical features, and rarity (0.7 cases/100,000 [32]) GN is difficult to diagnose and adequate treatment is often delayed several years [71]. Pain location in GN is dictated by which of the two sensory branches are affected [6]. Pain in pharyngeal-GN is usually located in the pharynx, tonsil, soft palate, or posterior tongue-base and radiates upward to the inner ear or the angle of the mandible. Tympanic-GN is characterized by pain that either remains confined to or markedly predominates in the ear but may subsequently radiate to the pharynx. Bilaterality is not uncommon and occurs in up to a quarter of patients [32].

Pain is usually described as sharp, stabbing, shooting, or lancinating and is stereotyped within patients [6]. Some patients may report a scratching or foreign body sensation in the throat. Attacks of GN are commonly mild but may vary in intensity to excruciating [32]. Usually no warning sign precedes an oncoming attack, but some cases report preattack discomfort in the throat or ear.

Typically GN trigger areas are located in the tonsillar region and posterior pharynx and are activated through swallowing, chewing, talking, coughing, or yawning [6]. Sneezing, clearing the throat, touching the gingiva or oral mucosa, blowing the nose, or rubbing the ear also trigger pain [32]. Topical analgesia to trigger areas will eliminate both trigger and pain and may help diagnose GN, although the areas may be difficult to reach.

Pain usually lasts from 8 to 50 seconds but may continue for up to 40 minutes or even recur in rapid succession [72]. Frequency of paroxysms may be 5 to 12 per hour, reaching 150 to 200 per day. After an individual attack a refractory period occurs [6]. Attacks may occur in clusters lasting weeks to months, then relapse for up to several years [6]. Spontaneous remissions are common, but some have no periods of pain relief. GN is reported to induce syncope, probably mediated by functional central connections between visceral afferents of cranial nerves (IX and X) and autonomic medullary nuclei. Cardiac arrhythmias are common, particularly bradycardia. Imaging of the head and neck to rule out pathology is indicated. An electrocardiogram should be performed before and after treatment.

### *Differential diagnosis*

The most common differential is TN, particularly when pain of GN spreads to trigeminal dermatomes. Moreover, the co-occurrence of TN is reported in 10% to 12% of patients who have GN [73]. As observed in TN, a significant association between GN and MS has been reported [74]. Regional infectious or inflammatory processes and cerebellopontine angle or pontine lesions may cause GN-like symptoms [75]. Tonsillar carcinoma invading the parapharyngeal space and other regional tumors (tongue, oropharyngeal) may mimic GN [76].

### *Treatment*

Pharmacotherapy for GN is based on drugs successfully used for TN. Microvascular decompression of the glossopharyngeal nerve root also has been used successfully. Life-threatening arrhythmias may require cardiac pacing.

### *Glossopharyngeal neuralgia: oral and maxillofacial surgery perspective*

GN is an extremely rare syndrome that is difficult to diagnose. Although pain located in the ear may be confused with temporomandibular joint problems, the pain characteristics are very different.

### *Acute herpes zoster*

Acute herpes zoster (HZ or shingles) is reactivation of latent HZ virus that causes a disease of the dorsal root ganglion with dermatomal vesicular eruption. Every year approximately 0.1% to 0.5% of the population develops HZ, with 1% occurring in individuals older than 80 years [77]. The overall lifetime risk of HZ is 10% to 20%, and more than 50% in patients older than 80 years. Trigeminal and cervical nerves are affected in 8% to 28% and 13% to 23% of acute HZ cases, respectively [78,79]. The ophthalmic branch is affected in more than 80% of trigeminal cases, particularly in elderly men, and may cause sight-threatening keratitis. Unilateral, intraoral vesicles may be observed in HZ of the maxillary or mandibular branches. These rapidly break down to small ulcers that may coalesce.

Acute HZ eruption begins with a prodrome of pain, headache, itching, and malaise [78]. Pain usually precedes the skin eruption by 2 to 3 days (<7 days) and may continue for up to 3 to 6 months with varying intensity. The acute stage is characterized by a unilateral, dermatomal, red maculopapular rash that develops into a vesicular eruption over 3 to 5 days; this usually dries out within another 7 to 10 days. Constant pain is

present, often with superimposed lancinating pains [79]. Stimulus-dependent pain, mechanical allodynia, and disturbed sensory thresholds are often seen and usually spread to adjacent dermatomes and bilaterally [79,80]. Descriptions of pain include burning, stabbing, shooting, tingling, and aching [78]. Intensity may be moderate to severe (VAS 6.2), but up to 25% of patients may report no pain [79,81]. High pain severity correlates with an increased incidence of postherpetic neuralgia (PHN) [81].

#### *Pathophysiology*

Viral DNA is found in most ganglion cells, with resultant cell degeneration, satellitosis, and lymphocytic infiltration of the nerve root. Acute inflammatory changes are maximal within the ganglion of the affected dermatome but also extend peripherally along the length of the sensory nerve (neuritis), followed by neuronal destruction [82]. These events lead to central sensitization. Viral-induced damage spreads within the spinal cord, involving adjacent segments (bilaterally) and in severe cases the ventral horn with resultant motor paralysis.

#### *Treatment*

Therapy is directed at controlling pain, accelerating healing, and reducing the risk for complications such as dissemination, PHN, and local secondary infection [83]. When antivirals are initiated early (<72 hours from onset of rash), particularly in patients older than 50 years, they decrease rash duration, pain severity, and the incidence of PHN [81]. Amitriptyline will provide analgesia, may shorten illness duration, and provides added protection from PHN [84]. When patients do not respond to analgesics, some experts recommend the use of corticosteroids [83]. However, all recent studies show that corticosteroids do not reduce the incidence of PHN [83]. Vaccinating individuals who are at risk, such as those who are elderly and immunocompromised, may be an efficacious technique to prevent HZ and PHN [85].

#### *Herpes zoster: oral and maxillofacial surgery perspective*

Oral and maxillofacial surgery departments often cover emergency rooms where some HZ cases may appear. The early detection of HZ cases and rapid initiation of antiviral and adjuvant therapy may substantially reduce long-term morbidity.

#### *Postherpetic trigeminal neuralgia*

A proportion (16%–22%) of patients who have acute HZ will report pain 3 to 6 months after initial onset, and these are categorized as having PHN. By 1 year, only 5% to 10% continue to experience pain. Several risk factors for persistent pain have emerged and include advanced age and severe prodromal pain, acute pain, and rash [86]. In the older age group (>60 years), 50% or more will continue to experience pain lasting more than 1 year.

#### *Clinical features*

Trigeminal PHN is a direct complication of acute HZ of the trigeminal nerve and will therefore localize to the affected dermatome, usually the ophthalmic branch. Pale sometimes red/purple scars may remain in the affected area. These scars are usually hypoesthetic or anesthetic and may paradoxically exhibit allodynia and hyperalgesia. Pain in PHN is burning, throbbing, stabbing, shooting, or sharp [87]. Itching of affected areas is common in trigeminal dermatomes and may be prominent and bothersome [88]. PHN is usually severe, with VAS ratings of 8 on a 10-cm scale, but is characterized by fluctuations [87].

#### *Pathophysiology*

PHN is a neuropathic pain syndrome resulting from viral-induced nerve injury. Scarring of sensory ganglia, peripheral nerves, and loss of large myelinated fibers is commonly found in patients who have PHN [89]. Skin biopsies from affected and contralateral sites show bilateral peripheral nerve damage that correlates with the persistence of PHN [90]. PHN is believed to progress from peripheral to central structures. Ongoing activity in peripheral nociceptors has been shown to be important in the early stages (<1 year) of PHN, whereas central mechanisms may become prominent in later stages [91]. The degree at which these processes are prominent define the clinical phenotype.

#### *Treatment*

Evidence-based treatment options for PHN include tricyclic antidepressant drugs, gabapentin, pregabalin, opioids, and topical lidocaine patches [92]. For PHN the overall NNT for effectiveness of antidepressants was 2.2; NNTs for amitriptyline vary from 1.6 to 3.2. Lidocaine patches are very effective in patients who have allodynia, with an NNT of 2. Gabapentin (NNT, 3.9–4.39), pregabalin (NNT, 3.3–4.93), and opioids (NNT, 2.5–3) are

beneficial [45,93]. More invasive modalities include epidural and intrathecal steroids and various neurosurgical techniques. Ophthalmic PHN is most resistant to treatment, but overall PHN carries a better prognosis than TN.

*Postherpetic neuralgia: oral and maxillofacial surgery perspective*

PHN is a chronic disease most often treated in pain clinics or neurology centers. Trigeminal PHN may be confused with dental or other orofacial pain, but the history is usually very clear.

*Central causes of orofacial pain*

Central pain may be caused by direct damage as in stroke and spinal cord trauma, secondary to centrally occurring diseases such as MS or other nervous system dysfunction. A central pain of particular interest to oral and maxillofacial surgeons is burning mouth syndrome, which is discussed extensively in the article by Klasser, Fischer, and Epstein in this issue.

*Traumatic orofacial neuropathies*

Micro- or macrotrauma (surgery, accidents) to orofacial structures may induce nerve injury that may ultimately result in chronic neuropathic pain. After zygomatic complex fractures, residual mild hypoesthesia of the infraorbital nerve is common, but chronic neuropathic pain is rare (3.3%) [94]. This rate of residual neuropathic pain is less compared with other body regions [95]. After dental implant and orthognathic surgery, 1% to 8% and 5% to 30% of patients, respectively, may have permanent sensory dysfunction, but the incidence of chronic pain is unclear [96–99]. Fig. 1B shows a case of nerve damage secondary to implant placement. Third molar extractions are associated with transient hypoesthesia [100]. Disturbed sensation may remain in 0.3% to 1% of cases for varying periods [101] but is rarely associated with chronic neuropathic pain [102]. Patient complaints of tongue dysesthesia after injury may remain in a small group of patients (0.5%) [103].

Persistent pain after successful endodontics was found to occur in 3% to 13% of cases [104,105], whereas surgical endodontics resulted in chronic neuropathic pain in 5% [106]. Factors significantly associated with persistent pain were long duration of preoperative pain, marked symptomatology from the tooth, previous chronic pain problems or a history of painful treatment in the orofacial region, and female gender [104].

*Clinical features*

Painful neuropathies often present with a clinical phenotype involving combinations of spontaneous and evoked pain. Positive (eg, dysesthesia) and negative symptomatology (eg, numbness) may be present, particularly if a major nerve branch (eg, infraorbital, inferior alveolar) was injured. Pain is of moderate to severe intensity and usually burning but may possess paroxysmal qualities. Pain is unilateral and may be precisely located to the dermatome of the affected nerve, but may be diffuse and spread across dermatomes. Patients may complain of swelling or a feeling of swelling, foreign body, hot or cold, local redness, or flushing.

*Possible syndromes of painful traumatic trigeminal neuropathy*

*Persistent idiopathic facial pain (previously atypical facial pain)*. Much data collected on atypical facial pain (AFP) suggest a continuous neuropathic condition, and many patients who have AFP show some degree of sensory dysfunction [107]. The International Headache Society (IHS) criteria for persistent idiopathic facial pain (PIFP) include the presence of daily or near daily pain that is initially confined but may subsequently spread. The pain is not associated with sensory loss and cannot be attributed to any other pathologic process. This definition is rather loose and has not been field tested, and therefore it may misleadingly allow the classification of a large number of chronic facial pain disorders. Until specific data on PIFP accumulate, the features of AFP are briefly described.

**Clinical features.** Pain is usually poorly localized, radiating, and mostly unilateral, although up to 40% of cases may describe bilateral pain [12,108]. AFP is commonly described as burning, throbbing, and often stabbing [108,109]. Intensity is mild to severe and rated approximately 7 of 10 on a VAS [110]. Most patients report long-lasting (years) chronic daily pain, although pain-free periods have been reported [12,108]. Pain onset is often associated with surgical or other invasive procedures [108]. Although no sensory deficits should be present, they have been reported in up to 60% of cases [107,108]. The lack of a clear pathophysiologic basis precludes the establishment of a treatment protocol. The use of tricyclic antidepressants and anticonvulsants may be beneficial.

*Atypical odontalgia.* Atypical odontalgia is defined by the International Association for the Study of Pain as a severe throbbing pain in the

tooth without major pathology [1]; however, the IHS does not classify atypical odontalgia and suggests that it may be a subentity of PIFP. Whether atypical odontalgia is a neurovascular or neuropathic syndrome is the source of controversy, but most researchers consider atypical odontalgia to be neuropathic, most probably a subentity of AFP [111–114].

*Complex regional pain syndrome.* Complex regional pain syndrome (CRPS) has been previously termed *sympathetically maintained pain*, *reflex sympathetic dystrophy*, or *causalgia*. These early terms were based on observations of the clinical phenotype that often suggested involvement of the sympathetic nervous system. However, the link between nociceptive neurons and postganglionic sympathetic activity is inconsistent, with sympathetic blocks sometimes altering the syndrome at least temporarily and sometimes not [115]. Adrenergic mechanisms in some form seem to be involved in some of these conditions, but measurements of sympathetic responses have often shown normal results [116]. The current terminology attempts to solve these issues and is not suggestive of suspected etiologic mechanisms.

CRPSs are painful disorders that develop because of injury; CRPS I was previously referred to as reflex sympathetic dystrophy and CRPS II was previously referred to as causalgia [1]. Both entities present with spontaneous pain accompanied by allodynia and hyperalgesia that are not limited to dermatomal regions [117]. Additional signs include edema, abnormal blood flow in the skin, and abnormal sudomotor activity. CRPS I may develop as a consequence of remote trauma or after minor local trauma, such as sprains or surgery. These result in minor or no identifiable nerve lesions with disproportionate pain. The less frequent form, CRPS II, is characterized by a substantiated injury to a major nerve. Both syndromes may have clinical evidence to support the involvement of the sympathetic nervous system, in which case the term *sympathetically maintained pain* is added. However, this finding is not a prerequisite for diagnosing CRPS.

**Clinical features.** CRPS is most often reported in the extremities. Pain is usually of a burning or pricking character felt deep within the most distal part of the affected limb [118]. Most patients describe pain at rest, but movement and joint pressure will elicit or worsen pain [119]. Reduced sensitivity to thermal and mechanical stimuli is usually present and may spread to involve the adjacent body quadrant or even half of the body,

suggesting central involvement. Other sensory abnormalities include mechanical/thermal allodynia and hyperalgesia not restricted to nerve territories [119]. Paresthesias are rare, but approximately one third will complain of a foreign, neglect-type feeling in the affected limb. Weakness, contraction, fibrosis, and tremor of the affected site are observed [119]. During the acute stage, more than 80% have edema and cutaneous vasodilation occurs, with the skin appearing red [119]. In the chronic stages, this may subsequently reverse into vasoconstriction, resulting in cold, bluish skin [120]. Increased sweating and trophic phenomena are common. Over time, atrophic changes appear in skin, nails, and muscles.

Therapy should be aimed at restoration of function and reduction of pain. Depending on the disease stage and symptomatology, steroids and sympathetic blocks may be indicated. Antidepressants and anticonvulsants may relieve neuropathic pain components, and opioids should be tried if these fail [119].

**Complex regional pain syndrome in the orofacial region.** The historical dependence on sympathetic involvement for diagnosing CRPS has probably prevented the identification and documentation of head and neck cases. Thus, reports have relied on cervical sympathectomy, clonidine, guanethidine, and stellate ganglion blockade to confirm CRPS [121]. Certain features, such as trophic changes and skin atrophy, are unreported in the trigeminal region and motor disturbances are rare. The particular clinical phenotype may reflect the trigeminal system's differential response to trauma [122].

**Pathophysiology of complex regional pain syndrome.** Research has suggested that particular processes are important in CRPS, including neurogenic inflammation, up-regulated neuropeptide release with impaired inactivation, and enhanced sensory sympathetic interactions [119].

#### *Pathophysiology of painful traumatic neuropathies*

Pain in neuropathy varies among patients, even after identical injuries. This variability is probably caused by a combination of environmental, psychosocial, and genetic factors. The pathophysiology of painful inflammatory or traumatic neuropathies involves a cascade of events in nervous system function that includes alterations in functional, biochemical, and physical characteristics [123–125], which are collectively termed *neuronal plasticity*. The prominent events are summarized in Fig. 2. Some of the pathophysiologic

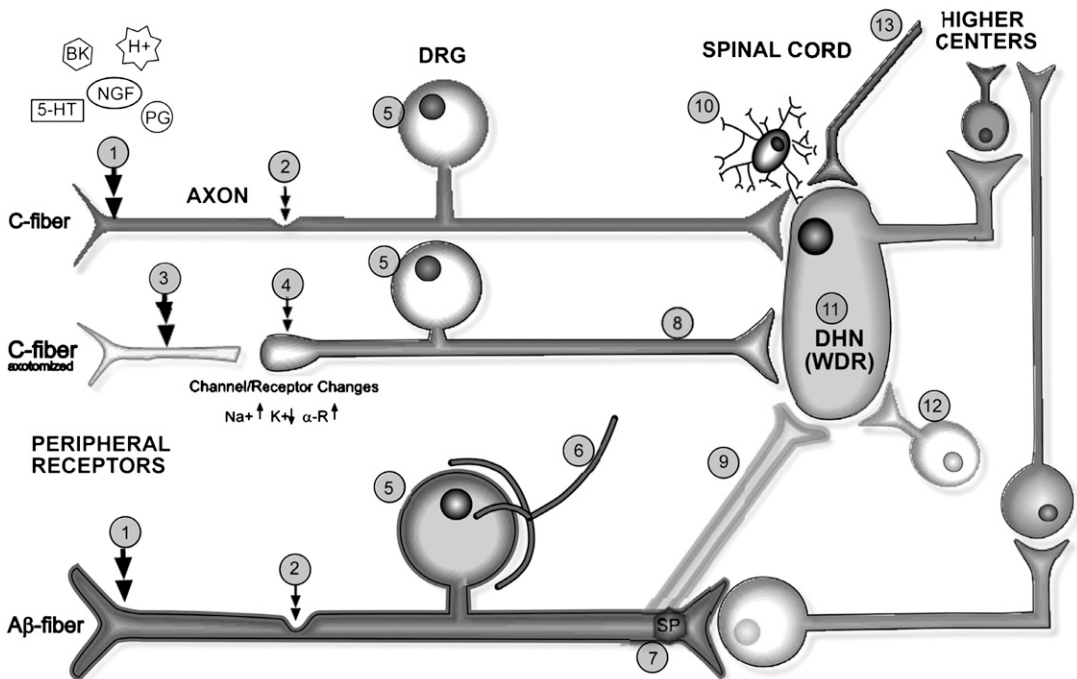


Fig. 2. Peripheral and central nervous system changes in chronic pain. In peripheral sensitization, tissue damage (1) releases inflammatory mediators, such as bradykinin (BK), nerve growth factor (NGF), serotonin (5-HT), prostaglandins (PG) and protons (H<sup>+</sup>). This “inflammatory soup” of bioactive molecules induces increased sensitivity of peripheral nociceptors leading to allodynia and hyperalgesia. Axonal injury (transection, crush, or chronic pressure and inflammation) induces increases in sodium (Na<sup>+</sup>) and  $\alpha$ -adrenoreceptors ( $\alpha$ -R) (2), initiating ectopic activity and increased sensitivity to mechanical and chemical stimuli. Axotomy may induce neuronal cell death. Alternatively, death of the distal part of the nerve may occur (3) while the proximal section survives with healing and neuroma formation (4). Neuromas may possess ectopic electrophysiologic activity, secondary to changes in specific ion channels. This activity leads to altered gene expression in the neuronal cell bodies located in the ganglia (DRG) and may induce ectopic activity origination from DRG cells (5). These phenomena explain spontaneous pain and the pain experienced when neuromas are touched. Nerve injury may lead to sympathetic nerve fiber sprouting (6), particularly around the larger DRG cells; this has not been detected in trigeminal ganglion cells. A-beta fibers undergo a phenotypic change (7), resulting in novel expression of neurotransmitters associated with nociceptors, such as substance P (SP). Injury-induced C-fiber degeneration (8) may result in sprouting of A-beta fibers from deep to superficial dorsal horn layers (9), augmenting allodynia. Primary afferents and dorsal horn neurons activate glial cells in the dorsal horn (10), and these compromise opioid analgesia and enhance dorsal-horn-neuron and primary afferent activity and excitability. Persistent nociceptive input also results in the direct sensitization of wide dynamic range (WDR) dorsal horn neurons (DHN) (11) and excitation of adjacent neurons (central sensitization). Central sensitization involves the activation and sensitization of the N-methyl-D-aspartate receptor. Glutamate released by nerve fibers is excitotoxic and reduces the number of inhibitory interneurons, augmenting excitation (12). Persistent pain initiates descending modulation, which in pathologic states tends toward facilitation (13). (From Benoliel R, Heir G, Eliav E. Neuropathic orofacial pain. In: Sharav Y, Benoliel R, editors. Orofacial Pain and Headache. Elsevier, in press; with permission.)

events are probably common to various neuropathies described earlier; each clinical entity is characterized by specific events and features, and these have been reviewed individually.

**Indirect macrotrauma.** Evidence shows that indirect macrotrauma may induce central nervous system damage. Even after minor head trauma, progressive and extensive axonal injury caused by

widespread shearing occurs and is commonly known as *diffuse axonal injury* [126,127]. This phenomenon may underlie chronic pains associated with closed head trauma.

#### *Treatment of painful traumatic trigeminal neuropathies*

The inescapable progression of events after nerve or extensive tissue damage suggests that

early intervention is most important. With preemptive analgesia, preoperative treatment is designed to reduce or eliminate the initial sensory barrage and prevent central sensitization. The strategies include the use of preoperative local anesthetics and analgesics. In the dental setting, local anesthetics are routine and analgesics are usually ingested perioperatively, establishing the basis for a preemptive strategy.

*Strategies for established painful trigeminal neuropathies.* The goal of therapy is to reduce pain intensity and onset frequency. Research shows that approximately a 30% reduction represents meaningful pain relief for patients who have neuropathic pain [128].

The role of surgery in the management of painful TNs is unclear. In the authors' clinical experience, most patients who have undergone peripheral surgical procedures (exploration, further apicoectomies) for traumatic TN end up with more pain. Some cases reported in the literature were treated with peripheral glycerol injections with some success, but the authors have found no prospective controlled trials. Based on this experience, the authors recommend that patients who have painful traumatic neuropathies should not to undergo further surgery, but this has not been rigorously tested.

Some injuries to the lingual or inferior alveolar nerves may induce significant discomfort to patients, including liquid incompetence and untoward effects on speech, chewing, gustation, and swallowing. Several patients may present with pain and neurosensory dysfunction [129]. Most cases are secondary to surgical removal of impacted third molars [130–132]. Microsurgical repair may be warranted in these cases and an operative management protocol has been suggested [133]. Best results are probably obtained when nerve injuries are operated on early (<10 weeks). Surgery is more successful in

inferior alveolar than in lingual nerve injuries [134], and the presence of a neuroma is a negative prognostic factor [129]. However, even in case series with repair within 1 year of injury, success rates as measured through sensory recovery are high [129–132]. Approximately 50% of repaired cases will recover full sensory function by 7 months [129]. Although most studies report sensory improvement, only a limited number of studies focus on pain accompanying nerve damage [129,132]. In some patients, microsurgery may offer successful management of pain and neurosensory dysfunction [129].

No prospective trials were found on central procedures for treating painful traumatic neuropathy. Anecdotal evidence suggests that central procedures may be useful for recalcitrant cases [135,136]. The authors suggest that the primary choice of operation should be minimally invasive, such as a trigeminal tractotomy nucleotomy (surgical division of the descending fibers of the trigeminal tract in the medulla effectively ablating pathways that carry sensation from the face). Trigeminal dorsal root entry zone operation (surgical damage to a portion of neurons in the trigeminal nerve root at brainstem level) may subsequently be performed for failures [136].

Available evidence confirms that successful pharmacotherapy of neuropathic pain relies on the anticonvulsant drugs and antidepressants, particularly the tricyclic antidepressants [137] (see Table 3; Table 4). Anticonvulsant drugs are heterogenous in their efficacy for the treatment of painful neuropathies [45]. Phenytoin (NNT, 2) has been shown superior to both carbamazepine (NNT, 3.3) and gabapentin (NNT, 3.8) but has significant side effects. For TN, anticonvulsant drugs, particularly carbamazepine, are preferred [45]. Based on the efficacy of pregabalin and gabapentin in peripheral neuropathies (PHN or diabetic neuropathy), they may also be good treatment options in traumatic neuropathy.

Table 4

Antidepressant drugs and dose schedules commonly used in the treatment of painful trigeminal neuropathies

Drug	Initial dose (mg)	Target or maximal dose (mg) <sup>a</sup>	Dose increase (titration) <sup>a</sup>	Schedule
Amitriptyline	10	35–50	10 mg/wk	Bedtime
Imipramine	12.5	25–50	12.5 mg/wk	Bedtime
Venlafaxine	37.5	75–150	75 mg every 4–7 days	2–3 times per day
Venlafaxine XR	37.5	75–225	75 mg every 4–7 days	1 per day
Duloxetine	20–40	60	20 mg/wk	1–2 times per day

*Abbreviation:* XR, extended release.

<sup>a</sup> Titrate according to response and side effects.

Analgesic trials with tricyclic antidepressants show that drugs with mixed serotonin/noradrenaline or specific noradrenaline reuptake inhibition are superior to the selective serotonin reuptake inhibitors, such as fluoxetine or paroxetine [138]. Calculations of the NNT show that tricyclic antidepressants such as amitriptyline benefit approximately every other patient (NNT, 2.2) experiencing painful polyneuropathies [139]. With careful dose titration, an NNT of 1.4 for imipramine may be attained in the treatment of traumatic neuropathies. In contrast, selective serotonin reuptake inhibitors have an NNT of 7 in painful polyneuropathies. Venlafaxine has an NNT of around 4 for painful polyneuropathy and duloxetine has an NNT of 4.1 for diabetic neuropathy; both have fewer side effects than the tricyclic antidepressants and may be attractive alternatives [137].

Based on a large literature review and the authors' clinical experience, tricyclic antidepressants or gabapentin/pregabalin would be the first drugs indicated in painful peripheral neuropathy. The efficacy of tricyclic antidepressants is counterbalanced by the excellent side effect profile of the newer anticonvulsant drugs. If initial tricyclic antidepressants or gabapentin are unsuccessful, patients should be transferred to their counterparts (ie, tricyclic antidepressants to gabapentin and vice versa) [137]. If individual drugs (tricyclic antidepressants, gabapentin) are partly successful, combination approaches may be used. Third-line monotherapy or add-on therapy may be attained with opioids or tramadol or newer agents such as duloxetine.

*Combination therapies.* Neuropathic pain involves multiple mechanisms at various sites with complex interactions. Theoretically, the use of drugs with different modes and sites of action may lead to improved efficacy with reduced side effects. For example, the combination of gabapentin and morphine produced significant analgesia in patients who had neuropathic pain (PHN and diabetic neuropathy) at a lower dose than each drug separately [140]. In patients who had painful diabetic neuropathy who did not respond to gabapentin monotherapy, the addition of venlafaxine in a double-blinded fashion resulted in significant pain improvement [141].

#### *Neuropathy secondary to neuritis*

The term *peripheral neuritis* was commonly used to describe generalized neuropathies related to chemical poisoning, autoimmunity, alcohol,

or nutritional deficiencies that may have an inflammatory component. Currently, *neuritis* is used to describe localized nerve pathologies secondary to inflammation. Inflammation anywhere along a nerve can be a source of pain felt in the organ supplied by the nerve. Inflammation may affect the nerve either through direct effects of mediator secretion, mainly cytokines, or secondary to pressure induced by the accompanying edema [142]. Both processes can induce nerve damage if allowed to persist [3]. Studies have characterized the symptoms accompanying this condition and shown tactile allodynia with a dominant role for myelinated nerve fibers [3,143].

In the orofacial region, dental and other invasive procedures can generate temporary perineural inflammation, but it is usually asymptomatic. However, misplaced implants or periapical inflammation close to a nerve trunk can produce symptoms. Other conditions, such as temporomandibular joint pathologies [4], paranasal sinusitis [5], or early malignancies [144], can induce symptomatic perineural inflammation, pain, and other aberrant sensations.

The involvement of inflammation in a clinical painful neuropathy is a clear indication for anti-inflammatory therapy. Early treatment with anti-inflammatory medication (corticosteroids or nonsteroidal anti-inflammatory drugs) can be beneficial because perineural and neural inflammation have a role in most neuronal pathologies.

#### *Traumatic neuropathy: oral and maxillofacial surgery perspective*

Although most surgical procedures heal with no residual problems, a small percentage of patients may present with continuing pain. Patients who have traumatic neuropathy must be separated from those who have recurrent pathology; the former may worsen with further surgeries. Additionally, careful surgical technique to avoid extensive tissue damage and direct neuronal injury is essential. Adequate local anesthesia and a comprehensive postoperative protocol for analgesia may be important in preventing chronic pain. Patients who have macrotrauma and fractures to the facial skeleton are often managed by oral and maxillofacial surgeons. Although early management is directed at life-saving interventions and restoring form and function, attention to pain and nerve injury is important. Early treatment of trauma-related pain probably allows a better prognosis. In selected cases, oral and maxillofacial surgeons may

be involved in the microsurgical reconstruction of damaged nerve trunks. Early distinction between sensory dysfunction secondary to nerve damage or operative edema is clinically difficult; QST may be crucial in these situations.

## References

- [1] Merskey H, Bogduk N. Classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms. 2nd edition. Seattle: IASP Press; 1994.
- [2] Okeson JP. Orofacial pain: guidelines for assessment, classification, and management. The American Academy of Orofacial Pain. Illinois (IL): Quintessence Publishing Co., Inc.; 1996.
- [3] Eliav E, Gracely RH, Nahlieli O, et al. Quantitative sensory testing in trigeminal nerve damage assessment. *J Orofac Pain* 2004;18(4):339–44.
- [4] Eliav E, Teich S, Nitzan D, et al. Facial arthralgia and myalgia: can they be differentiated by trigeminal sensory assessment? *Pain* 2003;104(3):481–90.
- [5] Benoliel R, Biron A, Quek SY, et al. Trigeminal neurosensory changes following acute and chronic paranasal sinusitis. *Quintessence Int* 2006;37(6):437–43.
- [6] Olesen J, Boussier M-G, Diener HC, et al. The international classification of headache disorders. 2nd edition. *Cephalalgia* 2004;24(suppl 1):24–150.
- [7] Katusic S, Beard CM, Bergstralh E, et al. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945–1984. *Ann Neurol* 1990;27(1):89–95.
- [8] Rasmussen P. Facial pain. III. A prospective study of the localization of facial pain in 1052 patients. *Acta Neurochir (Wien)* 1991;108(1–2):53–63.
- [9] Benoliel R, Sharav Y. Trigeminal neuralgia with lacrimation or SUNCT syndrome? *Cephalalgia* 1998;18(2):85–90.
- [10] Zakrzewska JM, Jassim S, Bulman JS. A prospective, longitudinal study on patients with trigeminal neuralgia who underwent radiofrequency thermocoagulation of the Gasserian ganglion. *Pain* 1999;79(1):51–8.
- [11] Bowsher D. Trigeminal neuralgia: a symptomatic study of 126 successive patients with and without previous interventions. *Pain Clinic* 2000;12(2):93–8.
- [12] Rasmussen P. Facial pain. II. A prospective survey of 1052 patients with a view of: character of the attacks, onset, course, and character of pain. *Acta Neurochir (Wien)* 1990;107(3–4):121–8.
- [13] Nurmikko TJ, Eldridge PR. Trigeminal neuralgia—pathophysiology, diagnosis and current treatment. *Br J Anaesth* 2001;87(1):117–32.
- [14] Sato J, Saitoh T, Notani K, et al. Diagnostic significance of carbamazepine and trigger zones in trigeminal neuralgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;97(1):18–22.
- [15] Bowsher D, Miles JB, Haggett CE, et al. Trigeminal neuralgia: a quantitative sensory perception threshold study in patients who had not undergone previous invasive procedures. *J Neurosurg* 1997;86(2):190–2.
- [16] Yang J, Simonson TM, Ruprecht A, et al. Magnetic resonance imaging used to assess patients with trigeminal neuralgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;81(3):343–50.
- [17] Yoshino N, Akimoto H, Yamada I, et al. Trigeminal neuralgia: evaluation of neuralgic manifestation and site of neurovascular compression with 3D CISS MR imaging and MR angiography. *Radiology* 2003;228(2):539–45.
- [18] Zakrzewska JM, Patsalos PN. Long-term cohort study comparing medical (oxcarbazepine) and surgical management of intractable trigeminal neuralgia. *Pain* 2002;95(3):259–66.
- [19] Tyler-Kabara EC, Kassam AB, Horowitz MH, et al. Predictors of outcome in surgically managed patients with typical and atypical trigeminal neuralgia: comparison of results following microvascular decompression. *J Neurosurg* 2002;96(3):527–31.
- [20] Fromm GH, Graff-Radford SB, Terrence CF, et al. Pre-trigeminal neuralgia. *Neurology* 1990;40(10):1493–5.
- [21] Mitchell RG. Pre-trigeminal neuralgia. *Braz Dent J* 1980;149(6):167–70.
- [22] de Siqueira SR, Nobrega JC, Valle LB, et al. Idiopathic trigeminal neuralgia: clinical aspects and dental procedures. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2004;98(3):311–5.
- [23] Taha JM, Tew JM Jr, Buncher CR. A prospective 15-year follow up of 154 consecutive patients with trigeminal neuralgia treated by percutaneous stereotactic radiofrequency thermal rhizotomy. *J Neurosurg* 1995;83(6):989–93.
- [24] De Simone R, Marano E, Brescia Morra V, et al. A clinical comparison of trigeminal neuralgic pain in patients with and without underlying multiple sclerosis. *Neurol Sci* 2005;26(Suppl 2):s150–1.
- [25] Hooge JP, Redekop WK. Trigeminal neuralgia in multiple sclerosis. *Neurology* 1995;45(7):1294–6.
- [26] Osterberg A, Boivie J, Thuomas KA. Central pain in multiple sclerosis—prevalence and clinical characteristics. *Eur J Pain* 2005;9(5):531–42.
- [27] Puca A, Meglio M, Vari R, et al. Evaluation of fifth nerve dysfunction in 136 patients with middle and posterior cranial fossae tumors. *Eur Neurol* 1995;35(1):33–7.
- [28] Puca A, Meglio M. Typical trigeminal neuralgia associated with posterior cranial fossa tumors. *Ital J Neurol Sci* 1993;14(7):549–52.
- [29] Cheng TM, Cascino TL, Onofrio BM. Comprehensive study of diagnosis and treatment of trigeminal neuralgia secondary to tumors. *Neurology* 1993;43(11):2298–302.

- [30] Nomura T, Ikezaki K, Matsushima T, et al. Trigeminal neuralgia: differentiation between intracranial mass lesions and ordinary vascular compression as causative lesions. *Neurosurg Rev* 1994;17(1):51–7.
- [31] MacDonald BK, Cockerell OC, Sander JW, et al. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;123(Pt 4):665–76.
- [32] Katusic S, Williams DB, Beard CM, et al. Incidence and clinical features of glossopharyngeal neuralgia, Rochester, Minnesota, 1945–1984. *Neuroepidemiology* 1991;10(5–6):266–75.
- [33] Love S, Coakham HB. Trigeminal neuralgia: pathology and pathogenesis. *Brain* 2001;124(Pt 12):2347–60.
- [34] Anderson VC, Berryhill PC, Sandquist MA, et al. High-resolution three-dimensional magnetic resonance angiography and three-dimensional spoiled gradient-recalled imaging in the evaluation of neurovascular compression in patients with trigeminal neuralgia: a double-blind pilot study. *Neurosurgery* 2006;58(4):666–73 [discussion: 666–673].
- [35] Taha JM, Tew JM Jr. Comparison of surgical treatments for trigeminal neuralgia: reevaluation of radiofrequency rhizotomy. *Neurosurgery* 1996;38(5):865–71.
- [36] Hamlyn PJ. Neurovascular relationships in the posterior cranial fossa, with special reference to trigeminal neuralgia. 2. Neurovascular compression of the trigeminal nerve in cadaveric controls and patients with trigeminal neuralgia: quantification and influence of method. *Clin Anat* 1997;10(6):380–8.
- [37] Meaney JF, Eldridge PR, Dunn LT, et al. Demonstration of neurovascular compression in trigeminal neuralgia with magnetic resonance imaging. Comparison with surgical findings in 52 consecutive operative cases. *J Neurosurg* 1995;83(5):799–805.
- [38] Devor M, Govrin-Lippmann R, Rappaport ZH. Mechanism of trigeminal neuralgia: an ultrastructural analysis of trigeminal root specimens obtained during microvascular decompression surgery. *J Neurosurg* 2002;96(3):532–43.
- [39] Beaver DL. Electron microscopy of the gasserian ganglion in trigeminal neuralgia. *J Neurosurg* 1967;26(1)Suppl:138–150.
- [40] Devor M, Amir R, Rappaport ZH. Pathophysiology of trigeminal neuralgia: the ignition hypothesis. *Clin J Pain* 2002;18(1):4–13.
- [41] Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci* 1999;19(19):8589–96.
- [42] Amir R, Devor M. Functional cross-excitation between afferent A- and C-neurons in dorsal root ganglia. *Neuroscience* 2000;95(1):189–95.
- [43] Hamlyn PJ. Neurovascular relationships in the posterior cranial fossa, with special reference to trigeminal neuralgia. 1. Review of the literature and development of a new method of vascular injection-filling in cadaveric controls. *Clin Anat* 1997;10(6):371–9.
- [44] Wiffen PJ, McQuay HJ, Moore RA. Carbamazepine for acute and chronic pain. *Cochrane Database Syst Rev* 2005;(3):CD005451.
- [45] Wiffen P, Collins S, McQuay H, et al. Anticonvulsant drugs for acute and chronic pain. *Cochrane Database Syst Rev* 2005;(3):CD001133.
- [46] Taylor JC, Brauer S, Espir ML. Long-term treatment of trigeminal neuralgia with carbamazepine. *Postgrad Med J* 1981;57(663):16–8.
- [47] Fromm GH, Terrence CF, Chattha AS. Baclofen in the treatment of trigeminal neuralgia: double-blind study and long-term follow-up. *Ann Neurol* 1984;15(3):240–4.
- [48] Zakrzewska JM, Chaudhry Z, Nurmikko TJ, et al. Lamotrigine (Lamictal) in refractory trigeminal neuralgia: results from a double-blind placebo controlled crossover trial. *Pain* 1997;73(2):223–30.
- [49] Cheshire WP Jr. Defining the role for gabapentin in the treatment of trigeminal neuralgia: a retrospective study. *J Pain* 2002;3(2):137–42.
- [50] Peters G, Nurmikko TJ. Peripheral and gasserian ganglion-level procedures for the treatment of trigeminal neuralgia. *Clin J Pain* 2002;18(1):28–34.
- [51] Quinn JH, Weil T. Trigeminal neuralgia: treatment by repetitive peripheral neurectomy. Supplemental report. *J Oral Surg* 1975;33(8):591–5.
- [52] Pradel W, Hlawitschka M, Eckelt U, et al. Cryosurgical treatment of genuine trigeminal neuralgia. *Br J Oral Maxillofac Surg* 2002;40(3):244–7.
- [53] Fardy MJ, Zakrzewska JM, Patton DW. Peripheral surgical techniques for the management of trigeminal neuralgia—alcohol and glycerol injections. *Acta Neurochir (Wien)* 1994;129(3–4):181–4 [discussion: 185].
- [54] Erdem E, Alkan A. Peripheral glycerol injections in the treatment of idiopathic trigeminal neuralgia: retrospective analysis of 157 cases. *J Oral Maxillofac Surg* 2001;59(10):1176–80.
- [55] Bouquot JE, Roberts AM, Person P, et al. Neuralgia-inducing cavitation osteonecrosis (NICO). Osteomyelitis in 224 jawbone samples from patients with facial neuralgia. *Oral Surg Oral Med Oral Pathol* 1992;73(3):307–19 [discussion: 319–20].
- [56] Gruppo R, Glueck CJ, McMahon RE, et al. The pathophysiology of alveolar osteonecrosis of the jaw: anticardiolipin antibodies, thrombophilia, and hypofibrinolysis. *J Lab Clin Med* 1996;127(5):481–8.
- [57] Zuniga JR. Challenging the neuralgia-inducing cavitation osteonecrosis concept. *J Oral Maxillofac Surg* 2000;58(9):1021–8.

- [58] Donlon WC. Long-term effects of jawbone curettage on the pain of facial neuralgia (commentary). *J Oral Maxillofac Surg* 1995;53(4):397–8.
- [59] Sciubba JJ. Long-term effects of jawbone curettage on the pain of facial neuralgia (commentary). *J Oral Maxillofac Surg* 1995;53(4):398–9.
- [60] Lopez BC, Hamlyn PJ, Zakrzewska JM. Systematic review of ablative neurosurgical techniques for the treatment of trigeminal neuralgia. *Neurosurgery* 2004;54(4):973–82 [discussion: 982–3].
- [61] Kalkanis SN, Eskandar EN, Carter BS, et al. 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 [discussion: 1261–2].
- [62] Barker FG 2nd, Jannetta PJ, Bissonette DJ, et al. The long-term outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med* 1996;334(17):1077–83.
- [63] Burchiel KJ, Clarke H, Haglund M, et al. Long-term efficacy of microvascular decompression in trigeminal neuralgia. *J Neurosurg* 1988;69(1):35–8.
- [64] Zakrzewska JM, Lopez BC, Kim SE, et al. Patient reports of satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. *Neurosurgery* 2005;56(6):1304–11 [discussion: 1311–2].
- [65] Broggi G, Ferroli P, Franzini A, et al. Microvascular decompression for trigeminal neuralgia: comments on a series of 250 cases, including 10 patients with multiple sclerosis. *J Neurol Neurosurg Psychiatr* 2000;68(1):59–64.
- [66] Lim JNW, Ayiku L. The clinical efficacy and safety of stereotactic radiosurgery (gamma knife) in the treatment of trigeminal neuralgia: National Institute for Clinical Excellence (NICE); 2004. Available at: <http://www.nice.org.uk/nicemedia/pdf/ip/173systematicreview.pdf>.
- [67] Fountas KN, Lee GP, Smith JR. Outcome of patients undergoing gamma knife stereotactic radiosurgery for medically refractory idiopathic trigeminal neuralgia: Medical College of Georgia's experience. *Stereotact Funct Neurosurg* 2006;84(2–3):88–96.
- [68] Pollock BE, Ecker RD. A prospective cost-effectiveness study of trigeminal neuralgia Surgery. *Clin J Pain* 2005;21(4):317–22.
- [69] Massager N, Murata N, Tamura M, et al. Influence of nerve radiation dose in the incidence of trigeminal dysfunction after trigeminal neuralgia radiosurgery. *Neurosurgery* 2007;60(4):681–7 [discussion: 687–8].
- [70] Sanchez-Mejia RO, Limbo M, Cheng JS, et al. Recurrent or refractory trigeminal neuralgia after microvascular decompression, radiofrequency ablation, or radiosurgery. *Neurosurg Focus* 2005;18(5):e12.
- [71] Patel A, Kassam A, Horowitz M, et al. Microvascular decompression in the management of glossopharyngeal neuralgia: analysis of 217 cases. *Neurosurgery* 2002;50(4):705–10 [discussion: 710–1].
- [72] Ekblom KA, Westerberg CE. Carbamazepine in glossopharyngeal neuralgia. *Arch Neurol* 1966;14(6):595–6.
- [73] Rushton JG, Stevens JC, Miller RH. Glossopharyngeal (vagoglossopharyngeal) neuralgia: a study of 217 cases. *Arch Neurol* 1981;38(4):201–5.
- [74] Minagar A, Sheremata WA. Glossopharyngeal neuralgia and MS. *Neurology* 2000;54(6):1368–70.
- [75] Huynh-Le P, Matsushima T, Hisada K, et al. Glossopharyngeal neuralgia due to an epidermoid tumour in the cerebellopontine angle. *J Clin Neurosci* 2004;11(7):758–60.
- [76] Pfendler DF. Glossopharyngeal neuralgia with tongue carcinoma. *Arch Otolaryngol Head Neck Surg* 1997;123(6):658.
- [77] Ragozzino MW, Melton LJ 3rd, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. *Medicine (Baltimore)* 1982;61(5):310–6.
- [78] Goh CL, Khoo L. A retrospective study of the clinical presentation and outcome of herpes zoster in a tertiary dermatology outpatient referral clinic. *Int J Dermatol* 1997;36(9):667–72.
- [79] Haanpaa M, Laippala P, Nurmikko T. Pain and somatosensory dysfunction in acute herpes zoster. *Clin J Pain* 1999;15(2):78–84.
- [80] Nurmikko T, Bowsher D. Somatosensory findings in postherpetic neuralgia. *J Neurol Neurosurg Psychiatr* 1990;53(2):135–41.
- [81] Dworkin RH, Nagasako EM, Johnson RW, et al. Acute pain in herpes zoster: the famciclovir database project. *Pain* 2001;94(1):113–9.
- [82] Wood M. Understanding pain in herpes zoster: an essential for optimizing treatment. *J Infect Dis* 2002;186(Suppl 1):S78–82.
- [83] Volpi A, Gross G, Hercogova J, et al. Current management of herpes zoster: the European view. *Am J Clin Dermatol* 2005;6(5):317–25.
- [84] Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage* 1997;13(6):327–31.
- [85] Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352(22):2271–84.
- [86] Coen PG, Scott F, Leedham-Green M, et al. Predicting and preventing post-herpetic neuralgia: are current risk factors useful in clinical practice? *Eur J Pain* 2006;10(8):695–700.

- [87] Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. *Pain* 1996;67(2-3):241-51.
- [88] Oaklander AL, Bowsher D, Galer B, et al. Herpes zoster itch: preliminary epidemiologic data. *J Pain* 2003;4(6):338-43.
- [89] Watson CP, Deck JH, Morshead C, et al. Postherpetic neuralgia: further post-mortem studies of cases with and without pain. *Pain* 1991;44(2):105-17.
- [90] Oaklander AL, Romans K, Horasek S, et al. Unilateral postherpetic neuralgia is associated with bilateral sensory neuron damage. *Ann Neurol* 1998;44(5):789-95.
- [91] Pappagallo M, Oaklander AL, Quatrano-Piacentini AL, et al. Heterogenous patterns of sensory dysfunction in postherpetic neuralgia suggest multiple pathophysiological mechanisms. *Anesthesiology* 2000;92(3):691-8.
- [92] Dubinsky RM, Kabbani H, El-Chami Z, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004;63(6):959-65.
- [93] van Seventer R, Feister HA, Young JP Jr, et al. Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial. *Curr Med Res Opin* 2006;22(2):375-84.
- [94] Benoliel R, Birenboim R, Regev E, et al. Neurosensory changes in the infraorbital nerve following zygomatic fractures. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;99(6):657-65.
- [95] Macrae WA. Chronic pain after surgery. *Br J Anaesth* 2001;87(1):88-98.
- [96] Gregg JM. Neuropathic complications of mandibular implant surgery: review and case presentations. *Ann R Australas Coll Dent Surg* 2000;15:176-80.
- [97] Cheung LK, Lo J. The long-term clinical morbidity of mandibular step osteotomy. *Int J Adult Orthodon Orthognath Surg* 2002;17(4):283-90.
- [98] Walton JN. Altered sensation associated with implants in the anterior mandible: a prospective study. *J Prosthet Dent* 2000;83(4):443-9.
- [99] Kraut RA, Chahal O. Management of patients with trigeminal nerve injuries after mandibular implant placement. *J Am Dent Assoc* 2002;133(10):1351-4.
- [100] Eliav E, Gracely RH. Sensory changes in the territory of the lingual and inferior alveolar nerves following lower third molar extraction. *Pain* 1998;77(2):191-9.
- [101] Valmaseda-Castellon E, Berini-Ayres L, Gay-Escoda C. Inferior alveolar nerve damage after lower third molar surgical extraction: a prospective study of 1117 surgical extractions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001;92(4):377-83.
- [102] Berge TI. Incidence of chronic neuropathic pain subsequent to surgical removal of impacted third molars. *Acta Odontol Scand* 2002;60(2):108-12.
- [103] Vora AR, Loescher AR, Boissonade FM, et al. Ultrastructural characteristics of axons in traumatic neuromas of the human lingual nerve. *J Orofac Pain* 2005;19(1):22-33.
- [104] Polycarpou N, Ng YL, Canavan D, et al. Prevalence of persistent pain after endodontic treatment and factors affecting its occurrence in cases with complete radiographic healing. *Int Endod J* 2005;38(3):169-78.
- [105] Lobb WK, Zakariassen KL, McGrath PJ. Endodontic treatment outcomes: do patients perceive problems? *J Am Dent Assoc* 1996;127(5):597-600.
- [106] Campbell RL, Parks KW, Dodds RN. Chronic facial pain associated with endodontic therapy. *Oral Surg Oral Med Oral Pathol* 1990;69(3):287-90.
- [107] Jaaskelainen SK, Forssell H, Tenovuo O. Electrophysiological testing of the trigeminofacial system: aid in the diagnosis of atypical facial pain. *Pain* 1999;80(1-2):191-200.
- [108] Pfaffenrath V, Rath M, Pollmann W, et al. Atypical facial pain—application of the IHS criteria in a clinical sample. *Cephalalgia* 1993;13(Suppl 12):84-8.
- [109] Melzack R, Terrence C, Fromm G, et al. Trigeminal neuralgia and atypical facial pain: use of the McGill Pain Questionnaire for discrimination and diagnosis. *Pain* 1986;27(3):297-302.
- [110] Agostoni E, Frigerio R, Santoro P. Atypical facial pain: clinical considerations and differential diagnosis. *Neurol Sci* 2005;26(Suppl 2):s71-4.
- [111] Baad-Hansen L, List T, Kaube H, et al. Blink reflexes in patients with atypical odontalgia and matched healthy controls. *Exp Brain Res* 2006;172(4):418-506.
- [112] Schnurr RF, Brooke RI. Atypical odontalgia. Update and comment on long-term follow-up. *Oral Surg Oral Med Oral Pathol* 1992;73(4):445-8.
- [113] Melis M, Lobo SL, Ceneviz C, et al. Atypical odontalgia: a review of the literature. *Headache* 2003;43(10):1060-74.
- [114] Vickers ER, Cousins MJ. Neuropathic orofacial pain part 1—prevalence and pathophysiology. *Aust Endod J* 2000;26(1):19-26.
- [115] Stanton-Hicks M. Complex regional pain syndrome. *Anesthesiol Clin North America* 2003;21(4):733-44.
- [116] Janig W, Baron R. Complex regional pain syndrome: mystery explained? *Lancet Neurol* 2003;2(11):687-97.
- [117] Janig W, Baron R. Experimental approach to CRPS. *Pain* 2004;108(1-2):3-7.
- [118] Baron R, Wasner G. Complex regional pain syndromes. *Curr Pain Headache Rep* 2001;5(2):114-23.

- [119] Birklein F. Complex regional pain syndrome. *J Neurol* 2005;252(2):131–8.
- [120] Wasner G, Schattschneider J, Baron R. Skin temperature side differences—a diagnostic tool for CRPS? *Pain* 2002;98(1–2):19–26.
- [121] Melis M, Zawawi K, al-Badawi E, et al. Complex regional pain syndrome in the head and neck: a review of the literature. *J Orofac Pain* 2002;16(2):93–104.
- [122] Fried K, Bongehiell U, Boissonade FM, et al. Nerve injury-induced pain in the trigeminal system. *Neuroscientist* 2001;7(2):155–65.
- [123] Devor M. Response of nerves to injury in relation to neuropathic pain. In: Koltzenburg M, McMahon SB, editors. *Wall and Melzack's textbook of pain*. Edinburgh: Churchill Livingstone; 2005.
- [124] Scholz J, Woolf CJ. Can we conquer pain? *Nat Neurosci* 2002;5(Suppl):1062–7.
- [125] Watkins LR, Hutchinson MR, Ledebor A, et al. Norman Cousins Lecture. Glia as the “bad guys”: implications for improving clinical pain control and the clinical utility of opioids. *Brain Behav Immun* 2007;21(2):131–46.
- [126] Inglese M, Makani S, Johnson G, et al. Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. *J Neurosurg* 2005;103(2):298–303.
- [127] Povlishock JT, Katz DI. Update of neuropathology and neurological recovery after traumatic brain injury. *J Head Trauma Rehabil* 2005;20(1):76–94.
- [128] Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94(2):149–58.
- [129] Susarla SM, Kaban LB, Donoff RB, et al. Functional sensory recovery after trigeminal nerve repair. *J Oral Maxillofac Surg* 2007;65(1):60–5.
- [130] Caissie R, Goulet J, Fortin M, et al. Iatrogenic paresthesia in the third division of the trigeminal nerve: 12 years of clinical experience. *J Can Dent Assoc* 2005;71(3):185–90.
- [131] Rutner TW, Ziccardi VB, Janal MN. Long-term outcome assessment for lingual nerve microsurgery. *J Oral Maxillofac Surg* 2005;63(8):1145–9.
- [132] Strauss ER, Ziccardi VB, Janal MN. Outcome assessment of inferior alveolar nerve microsurgery: a retrospective review. *J Oral Maxillofac Surg* 2006;64(12):1767–70.
- [133] Dodson TB, Kaban LB. Recommendations for management of trigeminal nerve defects based on a critical appraisal of the literature. *J Oral Maxillofac Surg* 1997;55(12):1380–6 [discussion: 1387].
- [134] Pogrel MA. The results of microneurosurgery of the inferior alveolar and lingual nerve. *J Oral Maxillofac Surg* 2002;60(5):485–9.
- [135] Bullard DE, Nashold BS Jr. The caudalis DREZ for facial pain. *Stereotact Funct Neurosurg* 1997;68(1–4 Pt 1):168–74.
- [136] Kanpolat Y, Savas A, Ugur HC, et al. The trigeminal tract and nucleus procedures in treatment of atypical facial pain. *Surg Neurol* 2005;64(Suppl 2):S96–100 [discussion: S100–1].
- [137] Finnerup NB, Otto M, McQuay HJ, et al. Algorithm for neuropathic pain treatment: an evidence based proposal. *Pain* 2005;118(3):289–305.
- [138] Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev* 2005;(3):CD005454.
- [139] Beniczky S, Tajti J, Timea Varga E, et al. Evidence-based pharmacological treatment of neuropathic pain syndromes. *J Neural Transm* 2005;112(6):735–49.
- [140] Gilron I, Bailey JM, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med* 2005;352(13):1324–34.
- [141] Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. *J Clin Neuromuscul Dis* 2001;3:53–62.
- [142] Zelenka M, Schafers M, Sommer C. Intraneural injection of interleukin-1beta and tumor necrosis factor-alpha into rat sciatic nerve at physiological doses induces signs of neuropathic pain. *Pain* 2005;116(3):257–63.
- [143] Neumann S, Doubell TP, Leslie T, et al. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. *Nature* 1996;384(6607):360–4.
- [144] Eliav E, Teich S, Benoliel R, et al. Large myelinated nerve fiber hypersensitivity in oral malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002;94(1):45–50.
- [145] Benoliel R, Heir G, Eliav E. Neuropathic orofacial pain. In: Sharav Y, Benoliel R, editors. *Orofacial Pain and Headache*. Elsevier, in press.