Neuropathic Orofacial Pain

Olga A. Korczeniewska, Eli Eliav, and Rafael Benoliel

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Abstract
Neuropathic pain (NP) is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.” Neuropathic pain syndromes are relatively common and induce significant suffering with loss of quality of life. In the area of the head and neck, there are a number of well-recognized painful neuropathic disorders affecting the cranial nerves, other regional nerves, and central nervous system structures. This chapter reviews the diagnosis, pathophysiology, and management of the more common neuropathic pain entities affecting the head and neck region.

Keywords
Trigeminal · Neuropathy · Neuralgia · Headache · Burning mouth syndrome

Introduction
This chapter focuses on painful neuropathies affecting oral and facial structures, or neuropathic orofacial pain (NOP). NOP (Benoliel et al. 2015) is an umbrella term and includes entities described in the section on painful lesions of the cranial nerves and other facial pain of the International Headache Society’s (IHS) classification (Headache Classification Subcommittee of the International Headache Society (IHS) 2018).

What Is Neuropathic Pain?
Neuropathic pain (NP) is defined as “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” (Treede et al. 2008). The definition gives little information on how it may differ from other “pains” a patient
may feel. Other pain terminology definitions are outlined in Table 1. Under normal conditions, pain is felt when signals originating within thinly myelinated (Aδ) and/or unmyelinated (C) nociceptive afferents reach a conscious brain. Pain’s most basic purpose is to protect. When a person is injured, the pain felt usually correlates with the noxious stimulus. This is nociceptive or “good” pain.

Minor tissue injuries or insults often cause inflammation with accompanying pain and changes in regional sensitivity (Tal et al. 2015). This is known as “inflammatory” pain. Typically, there are two types of changes in sensitivity, and these can be distinguished based on the stimulus-response properties. Pain in response to a normally painless stimulus is termed “allodynia.” The pain sensation felt in the inflamed tissue no longer correlates with the innocuous (non-noxious) stimulus (Jensen and Finnerup 2014). The second is “hyperalgesia,” where there is significantly increased pain in response to a normally painful stimulus (Jensen and Finnerup 2014). Inflammatory allodynia and hyperalgesia may be explained by an increase in the responsiveness of nociceptor endings (“peripheral sensitization”). This phenomenon is a result of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>International Association of the Study of Pain Taxonomy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Term</strong></td>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>Pain</td>
<td>An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage</td>
</tr>
<tr>
<td>Allodynia</td>
<td>Pain due to a stimulus which does not normally provoke pain. (e.g., touch, light pressure, or moderate cold or warmth)</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>An increased response to a stimulus which is normally painful</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td>Increased sensitivity to stimulation, excluding the special senses. Includes both allodynia and hyperalgesia</td>
</tr>
<tr>
<td>Hyperpathia</td>
<td>A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold</td>
</tr>
<tr>
<td>Hypoalgesia</td>
<td>Diminished pain in response to a normally painful stimulus</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Absence of pain in response to stimulation which would normally be painful</td>
</tr>
<tr>
<td>Hyperpathia</td>
<td>A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. May occur with allodynia, hyperesthesia, hyperalgesia, or dysesthesia</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>An abnormal sensation, whether spontaneous or evoked</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>Decreased sensitivity to stimulation, excluding the special senses</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>An unpleasant abnormal sensation, whether spontaneous or evoked. Hyperalgesia and allodynia are forms of dysesthesia</td>
</tr>
</tbody>
</table>

Based on terminology and definitions in: https://www.iasp-pain.org/
inflammatory mediators released in the injured tissue. The sensitized nociceptors respond at substantially reduced thresholds. Further mechanisms include activation of “silent” or “sleeping” C-fiber nociceptors.

In many ways, neuropathic pain resembles inflammatory pain in that spontaneous pain and hypersensibility are usually present. By definition the injury or disease in NP is in nerve tissue. Clinicians often rely on the history to identify NP. Mechanistically, however, there seems to be considerable overlap between neuropathic and inflammatory pain processes. Nociceptive and inflammatory pain are clearly adaptive and protective. The temporary hypersensibility in inflammatory pain protects against further damage by reducing use of the body part and suppressing activity. Neuropathic pain reflects pathophysiological dysfunction of the somatosensory system. It is maladaptive and has been termed “bad” pain.

Epidemiology of Neuropathic Pain

The exact prevalence of NP is unclear, partly due to inconsistent definitions and clinical criteria, and is best estimated between 6.9% and 10% (van Hecke et al. 2014). The prevalence of age-associated NP syndromes is expected to increase with increased life expectancy and disease survival rates. NP and its treatment present a major health care burden as they lead to impaired quality of life, reduced employment, low productivity, and extensive usage of healthcare facilities (McDermott et al. 2006; Meyer-Rosberg et al. 2001).

Classification of Regional Neuropathic Pain

The IHS’s classification, The International Classification of Headache Disorders (ICHD), serves as the basis for the definitions and descriptions of the clinical NOP syndromes described in this chapter. The ICHD is an invaluable resource detailing inclusion criteria for all painful head and neck neuropathies (http://www.ihs-headache.org), under the section on “painful lesions of the cranial nerves and other facial pain.” Conceptually, this section may be viewed under six major areas (Fig. 1). All except for the rarer facial (periorbital) pain conditions such as optic neuritis, ischemic ocular motor nerve palsy, Tolosa-Hunt syndrome, paratrigeminal oculosympathetic (Raeder’s) syndrome, and recurrent painful opthalmoplegic neuropathy are reviewed in this chapter (Table 2). It should be noted that neuropathies may present without pain (Smith and Cutrer 2011). All relevant diagnostic figures and tables are reproduced with permission of the International Headache Society.

General Features of Neuropathic Pain

The quality of pain across many NPs is often described as burning, sharp, or electric. Symptoms of NP may include stimulus-dependent (evoked, e.g., mechanical, thermal) as well as stimulus-independent (spontaneous) pain (Dworkin et al. 2003) with positive (e.g., hyperalgesia, allodynia) and/or negative (e.g., numbness) sensory signs that should be assessed and recorded employing accepted terminology (Table 1) (IASP Taxonomy IASP 2012). The mapping of affected areas using quantitative sensory testing (QST) and photographic documentation should constitute part of patient evaluation and follow-up. When advanced QST apparatus is unavailable, sensory function can be assessed using a simple pin, blunt instrument, warmed and cooled implements, or cotton wool (Baad-Hansen et al. 2013a). Additionally, changes in temporal summation and pain modulation can be examined using sensory testing protocols (Nasri-Heir et al. 2015; Yarnitsky et al. 2008).

Pain Attributed to a Lesion or Disease of the Trigeminal Nerve

Trigeminal Neuralgia

Introduction and Definition

Trigeminal neuralgia (TN) is characterized by excruciating, short-lasting, unilateral facial pain with clear diagnostic criteria (Table 3). The
ICHD-3 subdivides TN into three subtypes that may only be diagnosed following imaging. Classical trigeminal neuralgia (CTN) occurs with “demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes in the trigeminal nerve root.” Compression is typically associated with nerve atrophy or displacement. Secondary trigeminal neuralgia is reserved for a typical TN phenotype associated with a local or systemic disease. Finally, idiopathic trigeminal neuralgia has been introduced for patients with typical TN not associated with nerve compression, local or systemic disease. Both classical and idiopathic trigeminal neuralgia are subdivided into purely paroxysmal and those with concomitant persistent pain (Headache Classification Subcommittee of the International Headache Society (IHS) 2018).

Epidemiology
The epidemiology of the new subclassifications is yet to be accurately established. However, based on previous studies, TN is a rare condition with a lifetime prevalence of 70/100,000 population (MacDonald et al. 2000). Prevalence of TN increases with age and is estimated to be 17.5/100,000 person-years in 60–69-year-olds and rises to 25.9/100,000 person-years in >80-year-olds. The condition is extremely rare in children.
Table 2  ICHD (Chapter 13). Painful lesions of the cranial nerves and other facial pain*

### 13.1 Pain attributed to a lesion or disease of the trigeminal nerve

<table>
<thead>
<tr>
<th>13.1.1</th>
<th>Trigeminal neuralgia</th>
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<tbody>
<tr>
<td>13.1.1.1</td>
<td>Classical trigeminal neuralgia (CTN)</td>
</tr>
<tr>
<td>13.1.1.1.1</td>
<td>CTN, purely paroxysmal</td>
</tr>
<tr>
<td>13.1.1.1.2</td>
<td>CTN with concomitant continuous pain</td>
</tr>
<tr>
<td>13.1.1.2</td>
<td>Secondary trigeminal neuralgia (TN)</td>
</tr>
<tr>
<td>13.1.1.2.1</td>
<td>TN attributed to multiple sclerosis</td>
</tr>
<tr>
<td>13.1.1.2.2</td>
<td>TN attributed to space-occupying lesion</td>
</tr>
<tr>
<td>13.1.1.2.3</td>
<td>TN attributed to other cause</td>
</tr>
<tr>
<td>13.1.1.3</td>
<td>Idiopathic trigeminal neuralgia (ITN)</td>
</tr>
<tr>
<td>13.1.1.3.1</td>
<td>ITN, purely paroxysmal</td>
</tr>
<tr>
<td>13.1.1.3.2</td>
<td>ITN with concomitant continuous pain</td>
</tr>
</tbody>
</table>

### 13.1.2 Painful trigeminal neuropathy

| 13.1.2.1 | Painful trigeminal neuropathy attributed to herpes zoster |
| 13.1.2.2 | Trigeminal postherpetic neuralgia |
| 13.1.2.3 | Painful posttraumatic trigeminal neuropathy |
| 13.1.2.4 | Painful trigeminal neuropathy attributed to other disorder |
| 13.1.2.5 | Idiopathic painful trigeminal neuropathy |

### 13.2 Pain attributed to a lesion or disease of the glossopharyngeal nerve

<table>
<thead>
<tr>
<th>13.2.1</th>
<th>Glossopharyngeal neuralgia</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.2.1.1</td>
<td>Classical glossopharyngeal neuralgia</td>
</tr>
<tr>
<td>13.2.1.2</td>
<td>Secondary glossopharyngeal neuralgia</td>
</tr>
<tr>
<td>13.2.1.3</td>
<td>Idiopathic glossopharyngeal neuralgia</td>
</tr>
</tbody>
</table>

### 13.2.2 Painful glossopharyngeal neuropathy

| 13.2.2.1 | Painful glossopharyngeal neuropathy attributed to a known cause |
| 13.2.2.2 | Idiopathic painful glossopharyngeal neuropathy |

### 13.3 Pain attributed to a lesion or disease of nervus intermedius

<table>
<thead>
<tr>
<th>13.3.1</th>
<th>Nervus intermedius neuralgia (NIN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.3.1.1</td>
<td>Classical nervus intermedius neuralgia</td>
</tr>
<tr>
<td>13.3.1.2</td>
<td>Secondary nervus intermedius neuralgia</td>
</tr>
<tr>
<td>13.3.1.3</td>
<td>Idiopathic nervus intermedius neuralgia</td>
</tr>
</tbody>
</table>

### 13.3.2 Painful nervus intermedius neuropathy

| 13.3.2.1 | Painful nervus intermedius neuropathy attributed to herpes zoster |
| 13.3.2.2 | Postherpetic neuralgia of nervus intermedius |
| 13.3.2.3 | Painful nervus intermedius neuropathy attributed to other disorder |
| 13.3.2.4 | Idiopathic painful nervus intermedius neuropathy |

### 13.4 Occipital neuralgia

### 13.5 Neck-tongue syndrome

### 13.6 Painful optic neuritis

### 13.7 Headache attributed to ischemic ocular motor nerve palsy

### 13.8 Tolosa-Hunt syndrome

### 13.9 Paratrigeminal oculosympathetic (Raeder’s) syndrome

### 13.10 Recurrent painful ophthalmoplegic neuropathy

### 13.11 Burning mouth syndrome (BMS)

### 13.12 Persistent idiopathic facial pain (PIFP)

### 13.13 Central neuropathic pain

| 13.13.1 | Central neuropathic pain attributed to multiple sclerosis (MS) |
| 13.13.2 | Central post-stroke pain (CPSP) |

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Clinical Features of Classical Trigeminal Neuralgia

The initial diagnosis of CTN is based on the history and characteristic clinical signs and symptoms (Table 4). Most CTN patients report paroxysmal attacks of pain but up to 30% present with a history of concomitant background pain (Maarbjerг et al. 2017). Adequate oral
radiographs (bitewings, full mouth periapicals, panoramic) of oral structures are essential to rule out pathology and cranial nerves should be examined routinely. Neurovascular compression can be identified via imaging techniques such as magnetic resonance imaging (Fig. 2) or magnetic resonance tomographic angiography (Yoshino et al. 2003). Additionally, the most reliable electrophysiological test result in identifying secondary trigeminal neuralgia (STN) cases seems to be abnormal trigeminal reflexes (Gronseth et al. 2008).

Classical Trigeminal Neuralgia Purely Paroxysmal
The short, paroxysmal stabbing attacks of pain with no pain in-between has been the typical profile associated with TN.

Clinical Features of Classical Trigeminal Neuralgia Purely Paroxysmal
CTN is a unilateral facial pain syndrome (van Hecke et al. 2014). Bilateral pain is always a cause for concern (Di Stefano et al. 2017a). Nevertheless, very rarely bilateral pain may be reported but is usually preceded by pain in one side (Kuncz et al. 2006; Tacconi and Miles 2000; Maarbjerg et al. 2014a). Pain location is usually described according to the major branches of the trigeminal nerve (Fig. 3). Pain radiation is usually within the dermatome of origin. Although there are interindividual differences in the location, intensity, and triggers of CTN, these parameters are highly stereotyped within patients where each attack is comparable in location, duration and intensity.

CTN pain is most frequently described as paroxysmal, shooting, sharp, piercing, stabbing, or electrical in nature (70–95%) (Maarbjerg et al. 2014b; Haviv et al. 2016). Pain severity is ranked as extreme with ratings of 9–10 on 10 cm visual analogue scale (VAS) (Bowsher 2000; Reddy et al. 2013). In CTN, pain severity is ranked as extreme with ratings of 9–10 on 10 cm visual analogue scale (VAS) (Bowsher 2000; Reddy et al. 2013). According to the diagnostic criteria, CTN pain can be triggered by light, innocuous touch in trigger areas. Latency refers to the short break between stimulation of the trigger area and pain onset. However, CTN attacks may be perceived to be spontaneous with some patients

Table 4 Diagnostic criteria for classical trigeminal neuralgia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
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<tbody>
<tr>
<td>A Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia</td>
<td></td>
</tr>
<tr>
<td>B Demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes in the trigeminal nerve root</td>
<td>Typically with atrophy or displacement</td>
</tr>
</tbody>
</table>

Diagnostic criteria for classical trigeminal neuralgia, purely paroxysmal

| A Recurrent paroxysms of unilateral facial pain fulfilling criteria for classical trigeminal neuralgia | Classical trigeminal neuralgia without persistent background facial pain |
| B Pain-free between attacks in the affected trigeminal distribution | Usually responsive, at least initially, to pharmacotherapy, especially carbamazepine or oxcarbazepine |

Diagnostic criteria for classical trigeminal neuralgia with concomitant persistent facial pain

| A Recurrent paroxysms of unilateral facial pain fulfilling criteria for classical trigeminal neuralgia | Seen in about 30% of patients |
| B Concomitant continuous or near-continuous pain between attacks in the affected trigeminal distribution | Previously used terms: Persistent facial pain, atypical trigeminal neuralgia, trigeminal neuralgia type 2 Central sensitization may account for the persistent facial pain. Neurovascular compression on MRI is less likely to be demonstrated. responds poorly to conservative treatment and to neurosurgical interventions. Less likely to be triggered by innocuous stimuli |

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not reporting a clear trigger. It is worth considering that trigger-like areas may be identified in about 9% of other orofacial pain syndromes and are not therefore considered pathognomonic for CTN (Sato et al. 2004). Trigger areas are typically found in the dermatomes of the affected trigeminal branches, predominantly around the lips; however, they may also be found in locations other than trigeminal and may even change location (Bowsher 2000; Di Stefano et al. 2017b). Intraoral trigger points are most often associated with the gingival area (Bowsher 2000; de Siqueira et al. 2004). Innocuous stimuli such as talking (76%), chewing (74%), touch (65%), temperature (cold 48%, heat 1%), wind, and shaving are the most common triggers (Bowsher 2000).

CTN pain attacks are short lasting (by definition up to 2 min) and are characterized by a rapid onset and peak. Pain is followed by a refractory period, during which pain may not be triggered. Most CTN attacks occur during the day; however, nocturnal pain has been reported (Benoliel et al. 2009; Devor et al. 2008). Based on follow-up of CTN patients, the median active period was estimated at around 49 days and periods of remission were estimated to last from days to years (days 16%, weeks 16%, and months 36%, more than a year 6%, some patients have continuous pain). About 20% of patients, however, experience continuous attacks. While most CTN attacks occur abruptly, some are preceded by a rare syndrome referred to as pretrigeminal neuralgia (Fromm et al. 1990).

The natural history of CTN has historically been considered to include remissions but with a progressive worsening and poor prognosis.
(Zakrzewska and Lopez 2004). However, a more recent study has shown that worsening of pain over time and drug-resistance occurred in a very small minority of patients (Di Stefano et al. 2014). This may reflect the improvement in the diagnosis and identification of patients. In drug-resistant patients, microvascular decompression (MVD) is often required (Zakrzewska and Patsalos 2002), and it is unclear if the disease duration affects surgical prognosis (Brogi et al. 2000).

CTN pain attacks are accompanied by classic contraction of the facial muscles, thus the historical terms *tic douloureux* and *tic convulsif*. Although lacrimation is not considered a sign of neuropathic pain, it occurs in about a quarter of CTN cases (Haviv et al. 2016; Simms and Honey 2011) and seems to be associated with increasing pain severity. Poorer prognosis for pharmacotherapy and surgery have been reported in CTN cases with lacrimation (Simms and Honey 2011; Benoliel et al. 2016). About 30% of CTN cases present with sensory abnormalities, for example, hypoesthesia, and these are more readily detected with advanced QST methods (Maarbjerg et al. 2014b; Maier et al. 2010).

With such severe pain and common medication side-effects, CTN patients report reduced quality of life (Bowsher 2000; Zakrzewska 2001) and

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**Fig. 3** Pain distribution in trigeminal neuralgia: most cases (36–42%) report pain in only one branch. The maxillary (16%) or the mandibular (18%) branch is the most common, while the ophthalmic branch will singly be affected in only about 2% of cases. The maxillary and mandibular branches will be affected together in 35% of cases and all three branches will be involved in 14% of patients. (Original drawing by Dr Hala Al Janaby, Perth WA, Australia)
are often depressed and anxious (Macianskyte et al. 2011).

**CTN with Concomitant Persistent Facial Pain**

The exact mechanisms involved in the etiology of the persistent pain are unclear. A faulty pain modulation system and/or central sensitization have been implicated (Hu et al. 2010; Leonard et al. 2009). CTN patients with persistent pain were suggested to have a deficient descending inhibitory system as experimentally induced conditioned pain modulation was not observed in these patients (Leonard et al. 2009). Patients with concomitant pain have more tender points than purely paroxysmal CTN patients or healthy controls, suggesting that in CTN patients with background pain, central sensitization extends beyond the trigeminal system (Leonard et al. 2009). Overactive central sensory transmission, in particular central facilitation of trigeminal nociceptive processing, has been suggested to contribute to the etiology of CTN with background pain (Obermann et al. 2007).

**Clinical Features of CTN with Concomitant Persistent Facial Pain**

About 35–49% of CTN patients report two types of pain, the characteristic of CTN paroxysmal attacks of short, sharp, stabbing pain as well as dull, throbbing, and burning background pain that varies in duration and intensity (mean VAS of 4.6) (Maarbjerg et al. 2014a; Benoliel et al. 2009; Nurminnko and Eldridge 2001). Bilateral pain is significantly more common in CTN with background pain compared to purely paroxysmal CTN (Maarbjerg et al. 2014a). CTN patients with concomitant persistent facial pain are usually younger and more often females. Longer attacks of paroxysmal pain have been reported in CTN patients with persistent pain (Maarbjerg et al. 2014a; Haviv et al. 2016).

**Secondary Trigeminal Neuralgia**

This is a clinically typical trigeminal neuralgia that is caused by an identifiable underlying disease (Table 5). Clinical examination shows sensory changes in a significant proportion of these patients, suggesting that these could be better classified as neuropathies than neuralgias. Nevertheless, the clinical pain phenotype in these cases is that of a paroxysmal pain, with or without background pain that mimics CTN. To establish a diagnosis of secondary trigeminal neuralgia (STN), the clinical criteria for CTN must be met, but an underlying disease has been demonstrated known to be able to cause neuralgia. Cases of STN are usually caused by one of three conditions: a tumor in the cerebellopontine angle, arteriovenous (AV)-malformation, or multiple sclerosis (MS). Because the clinical phenotype in STN is so similar to that of CTN, imaging is essential and MRI is the best modality to detect an underlying cause (Fig. 4). Other investigations

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Diagnostic criteria for secondary trigeminal neuralgia</th>
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<tbody>
<tr>
<td><strong>Criteria</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td>A</td>
<td>Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia, either purely paroxysmal or associated with concomitant continuous or near-continuous pain</td>
</tr>
<tr>
<td>B</td>
<td>An underlying disease has been demonstrated known to be able to cause, and explaining, the neuralgia</td>
</tr>
<tr>
<td>C</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>
include neurophysiological recording of trigeminal reflexes and trigeminal evoked potentials, particularly for patients who cannot undergo MRI. Brainstem reflexes are more consistent in distinguishing STN from CTN. Patients with STN present with abnormal laser evoked potentials while only a proportion of CTN patients present with this abnormality (Cruccu et al. 2001).

**Trigeminal Neuralgia Attributed to Multiple Sclerosis**

To establish this diagnosis, trigeminal neuralgia must be caused by a multiple sclerosis (MS) related plaque/s in the pons or trigeminal nerve root entry zone and is associated with other symptoms, clinical signs, and laboratory findings indicative of MS (Table 6).

MS is a disabling disease that primarily affects individuals between the ages of 20–40 years. It is characterized by periventricular lesions in either cerebral hemispheres or infratentorially on MRI. MS neuropathology involves periventricular inflammation, neuronal demyelination, and ultimately gliosis. Positive oligoclonal bands are found in the cerebrospinal fluid and increased IgG levels and synthesis rates are observed in MS patients. Some of the characteristics of MS patients include paresthesia, numbness, motor weakness, and a painful optic neuritis with visual blurring. During the course of the disease, more than half of MS patients will experience some type of pain (Osterberg et al. 2005; Foley et al. 2013) and over a quarter will experience bilateral, constant, aching, burning, or pricking central pain.

Clinical signs predictive of MS in TN patients include bilateral pain (14% in MS) and young age (De Simone et al. 2005). Although MS patients are at 20 times greater risk of developing TN compared to the general population, TN rarely heralds underlying MS (0.3% of MS cases). In reality, TN usually develops in up to 2–8% of established MS patients, about 12 years after onset (Osterberg et al. 2005; Foley et al. 2013; Danesh-Sani et al. 2013). TN in MS patients is possibly caused by demyelination of the trigeminal nerve; however, vascular malformations and nerve compression has also been demonstrated (Ariai et al. 2014). In these patients, it is thought that MS increases the susceptibility of the nerve root to the effects of compression, leading more readily to painful paroxysms.

**Trigeminal Neuralgia Attributed to Space-Occupying Lesion**

Defined as trigeminal neuralgia caused by contact between the affected trigeminal nerve and a space-occupying lesion (SOL) (Table 7). One study has
reported approximately 33% of patients with middle and posterior cranial fossa tumors present with trigeminal nerve dysfunction; however, in only about 13% was this the presenting symptom (Bullitt et al. 1986). About 10% of cases with intracranial tumors report TN-like symptoms (Moazzam and Habibian 2012), with posterior fossa tumors and meningiomas most likely to cause TN-like symptoms (Bullitt et al. 1986; Puca et al. 1995). Cerebellopontine angle tumors, such as acoustic neuromas, may also cause TN-like pain and this diagnosis is more likely when the patient is young and suffers pain in more than one trigeminal branch.

Intracranial tumors are present in about 10–13.4% of TN patients most of whom are usually younger than expected and present with neurological deficits (Nomura et al. 1994); approximately, 2% of these patients had CTN with no significant sensory abnormalities. Symptoms most typical for cranial masses are a reduced corneal reflex and hypoesthesia. MRI is the most sensitive diagnostic technique (Nomura et al. 1994). The prevalence of intracranial tumors or MS is extremely high (~100%) in TN patients under 29 years of age and decreases with age (Yang et al. 1996).

**Idiopathic Trigeminal Neuralgia**

This is the latest addition to the diagnosis of TN. It reflects increasing findings of patients with a very typical clinical phenotype of TN but not...
associated with nerve compression, local or systemic disease (Table 8).

**Pathophysiology of CTN**
In the majority of patients, compression of the trigeminal nerve at or near the dorsal root entry zone (DREZ) is believed to be the major causative or contributing factor in the development of TN (Nurmikko and Eldridge 2001; Love and Coakham 2001) and would be termed CTN (Fig. 5). However, several subgroups of CTN that share a common clinical phenotype have now been classified: (1) patients with neurovascular compression or other pathology and clear signs of nerve injury, (2) patients with a lack of neurovascular compression, and

**Table 8** Diagnostic criteria for idiopathic trigeminal neuralgia*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
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<tbody>
<tr>
<td>A</td>
<td>Recurrent paroxysms of unilateral facial pain fulfilling criteria for trigeminal neuralgia, either purely paroxysmal or associated with concomitant continuous or near-continuous pain</td>
</tr>
<tr>
<td>B</td>
<td>Neither <em>Classical trigeminal neuralgia</em> nor <em>Secondary trigeminal neuralgia</em> has been confirmed by adequate investigation including electrophysiological tests and MRI</td>
</tr>
<tr>
<td>C</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>

*Trigeminal neuralgia with neither electrophysiological tests nor MRI showing significant abnormalities

![Fig. 5](image-url) Targeting the neurovascular contact: panel (a) is view of the right trigeminal root through the operating microscope. An arterial loop of the superior cerebellar artery has been lifted off the root. There is a band-like grayish discoloration of the root where it had been compressed close to its entrance to the brainstem. In panel (b), the picture is represented in diagrammatic form with the anatomical landmarks identified. (With permission from: Rappaport 2015)
patients with a constant background pain accompanying paroxysmal pain.

The pathophysiology in patients with TN but no imaging evidence of nerve compression, classified as idiopathic TN (ITN), remains unclear. It has been suggested that central mechanisms may play a role in the pathophysiology of CTN with constant background pain; however, one study showed no differences in CNS structures in CTN patients with or without concomitant background pain (Obermann et al. 2013). Therefore, further imaging, neurophysiological, and psychophysical studies are needed to decipher the complex pathophysiology of the TN subtypes.

Classical Trigeminal Neuralgia and Neurovascular Compression

High rates of vascular compression of the nerve have been observed in CTN patients with arterial compressions being most common, but venous and combined compressions were also reported (Matsushima et al. 2004). Furthermore, 91% of cadavers of CTN patients demonstrated vascular contact with the trigeminal nerve adjacent to the brain stem, with the demonstrable groove present in most (Hamlyn 1997a). Evidence from imaging and correlated surgical findings (Benes et al. 2005; Cha et al. 2011; Chen et al. 2012), ultrastructural analysis of neuronal tissue (Devor et al. 2002a; Love et al. 1998), and clear histological damage to neurons (axonal loss) and their myelin sheaths (demyelination) (Love and Coakham 2001; Devor et al. 2002a) all support the concept of neurovascular compression as a major cause of CTN, with grooving or deformation of the nerve considered essential for the initiation of pain. Demyelination zones were often characterized by closely apposed groups of axons with no intervening glial process and the location of demyelination zones matched the point of vascular indentation with 2 mm extensions in each direction (Love and Coakham 2001). Additionally, impairment of the trigeminal nociceptive system caused by demyelination and/or axonal dysfunction was found in the symptomatic side and was located close to the DREZ in the brainstem (Obermann et al. 2007). Degenerative hypermyelination and microneuromata have been found in the trigeminal ganglion of CTN patients with no significant damage to neuronal soma observed.

Further Findings on Trigeminal Neuralgia and Neurovascular Compression

The pathophysiology of TN is complex and neurovascular compression may explain only part of it. Around 2% of all TN cases may be familial, and family clusters of TN indicate that it may have a genetic origin (Fernandez Rodriguez et al. 2017). Some of the suggested causes include: inherited anatomical changes affecting the base of the skull, which would promote compression of the trigeminal nerve by vascular structures, and mutations in the gene encoding calcium channels resulting in hyperexcitability (Fernandez Rodriguez et al. 2017), as well as mutations in the serotonin transporter gene (5-HTTLPR) that were associated with CTN and its severity (Cui et al. 2014). Therefore, certain individuals may be prone to develop pain following neurovascular compression while others may be resistant, as in traumatic neuropathies.

Neurovascular compression (NVC) is not identifiable in a significant number of CTN patients. For example, in a series of 219 patients with paroxysmal TN, 28.3% had no imaging evidence of NVC (Lee et al. 2014) and up to 17% of patients undergoing surgery for TN had no NVC (Ishikawa et al. 2002; Sindou et al. 2002). Moreover, NVC is prevalent both on the symptomatic and asymptomatic side (89% vs. 78%) in TN patients, but severe NVC is more prevalent on the symptomatic side (53% vs. 13%) (Maarbjerg et al. 2015). Interestingly, pain recurrence after initially successful MVD is often not accompanied by renewed nerve compression (Burchiel 2016).

Furthermore, 17% of age-matched TN-free controls have imaging evidence of NVC (Hamlyn 1997a, b; Miller et al. 2009; Peker et al. 2009; Antonini et al. 2014). Moreover, 14% of cadavers
with no history of CTN demonstrate vascular contacts, although these had minimal grooving (Hamlyn 1997a, b). Classifying CTN and ITN separately allows further study of these groups. TN patients with no NVC are typically younger and three times more likely to be female (Ko et al. 2015), supporting the clinical value of the new classification.

Observing neurovascular contact of itself therefore has low predictive value in establishing a diagnosis of CTN. The presence of anatomical changes associated with the neurovascular contact increases specificity and positive predictive value (Antonini et al. 2014). Although NVC clearly plays a role in individual patients, at a population level, the high prevalence of NVC and the rarity of CTN suggest that a finding of NVC in CTN may often be insignificant. Current evidence postulates that TN is a far more complex disease (or cluster of diseases) than previously appreciated.

**Other Considerations in the Pathophysiology of Trigeminal Neuralgia**

Dysfunction of the trigeminal system has been implicated in CTN patients, yet clinically detectable neurosensory dysfunction is not always present in these patients. When present, dysfunction is usually mild and involves primarily touch and thermal sensation. The neurosensory dysfunction is most often present in the symptomatic division of the trigeminal nerve but may also affect the other two ipsilateral trigeminal branches, suggesting central mechanisms (Sinay et al. 2003). The observed sensory changes resolve following successful microvascular decompression, providing additional evidence for the involvement of neurovascular compression in neuronal damage and pain.

TN patients show significant reduction in the volume of the affected trigeminal nerve (Horinek et al. 2009; Kress et al. 2005), reflecting nerve atrophy. Additional abnormalities such as nerve degeneration, neuroinflammation, edema, loss of anisotropy in the affected trigeminal nerves (Leal et al. 2011; Herweh et al. 2007; DeSouza et al. 2014), as well as reduced gray matter volume (Obermann et al. 2013) have been observed. The decrease in gray matter in the anterior cingulate cortex, parahippocampus, and temporal lobe areas was shown to correlate with increased disease duration (Obermann et al. 2013), suggesting a possible role of these structures in the long-term changes associated with altered pain characteristics and response to pharmacotherapy. The observed alterations in the white matter of CTN patients are related to the structural changes induced by neurovascular compression at the root entry zone (DeSouza et al. 2014).

CTN patients, pre- and post-MVD, have similar activation patterns of the sensory cortex in trigeminal and extra trigeminal sites to those observed in healthy controls. However, activation is significantly reduced in CTN patients, both pre- and post-MVD, compared to healthy controls (Blatow et al. 2009), suggesting extensive changes in somatosensory processing in CTN patients. An earlier study investigating the effects of surgical treatment on opioid receptor binding in CTN patients found that successful surgical treatment resulted in significant increases in binding capacity (Jones et al. 1999), suggesting decreased levels of endogenous opioids and greater receptor occupancy.

**The Triggering Phenomenon**

In CTN, light mechanical stimulation disproportionately triggers extreme pain. Abnormal laser evoked potentials in some CTN patients suggest dysfunction of nociceptive fibers or dysfunction of CNS pathways evoked by nociceptive afferent stimulation. Nociceptive fiber dysfunction may be a peripheral mechanism for the establishment of trigger points in CTN (pain induced by innocuous stimuli).

Preclinical observations demonstrate neuronal hyperactivity following nerve injury, caused by an increased number of neurons with sub-threshold oscillations (pacemaker activity) that bring neurons close to the firing threshold. Spontaneously or following external stimulation, hyperactive neurons often generate ectopic discharge lasting a few seconds (“afterdischarge”) (Liu et al. 2000). Additionally, stimulation of peripheral fibers (mainly low-threshold mechanoreceptors A-β fibers) or the dorsal root
generates a temporary “cross-depolarization” in passive, neighboring C-fiber neurons in the same ganglion (Amir and Devor 2000), which results in prolonged activity in neighboring neurons (crossed “afterdischarge”). These findings gave rise to the “ignition hypothesis” (Devor et al. 2002b), which suggests that hyperexcitable axons and axotomized somata produce synchronized after-discharge activity, cross-excitation of nociceptors, and pain paroxysms following light touch.

**Pretrigeminal Neuralgia**

In about 18% of CTN patients, the typical episodes of flashing pain are preceded by a period (from days to years) of continuous, dull pain (Fromm et al. 1990). This early form of CTN is termed “pretrigeminal neuralgia” and transitions to characteristic flashes of pain over time. At present, there are no clear and consistent diagnostic criteria for pretrigeminal neuralgia. The throbbing character of pretrigeminal neuralgia pain as well as its responsiveness to regional anesthesia contribute to its frequent misdiagnoses as dental pathology. Therefore, careful dental assessment to differentiate between the two entities is critical. Additionally, pretrigeminal neuralgia is highly responsive to anticonvulsants such as carbamazepine.

**CTN Comorbidity**

**Combination Syndromes**

Trigeminal neuralgia is predominantly a single pain syndrome. However, occasionally it occurs with cluster headache (cluster-tic) or with paroxysmal hemicrania (chronic paroxysmal hemicranias-tic).

**Hypertension**

Individuals with hypertension were found to be at increased risk of CTN (by a factor of 2.1 in females and 1.5 in males) (de Siqueira et al. 2004; Katusic et al. 1990; Pan et al. 2011). In these cases, hypertension has been linked to arterial compression of the ventrolateral aspect of the rostral medulla in the region of the glossopharyngeal and vagus nerve roots.

**Other Neuralgias**

CTN may share some pathophysiology with glossopharyngeal neuralgia as these two forms of neuralgia may occur simultaneously. Around 10% of glossopharyngeal neuralgia patients may also present with CTN (Gaul et al. 2011).

**Differential Diagnosis**

**Dental**

CTN mimics dental pain and up to a quarter of CTN cases will initially consult a dentist (de Siqueira et al. 2004). About 33–65% of patients with CTN undergo unwarranted dental interventions and up to 12% may be rendered edentulous (Bowsher 2000; de Siqueira et al. 2004). Therefore, in the absence of positive anamnestic, clinical, and radiographic signs, invasive dental treatments must not be provided.

**Short-Lasting Unilateral Neuralgiform Headache Attacks (SUNHA) and Cluster-Tic Syndrome**

CTN shares signs and symptoms with short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and an atypical (shorter) cluster-tic syndrome (CTS). SUNCT is characterized by neuralgiform pain with very prominent autonomic signs, such as lacrimation. No trigeminal sensory pathway abnormalities have been reported in SUNCT suggesting that it is not a neuropathic type of pain (Pareja and Cuadrado 2005) and the neuroimaging studies suggest that SUNCT is related to the trigeminal autonomic cephalgias (Matharu and May 2008). Nevertheless, the clinical overlap between these two entities is striking.

Moreover, a confusing combination of clinical features between CTN and SUNCT has been reported and may make the diagnosis extremely challenging. Both entities can occur at the same age of onset, present with severe, unilateral trigeminal pain triggered by innocuous stimuli, and are accompanied by constant background pain and cranial autonomic signs. The complexity of this differential diagnosis may be better solved by giving both SUNCT and CTN diagnoses to such cases. There is a suspicion that CTN and SUNCT
exist on a spectrum of disease ranging from typical CTN attacks to typical SUNCTs with a mixed phenotype in the middle (Lambru and Matharu 2014; Benoliel et al. 2017).

Cluster-tic syndrome (CTS) is characterized by a unilateral cluster headache occurring with CTN, both of which respond well to carbamazepine treatment. CTS occurs mostly in females between 40 and 50 years of age; however, onset may occur at any age.

Treatment
Pharmacotherapy remains the cornerstone of TN management (Nurmikko and Eldridge 2001) and is still needed pre/postoperatively for patients who undergo microvascular decompression (MVD) or other surgical intervention. CTN patients with concomitant background facial pain have a poorer response to pharmacologic and surgical interventions (Maarbjerg et al. 2014a; Nurmikko and Eldridge 2001; Haines and Chittum 2003; Obermann et al. 2008; Zhang et al. 2013; Tyler-Kabara et al. 2002; Young et al. 2013; Degn and Brennum 2010).

Pharmacological
At present, carbamazepine remains the drug of choice for the management of CTN. The “number needed to treat” (NNT) is an elegant way to express the efficacy of a given drug in providing pain relief (Table 9). The lower the NNT, the more efficacious the drug is. Carbamazepine’s NNT for any pain relief in CTN is 1.9 and for significant relief is 2.6 (Wiffen et al. 2005a, b). Nevertheless, some patients may not respond and others may become refractory to carbamazepine treatment (Sato et al. 2004). Oxcarbazepine, a carbamazepine derivative with fewer side effects, is an alternative treatment option for CTN (Zakrzewska and Patsalos 2002). Baclofen, a muscle relaxant, is also efficacious and has a low adverse effect profile. It can therefore be titrated to relatively high doses (80 mg/d) with a reported NNT of 1.4. It has strong synergistic effects with carbamazepine and phenytoin that has made it popular as add-on therapy. The newer anticonvulsants, such as gabapentin and pregabalin, have fewer side effects and have been shown to be effective for some cases as mono- or add-on therapy. Gabapentin has not been extensively tested in CTN (Saarto and Wiffen 2005). Pregabalin (150–600 mg/day) induced significant improvement in pain following 8 weeks of treatment in 60–70% of CTN cases (Obermann et al. 2008; Perez et al. 2009). Lamotrigine has been tested as an add-on therapy but has significant side effects (Wiffen et al. 2013a). The effectiveness of topiramate in CTN is unclear (Gilron et al. 2001; Zvartau-Hind et al. 2000).

### Table 9 Drugs commonly used in the treatment of trigeminal neuralgia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial dose (mg)</th>
<th>Target dose (mg)*</th>
<th>Dose increase (Titration)*</th>
<th>Schedule</th>
<th>Evidenceb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>100–200</td>
<td>1200</td>
<td>100–200 mg/2 days</td>
<td>×3–4/ day</td>
<td>A</td>
</tr>
<tr>
<td>Carbamazepine-CR</td>
<td>200–400</td>
<td>1200</td>
<td>Usually transfer from regular format at equivalent dose</td>
<td>×2/day</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>300</td>
<td>1200–2400</td>
<td>300–600 mg/week</td>
<td>×3/day</td>
<td>B</td>
</tr>
<tr>
<td>Baclofen</td>
<td>5–15</td>
<td>30–60</td>
<td>5 mg/3 days</td>
<td>×3/day</td>
<td>A</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25–0.5</td>
<td>1–4</td>
<td>0.25 mg/week</td>
<td>Bedtime</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300</td>
<td>900–2400</td>
<td>300 mg/12 days</td>
<td>×3/day</td>
<td>B</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150</td>
<td>300–600</td>
<td>50 mg/2–3 days</td>
<td>×2–3/ day</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>25</td>
<td>400–600</td>
<td>25–50 mg/week</td>
<td>×1–2/ day</td>
<td>A*</td>
</tr>
<tr>
<td>Topiramate</td>
<td>25</td>
<td>100</td>
<td>25 mg/week</td>
<td>×2/day</td>
<td></td>
</tr>
</tbody>
</table>

*aTitrate according to response and side effects
bEvidence for efficacy rated A (best) or B (moderate)
cEvidence for efficacy based on study using lamotrigine as add-on therapy
Based on current evidence, CTN patients should be treated with carbamazepine and at the earliest opportunity transferred to the controlled release formulation that has fewer side effects. When carbamazepine causes troublesome side effects, the dose may be reduced and baclofen added. Gabapentin shows great potential (Solaro et al. 2000) and slow release formulations are currently available in many countries. Pregabalin (Perez et al. 2009), topiramate (Wang and Bai 2011), valproate, and phenytoin may be tried (Cheshire 2002; Sindrup and Jensen 2002). Even in successfully managed patients, breakthrough pain may occur in which case dose adjustments may be required and in extreme cases in-patient care with intravenous phenytoin may be needed (Sindrup and Jensen 2002).

Careful follow-up of patients and close collaboration with the family physician should be maintained during anticonvulsant therapy as they increase the risk for suicidality. Initiation of anticonvulsant therapy should be preceded by baseline hematological, electrolyte, and liver function tests that should be regularly repeated. In patients of Asian origin, there is a significantly increased risk of carbamazepine-induced Stevens Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN). Therefore, the FDA recommends genotyping for HLA-B*1502 allele in these patients before initiation of carbamazepine therapy. Patients at risk for carbamazepine-induced SJS/TEN also carry an increased risk with other antiepileptic drugs.

Surgical Approach to CTN Treatment
CTN patients who do not respond well or suffer significant side effects associated with pharmacotherapy are candidates for surgical treatment. Factors such as the patient’s age, physical condition, profession, availability of surgical facilities, and expertise must be considered in tailoring the surgical approach. Alternative neurosurgical procedures should be presented clearly to the candidate.

Surgery may be aimed at the affected branches, at the trigeminal ganglion or the nerve root. The best results are observed when surgeries are used as the initial approach in the treatment of CTN. Based on a retrospective analysis of trends in neurosurgical management of TN, MVD seems to have become the most popular option (Wang et al. 2013).

Peripheral Procedures

Local Anesthetic
Nerve blocks may provide hours of pain relief in CTN patients. Depending on the nerve branch involved, continuous peripheral nerve block may be feasible in a hospital setting (Ilfeld 2011; Umino et al. 2002).

Neurectomy
Peripheral neurectomy is minimally invasive, simple to perform, and a relatively inexpensive procedure. It has therefore been an attractive treatment option for TN. However, studies have reported conflicting success rates (50–80%) and indicate that it may result in traumatic neuropathic pain (Peters and Nurmikko 2002; Freemont and Millac 1981). A recent study showed that peripheral neurectomy was well tolerated with few complications, and among 28 TN patients who underwent the procedure, less than 10% reported recurrence during a 3-year follow-up (Agrawal and Kambalimath 2011). The recurrence time decreases with the number of surgeries: from between 12 and 18 months after the first neurectomy to about 9 and 12 months after the second one. Therefore, repeating the procedure more than three times is not recommended (Cerovic et al. 2009). In cases where neurectomy was done alone, pain relief duration varied from 15 to 24 months and when it was accompanied by obturation of the foramina with a stainless steel screw, all the patients were pain free at 2-year follow-up (Ali et al. 2012). Because neurectomy is a very simple, minimally invasive, medically safe, and a relatively effective option, it might be a useful option for elderly patients, for patients living in remote and rural areas with no access to neurosurgical facilities, and those who are unwilling to undergo major neurosurgical procedures.

Cryotherapy
Duration of pain relief following cryotherapy is significantly shorter than in thermocoagulation or
microvascular decompression (Zakrzewska 1991), but about one-third of cryotherapy patients develop “atypical facial pain” (Zakrzewska 1991). The majority of patients relapse within 6–12 months and pain affects the original site in 80% of patients (Zakrzewska 1991; Pradel et al. 2002). Cryotherapy can however be repeated (Zakrzewska 1991; Pradel et al. 2002).

Alcohol
Treatment of CTN using alcohol injections has proven to be difficult as injections are painful and repeated injections are technically challenging due to fibrosis. Additional complications associated with alcohol injections include mucosal ulceration, cranial nerve palsies, herpes zoster reactivation, bone necrosis, and postinjection neuropathic pain (Peters and Nurmikko 2002). Pain relief following a first alcohol injection was attained for between 13 and 19 months (Fardy et al. 1994). Alcohol injections are therefore not regarded as a suitable option.

Peripheral Glycerol
Some studies report success rates following peripheral glycerol injection of around 60% at 24 months, while others report pain relapse by 7 months (Fardy et al. 1994; Erdem and Alkan 2001). Reinjections are possible and were reported to provide good results (Erdem and Alkan 2001).

In summary, all peripheral procedures are based on the principle of inducing nerve damage and thus carry the risk of causing traumatic neuropathic pain. All carry high recurrence rates and are associated with significant complications. They offer no benefit over ganglion-level procedures and should be reserved for emergency use or in cases where more invasive procedures would be viewed as unsafe (Peters and Nurmikko 2002).

Ganglion and Nerve Root Procedures

Percutaneous Trigeminal Rhizotomy
Three modalities are used for percutaneous trigeminal rhizotomy: radiofrequency, glycerol injection, or balloon compression. The procedure is relatively short and carries minimal anesthesia risk. It is based on selective ablation of nociceptors (Aδ and C) with controlled heat (69–90 °C), a neurotoxin, or ischemic/mechanical damage, while theoretically preserving mechanoreceptors (Aβ). However, postoperative loss across sensory modalities is frequently observed. The three approaches are equivalent in initial levels of pain relief (approximately 90%) but vary in terms of the rates of recurrence and complications (Ammori et al. 2013; Nanjappa et al. 2013; Montano et al. 2013; Reddy et al. 2014; Cheng et al. 2013; Xu-Hui et al. 2011) (Figs. 6 and 7).

Radiofrequency rhizolysis offers the highest rates of initial pain relief (97%), and 58% of patients are pain free at 5 years (Cheng et al. 2013). Although radiofrequency allows for somatotopic nerve mapping and selective division lesioning, radiofrequency-based rhizotomy is frequently associated with facial and corneal numbness (Lopez et al. 2004). Glycerol rhizotomy provides 90% pain relief at 6 months and 54% at 3 years with median time to recurrence of approximately 16 months (Kouzounias et al. 2010). Balloon compression and glycerol rhizotomy are reported to have comparable pain relief outcomes (Cheng et al. 2013; Kouzounias et al. 2010).

Microvascular Decompression
Microvascular decompression (MVD) is based on the principle that pulsatile injury from intracerebral arteries on the trigeminal nerve root may cause TN. The decompression therefore aims at separating the nerve root from impinging intracerebral arteries. MVD results in high rates of pain relief (>90%) (Kalkanis et al. 2003; Zhong et al. 2012), especially when performed as a first intervention for CTN with very low recurrence rates (Tatli et al. 2008; Zakrzewska et al. 2005a). Following MVD, about 70% of CTN patients experience sustained pain relief for about 10 years and between 30% and 40% of patients relapse at 10 years follow-up (Kuncz et al. 2006; Barker et al. 1996). Sensory loss resulting from MVD resolves in many patients (McLaughlin et al. 1999) and is often related to the degree of neurovascular compression (Han-Bing et al. 2010; Leal et al. 2010). Surgical morbidity has now declined to approximately 0.3–3% making
the procedure safer; however, mortality remains a risk (Kalkanis et al. 2003). MVD appears to be the most cost-effective surgical approach (Pollock and Ecker 2005; Parmar et al. 2013) for CTN (Fransen 2012).

In CTN cases with background pain, MVD induces pain relief in 47–79% compared to 80–87% in purely paroxysmal CTN (Zhang et al. 2013; Tyler-Kabara et al. 2002). There are also poorer long-term results at follow-up (>5 years) in CTN patients with background pain compared to purely paroxysmal CTN (Zhang et al. 2013; Tyler-Kabara et al. 2002).

Gamma Knife
Gamma knife stereotactic radiosurgery (GKS) is a minimally invasive procedure that precisely delivers radiosurgical doses of 70–90 Gray units to the trigeminal nerve root at the point of vascular compression. In the absence of compressing vessels, a preselected position on the trigeminal nerve such as the site of the trigeminal nerve exit from the pons is treated. Higher radiosurgical doses have been shown to provide better outcomes but were associated with higher rates of sensory loss (Young et al. 2013). GKS can be used as first-line treatment for TN patients who are unsuited or reluctant to undergo microvascular decompression and is also effective in patients with refractory, recurrent CTN following previous procedures (Sanchez-Mejia et al. 2005). It provides fewer treatment-related morbidities and longer pain relief compared to glycerol rhizotomy but clearly requires more costly facilities that may not be available (Henson et al. 2005; National Institute for Clinical Excellence (NICE) 2004). GKS has been suggested to have cumulative effects; some delay before pain relief has been observed (Jawahar et al. 2005), and the percentage of pain-free GKS patients increases over 24 months (Loescher et al. 2012; Tuleasca et al. 2012).
Summary of Nonpharmacologic Outcomes
Almost all these procedures provide comparable and good initial pain relief; however, up to 40–50% of patients will relapse at 15 years. Peripheral procedures provide shortest pain relief, drug therapy, or rhizotomies intermediate and MVD the longest. In healthy patients with typical CTN, surgical treatments may be best when performed sooner rather than later. Although MVD procedure entails some risks, it remains the treatment of choice for CTN (Pagni et al. 2008).

Painful Trigeminal Neuropathy
The term “painful trigeminal neuropathy” (PTN) is an umbrella term bringing together a number of facial pains in the distribution(s) of one or more branches of the trigeminal nerve caused by a disorder than that associated with the trigeminal neuralgias and indicative of neural damage.

Importantly, in PTN, the primary pain is usually continuous or near-continuous, and commonly described as burning or squeezing, or likened to pins and needles. Superimposed brief pain paroxysms may occur, but these are not the predominant pain type. This combination distinguishes PTN from the subtypes of TN. Clinically detectable sensory deficits within the trigeminal distribution, mechanical allodynia, and cold hyperalgesia are prevalent findings in PTNs. Allodynic areas are different to the trigger zones present in TN; they are generally much larger than the punctate trigger zones, and allodynic areas lack both the “latency” and “refractory period” associated with TN triggers.

Painful Trigeminal Neuropathy Attributed to Acute Herpes Zoster
Introduction
Acute herpes zoster (HZ) or shingles is a reactivation of latent varicella virus infection that
may occur decades after the primary infection. The exact mechanisms leading to viral reactivation and the subsequent appearance of acute HZ are unknown. HZ is a disease of the dorsal root ganglion and therefore includes a dermatomal vesicular eruption. Clinical presentation of HZ is usually more severe in immunocompromised patients and includes a prolonged course, recurrent lesions mimicking a typical zoster infection and involvement of multiple dermatomes (Dworkin et al. 2008).

Diagnosis of HZ is based on the clinical presentation and laboratory testing (Sauerbrei 2016) (Table 10). The clinical features important to the diagnosis include a painful prodrome, a unilateral dermatomal distribution, a vesicular or papular eruption, a history of a rash in the same distribution and pain (Dworkin et al. 2008). Identification of viral DNA in vesicular or cerebrospinal fluid provides more definitive diagnosis (Gershon and Gershon 2013). Additionally, identification of HZ DNA in saliva has been suggested as a possible and less invasive diagnostic test (Gershon and Gershon 2013).

**Epidemiology**

HZ does not follow a seasonal pattern and does not generally appear in epidemics. The annual incidence of HZ has been reduced by approximately 75% since the introduction of the varicella vaccination in 1995 (Gershon et al. 2010). At present, approximately 0.3% of people will develop HZ every year and the incidence increases with age (Gershon et al. 2010). The overall lifetime risk of HZ is estimated at 30% and at more than 50% in patients over the age of 80 (Gershon et al. 2010). Therefore, HZ may normally affect young patients but this occurs less frequently. It remains to be determined if and when the presence of HZ in young patients should be interpreted as a sign of underlying immunosuppressive disease.

**Pathophysiology**

Activation of varicella zoster virus at the spinal root or cranial nerve neurons results in an inflammatory response that also encompasses the leptomeninges. Neuronal loss and fibrosis may occur when inflammation in the dorsal root ganglion is accompanied by focal necrosis of nerve cells and satellite cell bodies (Opstelten et al. 2010). Nerve damage following inflammation around the nerve trunk, including lymphocytic infiltration of the nerve root, contributes to pain in HZ.

Upon examination of thoracic and trigeminal ganglia, viral DNA was found in most cells. Additionally, cell degeneration and satelliotasis was

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Table 10  Diagnostic criteria for painful trigeminal neuropathy attributed to herpes zoster

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Unilateral facial pain in the distribution(s) of a trigeminal nerve branch or branches, lasting &lt;3 months</td>
</tr>
</tbody>
</table>
| **B**   | One or more of the following:  
  1. Herpetic eruption has occurred in the same trigeminal distribution  
  2. Varicella zoster virus (VZV) has been detected in the CSF by polymerase chain reaction (PCR)  
  3. Direct immunofluorescence assay for VZV antigen or PCR assay for VZV DNA is positive in cells obtained from the base of lesions | Facial herpes zoster mostly affects the ophthalmic branch. Ophthalmic herpes may be associated with IIIrd, IVth, and Vth cranial nerve palsies. Involvement of the geniculate ganglion causes an eruption in the external auditory meatus and may also present with facial palsy (Ramsay Hunt syndrome). In about 10% of cases, particularly in the immunocompromised, the typical eruption may be caused by herpes simplex |
| **C**   | Not better accounted for by another ICHD-3 diagnosis | Prodrome of pain occurs in about 75% of cases. Usually burning, stabbing/shooting, tingling, or aching and accompanied by cutaneous allodynia. Herpes zoster is common in immunocompromised patients, occurring in about 10% of those with lymphoma and 25% of those with Hodgkin’s disease |
observed in the infected DRG cells. The distribution of sensory changes and development of hyperalgesia were associated with the spread within the spinal cord involving adjacent segments, bilaterally. In severe cases, the spinal ventral horn may be involved with resultant paralysis.

Viral replication induces epithelial cell degeneration characterized by ballooning, followed by invasion of giant cells. Skin necrosis and bleeding are rare. As polymorphonucleocytes, fibrin and degenerated cells appear the vesicles become cloudy and later rupture releasing infectious contents.

**Clinical Features**

Acute HZ is characterized by a unilateral, dermatomal, red macopapular rash that develops into vesicular eruptions over 3–5 days. These subsequently “dry out” over a further 7–10 days, and complete healing may take 1 month. HZ virus most commonly affects the thoracic followed by the lumbar region. Trigeminal nerves are affected in 8–28% of cases. Among the trigeminal cases, the ophthalmic branch is most commonly affected, occurring in 80% of cases, particularly in elderly males. This can result in a vision-threatening keratitis. When the maxillary or mandibular branches are affected, the vesicles and pain are dermatomal and unilateral and will appear intraorally. Cervical nerves are affected in 13–23% of cases.

Pain in HZ is usually constant with superimposed lancinating attacks. In some patients, evoked (stimulus dependent) pain may be the prominent feature. Pain quality varies in HZ patients: burning (26%), stabbing (15%), shooting (15%), tingling (10%), and aching (9%) (Goh and Khoo 1997). Severity is moderate to severe (VAS 6.2), but up to 25% of patients report no pain (Dworkin et al. 2001). High pain severity correlates with an increased incidence of postherpetic neuralgia (PHN) (Dworkin et al. 2001). Acute HZ begins with prodromal pain (in three-quarters of patients), headache, itching, malaise, and fever (Dworkin et al. 2008; Haanpaa et al. 1999; Volpi et al. 2005; Jung et al. 2004). Pain usually develops 2–3 days (<7) prior to acute HZ and may last up to 3–6 months with varying intensity (Volpi et al. 2005). Patients with acute HZ often present with mechanical allodynia and disturbed sensory thresholds, which usually spread to adjacent dermatomes and occasionally bilaterally. Motor weakness may occur but is usually transient.

Dermatomal pain with no rash “zoster sine herpete” is very rare, and its diagnosis cannot be made based on clinical presentation alone and requires evidence of concurrent viral reactivation (Dworkin et al. 2007).

**Treatment**

Treatment of HZ is focused on controlling pain, accelerating healing, and reducing the risk of complications such as dissemination, postherpetic neuralgia (PHN), and local secondary infection (Volpi et al. 2005). Early (<72 h following onset of rash) initiation of antiviral treatment, particularly in patients >50 years old, decreases rash duration, pain severity, and frequency of PHN (Dworkin et al. 2001; Schmader 2001). The reduction of PHN incidence following antiviral treatment remains to be clarified as a meta-analysis reported no significant reduction in PHN incidence following oral acyclovir therapy (Chen et al. 2014).

**Antiviral Medications**

Valacyclovir (1000 mg × 3/day) is more efficacious than acyclovir (800 mg × 5/day) in terms of pain resolution (Table 11). Famciclovir (500 mg × 3/day) is also an effective and well-tolerated therapy that has the advantage of reduced frequency of dosing (Sauerbrei 2016). A direct comparison of famciclovir and valacyclovir showed that the two drugs were therapeutically equivalent, for both healing rate and pain resolution.

Brivudin is available in some countries for the early treatment of HZ in immunocompetent adults. Overall brivudin (125 mg daily) is superior to acyclovir (800 mg × 5/day); however, it has a mixed efficacy profile (Whitley et al. 2010). Brivudin and famciclovir (250 mg × 3/day) are comparable in effectiveness on pain and rash with similar tolerability. Systemic toxicity has been reported between brivudin and 5-fluorouracil (FU) and other 5-fluoropyrimidines; therefore,
brivudin should not be used along with 5-FU or its derivatives, capecitabine, flouxuridine, or flucytosine (Whitley et al. 2010). Newer anti-HZ drugs, including the bicyclic nucleoside analogue FV-100, the helicase-primase inhibitor ASP2151, and valomaciclovir (prodrug of the acyclic guanosine derivative H2G) have been evaluated in clinical trials and offer improved efficacy, reduced daily doses, and side effects (Andrei and Snoeck 2013).

Corticosteroids offer clinically significant benefits on acute pain and quality of life outcomes when administered systemically within 72 h after a rash onset. However, they do not have a clear effect on the incidence of PHN (Whitley et al. 2010). Analgesics such as paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) should be used to control fever and pain. Stronger pain may require analgesic/NSAID combination, and opioids or opioid combinations may be employed for nonresponsive pain. Amitriptyline and gabapentin are centrally acting analgesics that will provide pain relief. Although amitriptyline may shorten illness duration and reduce the incidence of PHN, it is associated with cardiovascular effects that limit its use in the elderly or medically compromised. Nortriptyline or desipramine are related drugs with a better side-effect profile.

**Table 11** Oral antiviral drugs used in the treatment of herpes zoster that may also reduce incidence of postherpetic neuralgia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg)</th>
<th>Times daily</th>
<th>Duration (days)*</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>800</td>
<td>5</td>
<td>7–10</td>
<td>Side effects may include rash, headache, nausea, vomiting, dizziness, and abdominal pain. Patients must maintain fluid intake to prevent renal drug deposition. May require dose adjustment in renal dysfunction and elderly. Precaution in immunocompromised patients as cases of severe thrombotic thrombocytopenic purpura have been reported. Pregnancy category B</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>1000</td>
<td>3</td>
<td>7</td>
<td>Most common side effects are headache paresthesia, nausea, and vomiting. Pregnancy category B. Elimination is impaired in renal dysfunction</td>
</tr>
<tr>
<td>Famiclovir</td>
<td>250–500b</td>
<td>3</td>
<td>7</td>
<td>Most common side effects are headache paresthesia, nausea, and vomiting. Pregnancy category B. Elimination is impaired in renal dysfunction</td>
</tr>
<tr>
<td>Brivudin</td>
<td>125</td>
<td>1</td>
<td>7</td>
<td>Most common side effect is nausea. Severe interaction with 5-fluorouracil and other 5-fluoropyrimidines. Contraindicated in pregnancy</td>
</tr>
</tbody>
</table>

*Longer treatment schedules not associated with increased benefit
bRecommended dosage in the United States

**Varicella Vaccine**

Varicella vaccine may offer an effective method of preventing HZ and PHN in at-risk individuals such as the elderly and infirm. An investigational zoster vaccine was shown to be 60% effective in reducing the incidence of PHN among older adults (Oxman et al. 2005) as well as to reduce the duration and severity of PHN (Oxman et al. 2008). Additionally, the vaccine has been shown to be 70% efficacious, safe and partially effective in younger subjects. The efficacy of the vaccine appears to decrease with age; however, this can be overcome by modifying the vaccine (Andrei and Snoeck 2013). The vaccine is approved and recommended for individuals over the age of 50 (Schmader et al. 2012). An increased overall health care cost attributed to the cost of administration and implementation of zoster vaccine in the elderly population limits its use (Andrei and Snoeck 2013).

Varicella vaccine is contraindicated in immunosuppressed individuals, a group at high risk for infection. Imparting passive immunity with an immune globulin preparation should be considered for postexposure prophylaxis of varicella for these patients (Sauerbrei 2016; Andrei and Snoeck 2013). VarizIG is a varicella zoster immunoglobulin preparation available in the United States through an investigational new drug
application expanded access protocol. There is a 10-day period after exposure to varicella zoster virus during which a patient may receive VariZIG (Centers for Disease Control and Prevention 2012); however, to achieve greatest effectiveness, VarZIG should be administered as soon as possible following virus exposure, ideally within 4 days.

Trigeminal Postherpetic Neuralgia

Introduction

Multiple risk factors contribute to trigeminal postherpetic neuralgia (PHN) including age, severe prodromal and acute pain, and severe rash (Jung et al. 2004; Bouhassira et al. 2012). Advanced age (>50 years old) and intense pain independently predict PHN at 3 months after the acute infection (Bouhassira et al. 2012; Coen et al. 2006). There is no consensus on when acute HZ transitions into PHN (Wood 1995; Arani et al. 2001). It has been suggested that pain associated with HZ should be viewed as a continuum until it resolves, if it does, and has been termed zoster associated pain. However, considering HZ associated pain as a continuum fails to differentiate acute pain from PHN which seem to have distinct pathophysiologies. Therefore, HZ-associated pain may be best classified into three phases: acute HZ (lasting less than 30 days), subacute HZ (more than 30 days but less than 120 days), and PHN (more than 120 days) (Dworkin et al. 2008). The proposed classification reconciles the variable reports of pain duration after acute HZ and is in line with evidence supporting that acute HZ and PHN have different pathophysiologies (Oaklander 2008).

Despite its preferred name, by definition PHN is actually a neuropathy. This is due to the fact that significant pathoanatomical changes have been shown in the nerve, ganglion, and nerve root. There is also evidence of the inflammation extending into the trigeminal brainstem complex. However, the terminology is so embedded in clinical practice that it has been kept despite the contradiction.

Epidemiology

The incidence of PHN is estimated at 3.9–42.0/100,000 person-years (van Hecke et al. 2014), but the specific incidence of PHN in the trigeminal region is unclear. The frequency of persistent pain at 3 months following acute HZ increases with age, ranging from 0.3% in under 44 year olds to 9% in the 75 and older (Opstelten et al. 2010). Between 5% and 40% of acute HZ patients will report pain 6 months following initial onset (Dworkin et al. 2008; Oxman et al. 2005). The persistence of pain beyond 6 months following initial onset has not been studied extensively, and it has been estimated that 5–10% of patients will report persistent pain at 1 year (Dworkin et al. 2008; Oxman et al. 2005). There is some variability in the reported durations of pain following acute HZ (Dworkin et al. 2008; Oxman et al. 2005; Reda et al. 2013).

Pathophysiology

PHN has a distinct pathophysiology from that of acute HZ. PHN is a neuropathic pain syndrome that develops following herpes virus induced nerve injury. Some of the characteristics commonly found in PHN patients include scarring of sensory ganglia, peripheral nerve damage (often bilateral) with loss of large myelinated nerve fibers (Opstelten et al. 2010). Both peripherally (irritable nociceptors) and centrally generated mechanisms are involved in PHN, and the extent to which each of the processes contributes to PHN will affect the clinical presentation (Nurmikko and Haanpaa 2005). Patients with the least residual epidermal neurites following acute HZ more often developed PHN suggesting mechanisms secondary to nerve damage (Opstelten et al. 2010). Interestingly, at 6 months, PHN patients do not recover cutaneous innervation at all (Petersen et al. 2010) and at 7.7 years, the innervation was not obvious suggesting that anatomical reinnervation of the skin and recovery of sensory function are not necessary for resolution of pain and allodynia (Reda et al. 2013). In patients with trigeminal PHN, neurophysiological abnormalities in the A-delta and C fibers were associated with the intensity of the constant burning pain and the dysfunction of A-beta fibers was correlated with paroxysmal pain (Truini et al. 2008). These findings imply the involvement of the pain/thermal pathways in the constant burning pain and...
contribution of abnormal impulses generated by demyelinated A-beta fibers to paroxysmal pain (Baron 2008).

PHN patients do not usually present with an active viral infection, and virus is not recovered from the spinal cord. PHN patients develop spinal dorsal horn atrophy that is not present in acute HZ patients not progressing PHN (Opstelten et al. 2010). Bilateral, severe, peripheral nerve pathology was observed in an ophthalmic PHN patient during postmortem examination (Dostrovsky 2000); however, the trigeminal ganglion and trigeminal root were unaffected, suggesting that PHN progresses from peripheral to central structures. Additionally, while ongoing activity in peripheral nociceptors plays an important role in the early stages (<1 year) of PHN, central mechanisms may become prominent in later stages (Pappagallo et al. 2000).

Clinical Features
Diagnostic criteria for trigeminal PHN are summarized in Table 12. The ophthalmic division of the trigeminal nerve is most commonly involved in trigeminal PHN (Liesegang 2008). The quality of pain associated with PHN has been described as burning, throbbing, stabbing, shooting, or sharp. Burning pain has been reported significantly more frequently in patients who did not undergo antiviral therapy in the acute HZ stage. Most PHN patients will report a constant, deep burning, or aching pain. However, variable temporal patterns of pain have been reported with some PHN patients presenting with constant pain and others with paroxysmal pain as the leading symptom (Truini et al. 2008).

Between 30–50% of PHN patients report itching of the affected area, termed postherpetic itch (Oaklander et al. 2003). Although postherpetic itch is usually mild to moderate; in some cases, it may be extremely bothersome and is often subjectively graded as worse than pain (Opstelten et al. 2010). When postherpetic itch is accompanied by anesthesia and may result in self-injury from persistent scratching (Oaklander et al. 2003). Pain associated with PHN is typically severe with VAS ratings of 8. Constant, burning pain is most frequently reported in PHN patients. When present, background pain fluctuates from moderate to excruciating.

Affected areas are usually hypoesthetic or anesthetic, with pale or red/purple scars persisting in the affected area. Paradoxically, these “anesthetic” scars exhibit allodynia and hyperalgesia. As in other neuropathic pain conditions, a heterogeneous mix of sensory signs and symptoms are observed in PHN (Truini et al. 2008). Most patients with PHN develop allodynia and diminished responses to temperature and pinprick.

| Table 12 Diagnostic criteria for trigeminal postherpetic neuralgia |
|---------------------|------------------|
| **Criteria**        | **Notes**        |
| A Unilateral facial pain in the distribution(s) of a trigeminal nerve branch or branches, persisting or recurring for >3 months and fulfilling criterion C | Following acute herpes zoster, postherpetic neuropathy is usually more common in patients >60 years old and the immunocompromised |
| B Herpes zoster has affected the same trigeminal nerve branch or branches | The first division of the trigeminal nerve is most commonly affected in, but the second and third divisions can be involved also |
| C Pain developed in temporal relation to the herpes zoster infection | Usually, pain will have developed while the rash was still active, but on occasion later, after rash has healed. In such cases, pale or light purple scars may be present as sequelae of the herpetic eruption. Typically the pain is burning and itching. Itching of affected areas may be very prominent and very bothersome. Sensory abnormalities and allodynia are usually present in the territory involved. Pale or light purple scars may be present as sequelae of the herpetic eruption |
| D Not better accounted for by another ICHD-3 diagnosis |
Treatment
Several evidence-based treatment options are available for PHN and these include tricyclic antidepressants (TCAs), gabapentin, pregabalin, opioids, and topical lidocaine or capsaicin patches (Attal et al. 2010; Dworkin et al. 2010a). As a general rule, early treatment of PHN improves prognosis. TCAs present an effective treatment option for PHN with overall NNT of 2.6. Amitriptyline is the most extensively studied TCA; however, little difference has been found in the effectiveness between available TCAs, and nortriptyline or desipramine may also be used. Gabapentin (NNT of 4.4) and pregabalin (NNT 3.3–4.93) have been proven to be efficacious and are relatively safe in elderly patients (Attal et al. 2010; Dworkin et al. 2010a). Opioids (NNT ~ 2.7) are an effective treatment option for PHN patients and tramadol is a reasonable but less effective alternative (NNT of 4.8) (Attal et al. 2010; Dworkin et al. 2010a). When PHN is accompanied by allodynia, lidocaine patches (NNT ~4) are useful, with significantly fewer side effects compared to systemic drugs (Wolff et al. 2011; Baron et al. 2009; Hans et al. 2009). High concentrations of topical capsaicin (8%) was shown to be an efficacious (NNT of 8.8) (Derry et al. 2013) and safe in the treatment of PHN; one application provides pain relief for up to 3 months (Derry et al. 2013). Higher concentrations of topical capsaicin (10% and 20%) have been tested (Peppin and Pappagallo 2014), while low concentrations have been shown to offer minimal relief (Derry and Moore 2012). For trigeminal PHN, capsaicin patches are not recommended and extreme care should be taken when applying treatments around the eyes (Sayanlar et al. 2012). Postherpetic itch is extremely difficult to treat. Postherpetic itch does not usually respond to antihistamines, and local anesthetics provide some temporary relief.

More invasive PHN treatment options include epidural and intrathecal steroids, sympathetic and sensory nerve blocks, spinal cord stimulation and neurosurgical techniques with dorsal root entry zone lesion providing pain relief in 59% of reported cases (Watson and Oaklander 2002; Wu and Raja 2008).

Painful Posttraumatic Trigeminal Neuropathy
Introduction
Neuropathy (sensory changes) may develop as a consequence of disease or damage to the somatosensory nervous system and when accompanied by pain is termed painful neuropathy. Painful traumatic trigeminal neuropathy (PTTN) has been previously described as: phantom tooth pain, atypical odontalgia, and atypical facial pain.

Neuropathies can be divided into peripheral neuropathy when pain originates in peripheral nerve, ganglionopathy when the ganglion is involved, radiculopathy when affecting the dorsal root or central neuropathic pain when this originates from the central nervous system. Often there are overlapping syndromes. This section will focus on pain resulting from damage to the trigeminal nerve that is, in its entirety, a peripheral nerve. Pain may occur from the damage to cell soma at the level of the trigeminal ganglion following rhizotomy, a treatment for trigeminal neuralgia. Damage at the level of the cell soma (trigeminal ganglion) may completely kill the afferent leading to deafferentation of the area. Similarly, injury to the dorsal root, which usually results from neurosurgery, may potentially cut all peripheral input to the central nervous system. On the other hand, injury at the level of the peripheral branch of the neuron may leave the cell soma and its central branch (nerve root) intact. Each of these injuries should be studied individually.

Craniofacial or oral trauma is probably the most common etiologies of PTTN (Benoliel et al. 1994, 2005). However, minor dental interventions may also result in PTTN (Polycarpou et al. 2005). Additionally, infection (acquired immune deficiency syndrome/AIDS), metabolic abnormalities (diabetes), malnutrition, vascular abnormalities (trigeminal neuralgia), infarction (central poststroke pain), neurotoxins, radiation, and autoimmune disease may induce PTTN. In orofacial pain clinics, onset of pain is often clearly associated with craniofacial or oral trauma (Benoliel et al. 2005); however, minor dental procedures such as nerve blocks, root canal treatment, and third molar extractions may also result
in pain (Polycarpou et al. 2005; Renton and Yilmaz 2011; Renton et al. 2010, 2012a; Penarrocha et al. 2012). In most cases, occurrence of iatrogenic PTTN or other posttraumatic neuropathies, such as complex regional pain syndrome (CRPS), does not reflect on the quality of the surgical intervention (Turner-Stokes et al. 2011). Orofacial CRPS is a further posttraumatic neuropathy whose occurrence in the orofacial region is unclear (see below).

**Epidemiology**

Traumatic injuries to the trigeminal nerve largely result in either no residual deficit or in a nonpainful neuropathy. Only a small portion, as discussed below, develops a painful neuropathy. Following identical injuries, there is wide interindividual variability in the onset and features of PTTN and a combination of environmental, psychosocial, and genetic factors likely play a role.

**Macrotrauma**

Mild hypoesthesia of the infraorbital nerve is frequently observed following zygomatic complex fractures; however, neuropathic pain develops in only 3.3% of patients followed up for 6 months (Benoliel et al. 2005) compared to around 5–17% in other body regions (Beniczky et al. 2005; Macrae 2001) (Fig. 8).

**Implants**

Neuropathy secondary to direct or indirect neural trauma may develop following implant placement. Between 0.6% and 36% of patients will experience neurosensory disturbances following implant placement (Albrektsson 1988; Albrektsson et al. 1988; Gregg 2000; Higuchi et al. 1995; Lazzara et al. 1996; Haas and Lennon 1995) as a result of damage to adjacent nerves that may also lead to pain (Ardekian and Dodson 2003; Schmidt et al. 1995; Renton et al. 2003). The large incidence range for neurosensory disturbances may imply that both transient and permanent changes were considered. However, the exact incidence of post-implant related PTTN is unclear. Direct damage may occur during site preparation and/or implant insertion, and indirect damage may result from bleeding and pressure buildup around the nerve or a perineural inflammatory response.

![Fig. 8](image_url) Displaced right zygomatic complex fracture. Axial bone-algorithm CT (a) showing significant posterior displacement and flattening of the right malar eminence (thick arrow) with comminuted fractures of the anterior (arrowhead) and posterolateral (dotted arrow) antral walls and bowing deformity and a subtle fracture (thin arrow) of the zygomatic arch. Volume-rendered CT reconstruction (b) in the same patient, showing in addition the fracture-diastasis of the zygomaticofrontal suture (dashed arrow). (Images courtesy of Dr Rudolf Boeddinghaus, Perth Radiological Clinic, Perth WA, Australia)
In some cases, a major nerve trunk, usually the inferior alveolar nerve, may be impinged to a variable degree (Juodzbalys et al. 2011, 2013), especially when the implant is over inserted (Fig. 9). In these cases, a significant sensory dysfunction is immediately present postoperatively, and the neuropathy is believed to result from inflammation and direct physical damage caused by the preparation and/or the implant. Additionally, a study based on a rat model found the resultant neuropathy may depend on the nature of the nerve injury (Zeltser et al. 2000).

A small group of patients develop pain in spite of no apparent complications and a good postoperative course. Pain and “sensitivity” to mechanical (chewing, brushing) and often thermal stimuli develop in these patients following implant loading and pain resolves when the implant is unloaded. The underlying mechanism leading to development of pain is unclear; however, it is believed to be neuropathic. There is evidence of extensive peri-implant innervation that could give rise to neuropathic pain (Huang et al. 2015).

Mandibular Third Molars

Some third molar extractions are associated with temporary hypoesthesia (Barron et al. 2004) (Fig. 10). Between 0.3% and 1% of cases report disturbed sensation in the lingual or inferior alveolar nerve that persists for varying periods (Valmaseda-Castellon et al. 2001). Lingual nerve damage is observed less frequently than inferior alveolar nerve injuries (Gomes et al. 2005; Queral-Godoy et al. 2006; Robert et al. 2005) but may reach 4% in specific extraction techniques involving nerve retraction (Fried et al. 2001).

A study of over 1900 patients failed to identify any neuropathic pain cases (Berge 2002; Valmaseda-Castellon et al. 2000). In a small group of patients (0.5%), tongue dysesthesia variably correlated with the presence of histologic chronic inflammation that may remain following injury (Fried et al. 2001; Vora et al. 2005). Some patients with extraction-related lesions to the mandibular branches of the trigeminal nerve develop comorbid pain and are likely to actively seek treatment (Renton et al. 2012a). Nonpainful neuropathies that may develop following dental interventions have a reasonably good prognosis and most patients report improvement (Pogrel et al. 2011).

Root Canal Therapy

Multiple factors including apical infection or inflammation (von Ohle and ElAyouti 2010; Ozkan et al. 2008), accidental injection of hypochlorite (Singh 2010; Motta et al. 2009; Witton et al. 2005), and extrusion of filling materials (Lopez-Lopez et al. 2012; Gambarini et al. 2011) may cause chemical/physical injury that may contribute to nerve damage following endodontic treatment. Between 3% and 13% of cases report persistent pain following successful endodontics (Polycarpou et al. 2005; Marbach et al. 1982; Lobb et al. 1996), and 5% of surgical endodontics...
cases will develop chronic neuropathic pain (Campbell et al. 1990). Multiple factors have been associated with persistent pain following endodontic treatment and these include: 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 (Klasser et al. 2011; Nixdorf et al. 2010). Additionally, patients with persistent pain following endodontic treatment may have a deficient endogenous inhibitory system (Nasri-Heir et al. 2015). However, it remains to be determined whether an inefficient endogenous inhibitory system is a causative factor or a result of chronic pain. The importance of preoperative pain parameters implies that some sensitization may have occurred predisposing to chronic pain.

Local Anesthetic Injections

Nerve injury may occur following local anesthetic injection secondary to physical trauma by the needle or by chemical insult from the anesthetic solution (Renton et al. 2010; Moon et al. 2012; Sambrook and Goss 2011; Smith and Lung 2006). These injuries more commonly occur during blocks to both the inferior alveolar and lingual nerves, with lingual nerve injuries being more permanent (Renton et al. 2010). Lingual nerve injury is more likely during repeated injections and when the injection was reported as painful (Renton et al. 2010). The signs associated with injury due to local anesthetic injection are similar to other PTTNs and include burning pain with paresthesia, allodynia, or hyperalgesia. It has been suggested that the degree of injury may be dependent on the type and toxicity of

Fig. 10 Cone beam computed tomography to assess relationship of lower third molar to inferior alveolar nerve canal. Sagittal oblique maximum-intensity projection (MIP) reconstruction (a) simulating a panoramic radiograph showing the canal (white arrow) overlying the roots of the partially erupted right mandibular third molar. On this view, it is not possible to tell whether the canal passes buccal to, lingual to, or between the roots. Axial (b) and coronal (c) images showing the canal (arrow) passing between the roots of right mandibular third molar. (Images courtesy of Dr Rudolf Boeddinghaus, Perth Radiological Clinic, Perth WA, Australia)
anesthetic agent used (e.g., lidocaine, prilocaine, mepivicaine, articaine) (Pogrel 2007; Haas 2006); however, the results have been ambiguous. Articaine 4%, when used as an inferior alveolar nerve block, was shown to be significantly associated with nerve injury and clinical symptoms (Hillerup et al. 2011); therefore, its use for nerve blocks should be limited.

Blunt Macrotrauma
Chronic pain resulting from blunt macrotrauma such as road traffic accidents may not present with tangible physical signs and therefore may be difficult to diagnose. The severity of the original injury may not always correlate with the intensity of the resultant pain and even minor trauma may result in significant disability. In some patients, major trauma often results in more than one pain syndrome.

Diagnosis
Thorough clinical and imaging evaluation of orofacial structures may be needed to assess the degree of injury. Trauma cases should be carefully assessed to detect fractures and other injuries. Diagnostic criteria for PTTN are summarized in Table 13. Imaging may be necessary to assess injury from a dental implant, detect foreign bodies, sequestra, etc. Depending on the case, plain radiography or cone beam computerized tomography may be used. Trauma cases should be carefully assessed for fractures and other injuries.

Sensory testing is recommended, preferably with quantitative dynamic assessment (Baad-Hansen et al. 2013a; Svensson et al. 2011), to evaluate the degree of injury. To identify distinct abnormalities more advanced electrophysiologic techniques might be needed, but they are usually not available in primary care (Baad-Hansen et al. 2006; Jaaskelainen 2004). When advanced quantitative sensory testing (QST) equipment is not available, dental instruments may be adapted to assess gross sensory changes associated with PTTN. For example, pin-prick sensation can be tested with a dental probe, thermal sensation with warm/cool instruments, and mechanosensation with cotton wool. The affected areas should be carefully mapped, marked, and photographed to become part of the patient’s documentation, evaluation, and follow-up.

Table 13 Diagnostic criteria for painful posttraumatic trigeminal neuropathy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
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<tbody>
<tr>
<td>A</td>
<td>Facial and/or oral pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion C</td>
</tr>
<tr>
<td>B</td>
<td>History of an identifiable traumatic event to the trigeminal nerve(s), with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypoesthesia, hypoalgesia) signs of trigeminal nerve dysfunction</td>
</tr>
<tr>
<td>C</td>
<td>Evidence of causation demonstrated by both of the following: 1. Pain is localized to the distribution(s) of the trigeminal nerve(s) affected by the traumatic event 2. Pain has developed &lt;6 months after the traumatic event</td>
</tr>
<tr>
<td>D</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>

Note: Most trigeminal nerve injuries do not result in pain

anesthetic agent used (e.g., lidocaine, prilocaine, mepivicaine, articaine) (Pogrel 2007; Haas 2006); however, the results have been ambiguous. Articaine 4%, when used as an inferior alveolar nerve block, was shown to be significantly associated with nerve injury and clinical symptoms (Hillerup et al. 2011); therefore, its use for nerve blocks should be limited.

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Clinical Features
The age of onset is around 45–50 years, with predominantly female patients (Penarrocha et al. 2012; Benoliel et al. 2012; Pigg et al. 2013; Siqueira et al. 2013). Pain is unilateral, occurs in the area of injury and may be precisely mapped to the dermatome of the affected nerve with demonstrable sensory dysfunction, particularly if a major nerve branch has been injured (Benoliel et al. 2012). In unilateral injuries, pain
may be diffuse and spread across dermatomes but rarely crosses the midline. However, in more extensive injuries, where multiple nerves are affected, bilateral pain may occur. Pain in PTTN is usually burning or shooting with a moderate to severe intensity (VAS 5–8) (Renton and Yilmaz 2011; Renton et al. 2012a; Benoliel et al. 2012; Pigg et al. 2013; Baad-Hansen et al. 2008). PTTN is usually a continuous long-pain lasting and present on most days (Benoliel et al. 2012). Presence of paroxysmal pain has also been reported, and it may occur spontaneously or be triggered by touch or function (Renton and Yilmaz 2011). Triggering mechanisms are relatively rare among the PTTN patients (Benoliel et al. 2012) and are usually not accompanied by a latency or refractory period. Severe allodynia or a positive Tinel’s sign occurs more frequently (Renton and Yilmaz 2011).

Painful neuropathies may be associated with positive (e.g., dysesthesia) and negative symptoms (e.g., numbness) (Svensson et al. 2011; Benoliel et al. 2012; Pigg et al. 2013). Some of the sensory symptoms frequently associated with PTTN include thermal and mechanical allodynia (Rasmussen et al. 2004). Changes should be assessed and recorded using accepted terminology (IASP Taxonomy [Internet]. IASP 2012). Additional sensory changes such as hyperalgesia may occur in extratrigeminal sites implying more extensive changes in central somatosensory processing (Baad-Hansen et al. 2013a, b; List et al. 2008). Thermal modalities are usually not affected (Siqueira et al. 2013; List et al. 2008). Patients may complain of swelling, a foreign body, hot or cold, local redness, or flushing, but these are not always verifiable and may reflect sensory disturbances (Renton and Yilmaz 2011; Benoliel et al. 2012).

PTTN is associated with substantial psychosocial burden (Pigg et al. 2013). Additionally, patients with more severe pain may present with elevated levels of depression, pain catastrophizing, reduced quality of life, and coping efficacy levels. Quality of life and emotional problems but not anxiety can be predicted based on the intensity of the pain (Smith et al. 2013a).

Treatment

Treatment modalities are aimed at eliminating pain and include systemic and topical pharmacotherapy, and surgery (Pigg et al. 2013). Prevention is preferable but not always attainable, and therefore, early treatment is essential. PTTN is unfortunately characterized by a poor prognosis. Improvement is observed in less than one-third of PTTN patients (Pogrel et al. 2011; Pigg et al. 2013) and only 10–20% will report significant improvement. Approximately, half of the patients reported no improvement or worsened pain. Some degree of pain was experienced by most cases even at an average of 13 years after onset (Pigg et al. 2013).

Strategies for Preventing Neuropathic Pain

It is unclear why some patients develop persistent postsurgical (or injury) pain and others do not. The factors contributing to the development of persistent postsurgical pain may be grouped into three overlapping phases (Wu and Raja 2011): (1) the preoperative phase includes risk factors specific to each patient such as psychosocial parameters, genetically controlled pain modulatory mechanisms, the presence of related preoperative pain (i.e., painful surgical site), and comorbidities such as other pain disorders, obesity, and sleep disorders (Johansen et al. 2014); (2) the intraoperative phase includes surgery-dependent factors such as technique, associated nerve and tissue injury, and the efficacy of analgesic regimens; and (3) the postoperative phase involves the patient’s coping ability, postoperative pain intensity, healing with scar formation, as well as possible additional confounding factors such as chemotherapy (Wu and Raja 2011; Clarke et al. 2012).

The aim of preventive analgesia is to avert persistent postsurgical pain. The current term replaces preemptive analgesia and focuses on possible strategies during all stages rather than only the preoperative phase. The timing of preventive interventions may be pre-, intra- and postoperative and usually involve various modalities. Although preventive analgesia has been studied extensively, currently there is not enough evidence supporting its routine implementation.
Nonetheless, it would appear reasonable to provide a preventive strategy in selected procedures and patients. Some of the preventive strategies may include an alternative surgical approach to minimize tissue damage and nerve involvement (stretching, crushing, or cutting), adequate (dosing and duration) of preoperative anti-inflammatory and analgesic regimens, deep local or regional anesthesia to ensure no intraoperative pain, and adequate postoperative analgesics.

Preoperative opioids reduce postoperative pain and secondary hyperalgesia (McGreevy et al. 2011), but their ability to prevent persistent pain remains unclear. Perioperative gabapentin and pregabalin have been shown to reduce the incidence of persistent postsurgical pain (Clarke et al. 2012). The researchers employed 1200 mg of gabapentin 2 h preoperatively and continued for 1–5 days postoperatively (Clarke et al. 2012). Preoperative anesthetic blocks reduce postoperative pain, but no protocol has been widely accepted yet (Kelly et al. 2001a, b). The use of local anesthetic blocks during surgery to prevent the injury-associated afferent barrage and resultant central sensitization has produced inconsistent results. Local anesthetics have been shown to have a strong positive effect on suppressing postoperative pain and analgesia consumption; however, their effects on preventing chronic pain remain unclear (Barreveld et al. 2013).

It has been suggested that patient’s pain modulatory capacity may be indicative of their risk to develop postoperative chronic pain (Yarnitsky et al. 2008; Weissman-Fogel et al. 2009; Landau et al. 2010), which could eventually translate to a chairside screening test to identify at risk patients.

Some of the factors contributing to lack of success in preventive strategies may include inadequate management of the initial sensory barrage and insufficient treatment duration (Kelly et al. 2001a, b). At present, the use of a preventive program, including at minimum preoperative and perioperative analgesics, deep local or regional anesthesia, and excellent postoperative analgesics, would be wise in selected procedures and patients.

Strategies for Established Painful Traumatic Trigeminal Neuropathies

Pharmacotherapy
Temporary perineural inflammation (neuritis) may develop in the orofacial region following dental and other invasive procedures. Anti-inflammatory therapy is clearly indicated for the treatment of clinically symptomatic neuritis as inflammation has been implicated in the pathophysiology of neuropathic pain. Standard NSAIDs (for example, naproxen 500 mg twice daily, ibuprofen 400 mg three times daily) are recommended to treat mild cases. The use of steroids, prednisone 40–60 mg initially then tapered over 7–10 days, dexamethasone 12–16 mg initially then similarly tapered, may be warranted in severe cases with marked pain and/or sensory changes. Preclinical data show that early dexamethasone may reduce neuropathic pain (Han et al. 2010), but there is no support from rigorous clinical studies. Early side effects associated with steroids treatment include facial flushing, dyspepsia, and sleeplessness; therefore, treatment should be as short as possible or alternatively (as above) tapered to reduce side effects from consistently high dosages. Antacids may be co-prescribed. If treatment is successful, patients may be transferred to a NSAID with an antacid and continue treatment for a further 7–10 days.

PTTNs are extremely difficult to manage (Haviv et al. 2014). Estimation of the number needed to treat (NNT) for neuropathic pain induced by peripheral nerve injury is challenging due to the insufficient number of controlled trials. However, the NNTs for drugs are largely similar across different neuropathic pains (Finnerup et al. 2010), with traumatic neuropathies possibly being the most recalcitrant to treatment (Haviv et al. 2014). Based on the efficacy studies in painful polyneuropathies, postherpetic neuropathy, mixed neuropathic pain, and central pain syndromes, the anticonvulsant drugs and tricyclic antidepressants (TCAs) remain the mainstays of treatment (Attal et al. 2010; Dworkin et al. 2010a; Finnerup et al. 2015).

Available pharmacotherapies such as antidepressants, anticonvulsants, and opioids provide
improved quality of life sleep and improved mood but often require high doses for neuropathic pain resulting in significant side effects. In neuropathic pain patients, a 30% pain reduction (traditionally 50%) is considered meaningful pain relief and only 20–40% of patients attain this (Duhmke et al. 2004; Eisenberg et al. 2005; McQuay et al. 1996; Rowbotham et al. 2004; Sindrup and Jensen 2001). Drugs with mixed serotonin/norepinepherine, such as amitriptyline and nortriptyline or serotonin and noradrenaline reuptake inhibitors (SNRIs), such as venlaflaxine and duloxetine, have been shown to be superior to the selective serotonin reuptake inhibitors (Lunn et al. 2014; Moore et al. 2012). The NNTs for TCAs such as amitriptyline in painful polyneuropathies is estimated to be 2.1 (Finnerup et al. 2015). The more novel antidepressant drugs, SNRIs have fewer side effects than TCAs and although less efficacious (NNT = 5) are attractive alternatives for the treatment of painful polyneuropathy (Finnerup et al. 2015).

Anticonvulsant drugs are extremely heterogeneous in their efficacy for painful neuropathies (Wiffen et al. 2013a, b). Carbamazepine or oxcarbazepine are efficacious in painful polyneuropathies (NNT = 3.7) but have more side effects than pregabalin (NNT = 4.5) or gabapentin (NNT = 6.4) (Finnerup et al. 2015). Based on the efficacy of pregabalin and gabapentin in other peripheral neuropathies, they are good options for managing PTTN. As a group, however, the anticonvulsant drugs are inferior to the antidepressants in the management of painful polyneuropathies.

Opioids have been shown to be efficacious in treatment of painful polyneuropathies (NNT = 2.6) but not as effective in treatment of traumatic neuropathies (NNT = 5) (Finnerup et al. 2015). Due to the complex etiology of pain, the combination of drugs with different modes and sites of action could theoretically offer improved efficacy with reduced side effects; however, the combination of duloxetine and pregabalin was reported to provide no significant advantage over high-dose monotherapy in the treatment of diabetic peripheral neuropathy (Tesfaye et al. 2013). In diabetic polyneuropathy or postherpetic neuralgia, combinations of nortriptyline and gabapentin or nortriptyline and morphine have been shown to be more efficacious than monotherapy (Gilron et al. 2009, 2015). Similarly, patients with painful diabetic neuropathy who did not respond to gabapentin monotherapy showed significant pain improvement when treated with the combination of gabapentin and venlafaxine (Simpson 2001). In diabetic neuropathy treatment, an oxycodone-gabapentin mix was shown to be more efficacious than gabapentin alone (Hanna et al. 2008). Gabapentin may also be combined with morphine to achieve significant analgesia in patients with neuropathic pain (PHN and diabetic neuropathy) at a lower dose than monotherapy with each drug (Gilron et al. 2005). Combination of gabapentin and an opioid was significantly superior to gabapentin in the treatment of neuropathic pain in adults, with more frequent side effects (Chaparro et al. 2012). To date, there is a lack of clear evidence supporting recommendation of any one specific drug combination for neuropathic pain (Chaparro et al. 2012).

Based on the available evidence, TCAs/SNRIs or gabapentin/pregabalin would be the first drugs indicated in painful peripheral neuropathy (Fig. 11) (Attal et al. 2010; Dworkin et al. 2010a; Finnerup et al. 2015). In patients initiated on amitriptyline that develop severe side effects, imipramine, desipramine, duloxetine, or venlafaxine should be trialed. If these fail or are contraindicated, gabapentin or pregabalin offer the best chances for success. Similarly, in patients on gabapentin/pregabalin, treatment failure is an indication for a trial of a TCAs or SNRIs. Combination therapy of a SNRI or TCA with gabapentin or pregabalin should be considered if the above avenues are only partly successful (Finnerup et al. 2015). Opioids or tramadol may be used as third-line monotherapy or an add-on therapy. It is important to keep in mind that opioid treatments pose a risk of addictive and abuse potential. Therefore, screening, preventive measures, and careful monitoring should be in place in all clinics prescribing opioids. Cannabinoids are increasingly being tested (Finnerup et al. 2015) and have NNTs of 3–5 in peripheral and
central neuropathic pain (Lynch et al. 2014; Wilsey et al. 2013).

When applying a widely accepted pharmacotherapy protocol for neuropathic pain in a cohort of PTTN patients, only 11% of patients achieved a ≥ 50% reduction in pain intensity, and patients with higher pain intensity scores were less likely to benefit from the therapy (Haviv et al. 2014). Comparable response rates have been reported in other painful neuropathies (Finnerup et al. 2015) emphasizing the need for new drugs and treatment options for chronic neuropathic pain.

Topical treatments offer the benefit of minimal side effects, fewer drug–drug interactions, and improved patient tolerance; however, the affected areas are not always amenable to treatment (Heir et al. 2008; Peppin et al. 2015). Evidence-based topical medications include lidocaine or capsaicin (low and high concentrations) patches and locally injected botulinum toxin A (Demant et al. 2015). Individually prescribed topical formulations are also in use (Heir et al. 2008).

Cognitive Behavioral Therapy
Cognitive behavioral therapy (CBT) or other psychosocial therapy might be beneficial in treatment of neuropathic pain as anxiety and depression are frequently comorbid. However, CBT does not have significant effects on pain intensity and quality of life measures in neuropathic pain patients (Wetering et al. 2010). Nonetheless, distressed patients should be offered psychotherapeutic support.

Surgical Modalities
Surgery is a well-established treatment option for nonpainful neuropathies and improves sensation in injured patients (Ziccardi 2011; Ziccardi and Steinberg 2007; Farole and Jamal 2008). Approximately, 50% of repaired cases will recover complete sensory function by 7 months (Susarla et al. 2007a) if treated within 1 year of injury (Ziccardi and Steinberg 2007; Caissie et al. 2005; Rutner et al. 2005; Strauss et al. 2006; Susarla et al. 2007b). Inferior alveolar nerve injuries have a marginally better prognosis with surgical

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**Fig. 11** Pharmacologic treatment algorithm for peripheral neuropathic pain. (1) The choice between tricyclic antidepressants (TCAs) or serotonin and noradrenaline reuptake inhibitors (SNRI) versus the use of gabapentin (GBP) or pregabalin (PGB) is based on the medical profile and other patient-based variables (profession, comorbidities). TCAs are more effective than GBP/PGB but have significantly more side effects. (2) SNRIs have not been as extensively tested as TCAs but seem less effective for neuropathic pain. (3) Patients initiated on GBP or PGB but are not responding to treatment may not be medically suitable for second-line therapy with TCAs/SNRIs. In these cases, the patient is transferred directly to opioids singly or together with GBP (Finnerup et al. 2015; Attal et al. 2010; Dworkin et al. 2010a)
treatment compared to lingual nerve injuries (Pogrel 2002; Ziccardi et al. 2009). The presence
of a neuroma is a negative prognostic factor (Susarla et al. 2007a, b).

The role of surgery for painful trigeminal neuropathies is contentious. Often patients with-traumatic trigeminal neuropathy that have undergone peripheral surgical procedures (exploration, further apicoectomies) end up with more pain. Therefore, unless there are specific indications, it is suggested that patients with painful traumatic neuropathies do not undergo further surgery and a more diverse and perhaps holistic strategy for management of pain be considered (Renton and Yilmaz 2012). In cases of nerve repair (larger branches such as lingual nerve) and restoration of sensation, there may be a parallel improvement in pain but no rigorous trials have been published. Surgical intervention for PTTN patients may be indicated for the release of scar tissue, decompression, and neuroma excision, all of which have been shown to have good success rates (Renton and Yilmaz 2012). Peripheral glycero1 injections may also be used for some painful trigeminal neuropathies; however, prospective controlled trials are needed to confirm the success rate of this treatment.

Surgical Management of Offending Dental Implants
Decompression of an injured nerve by removing the implant completely or shortening, it may promote healing and prevent neuropathy. In particular, the timing of the removal of offending implants needs to be considered. Each situation needs to be weighed individually according to the degree of nerve injury, type of injury, and time elapsed since insertion. Early removal or replacement of the offending implants (<24–48 h after placement) has been suggested to reduce incidence of neuropathy and pain (Renton and Yilmaz 2012; Renton et al. 2012b). Microsurgical repairs may be considered for total resections of nerve bundles such as the inferior alveolar nerve. In medically fit patients, pharmacotherapy should be considered in management of early nerve injury and neuritis.

When the offending implants have osseointegrated, the collateral damage in removing them may be significant. These cases rarely improve and implant removal must be weighed against the potential tissue damage and loss of function.

Central Surgery
In refractory cases, central procedures may be considered (Bullard and Nashold 1997; Kanpolat et al. 2005). The primary choice of surgery should be minimally invasive, such as computed tomography (CT)-guided percutaneous 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. When minimally invasive procedures are not successful, DREZ surgery (surgical damage a portion of neurons in the trigeminal nerve root at the brainstem level) may be performed (Kanpolat et al. 2005).

Orofacial Complex Regional Pain Syndrome
Orofacial Complex Regional Pain Syndrome (CRPS) are chronic, painful neuropathic disorders largely resulting from injury (Marinus et al. 2011). Three types of CRPS have been defined and these include: CRPS I (reflex sympathetic dystrophy), CRPS II (causalgia), and CRPS-NOS (not otherwise specified) to allow inclusion of patients not meeting all the criteria (Hauser et al. 2013). These entities present with spontaneous pain accompanied by allodynia and hyperalgesia not limited to dermatomal regions (Janig and Baron 2004).

CRPS is a type of traumatic neuropathy characterized by significant autonomic, trophic, and motor changes. The specific signs that significantly differentiate CRPS from non-CRPS neuropathic pain include regional changes in skin color, temperature, sweating, motor function, edema, and thermal allodynia (Harden et al. 2010). CRPS I may develop as a result of remote or relatively minor local trauma with surgery, fractures, crush injuries, and sprains being the most common causes (Bruehl 2010). Injections, local infection, and burns resulting in minor or
not identifiable nerve lesions with disproportionate pain have also been implicated (Borchers and Gershwin 2014). However, subsequent surgical attempts at treatment of the injury may be more important than the original injury in perpetuating pain and associated signs. CRPS II occurs less frequently and results from substantial injury to a major nerve, most often following high-velocity missile trauma or surgery. The major distinguishing characteristic of CRPS is the disproportionate severity of the syndrome relative to the injury and nondermatomal spread of pain over time (Marinus et al. 2011). Pain is felt in the most distal part of the affected limb. The need for subdivision into CRPS I and CRPS II is questionable as the two are often difficult to differentiate (Borchers and Gershwin 2014).

The question arises as to whether CRPS occurs in the craniofacial region. The cases reported in the literature rely on interventions aimed at interfering with sympathetic input to justify the diagnosis (Melis et al. 2002). Sympathetic involvement, however, is not essential in CRPS, which has probably prevented identification of more cases (Heir et al. 2012). CRPS features such as trophic and motor changes are not usually present in PTTN; however, the other listed criteria are distinctly similar to those observed in PTTN and other neuropathic pain cases. The particular clinical phenotype may reflect the trigeminal system’s differential response to trauma (Fried et al. 2001).

Pathophysiology of Painful Traumatic Neuropathies

The pathophysiology of painful traumatic neuropathies involves a series of events in the nervous system, involving changes in functional, biochemical, and physical characteristics of neurons and glia. These changes are time dependent and progress from the peripheral to the central nervous system (Salter and Beggs 2014; Lee and Tracey 2013; von Hehn et al. 2012; Nitzan-Luques et al. 2011; Devor 2009; Woolf and Salter 2000; Mogil 2012; Salter 2014). Selected aspects of these events are examined in the subsequent section (Fig. 12).

Peripheral Sensitization: Tissue Injury and Inflammation

Peripheral sensitization is often the result of tissue inflammation and is initiated by inflammatory mediators produced in response to a variety of stimuli or tissue damage. The released inflammatory mediators may directly activate or indirectly sensitize nociceptors. These changes develop rapidly but are reversible. The activated nociceptors display altered neurophysiological activity that may be spontaneous or stimulus induced. Development of sensory changes such as hyperalgesia and/or allodynia is characteristic of peripheral sensitization. Hyperalgesia, an exaggerated pain to a normally painful stimulus, is a phenomenon used routinely to diagnose an inflamed pulp; application of cold, which is normally mildly painful, induces extreme pain in irreversible pulpitis. Allodynia, pain to a normally nonpainful stimulus, is reflected in the observed sensitivity to percussion in teeth with periapical periodontitis.

Perineural inflammation alone can induce ectopic activity and spontaneous pain, and inflammation anywhere along a nerve has been shown to cause pain in the organ supplied by the nerve (Benoliel et al. 2002; Chacur et al. 2001). Inflammation may affect nerve function either by secretion of mediators such as cytokines or as a result of pressure induced by edema (Zelenka et al. 2005), both of which when allowed to persist result in nerve damage (Eliav et al. 2004).

Nerve Injury and Ectopic Activity

Trauma (e.g., transection) or severe inflammation may result in neuronal tissue injury leading to subsequent cell death. However, if the proximal stump survives, healing may occur, which involves disorganized sprouting of nerve fibers that form a neuroma. Neurona formation is often dependent on the degree of nerve damage and usually occurs when the perineurium is cut. Milder injuries, such as nerve constriction or compression, may cause focal demyelination and regions of neurona formation, which are characterized by ectopic discharge partially caused by upregulation of specific sodium and calcium channels and downregulation of potassium
Ectopic activity in neuromas is enhanced by mechanical and chemical stimulation resulting in the experience of pain when the injured area and neuromas are touched. Ectopic activity is also seen in the cell bodies of injured nerves in the dorsal root or trigeminal ganglia and together may partly explain spontaneous neuropathic pain. Experimentally, trigeminal nerve neuromas (in myelinated and unmyelinated axons) are less active than sciatic nerve neuromas. Similarly, mechanosensitivity and acute injury discharge in trigeminal neuromas were minimal suggesting relative resistance of the trigeminal nerve to trauma-induced hyperactivity.

**Phenotypic Changes**

Nerve injury results in altered expression of neurotropes in trigeminal ganglion suggesting functional modifications. For example, under normal circumstances, Aβ fibers transmit innocuous stimuli; however, in the presence of persistent inflammation or injury, there is a phenotypic

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**Fig. 12** Peripheral and central nervous system changes in chronic pain. Peripheral sensitization: tissue damage (1) releases inflammatory mediators, e.g., bradykinin (BK), nerve growth factor (NGF), serotonin (5-HT), prostaglandins (PG), and protons (H+). This “inflammatory soup” of bioactive molecules induces increased sensitivity of peripheral nociceptors leading to allodynia and hyperalgesia. Axonal injury (2), e.g., transection, crush or chronic pressure, and inflammation induce increases in sodium (Na+) and α-adrenoreceptors (α-R), initiating ectopic activity and increased sensitivity. Axotomy results in death of the distal part of the nerve (3), and if the proximal section survives, there is healing with neuroma formation (4). Some of the neurons will however die. This activity leads to altered gene expression in the neuronal cell bodies located in the ganglia (DRG) (5). Nerve injury may lead to sympathetic nerve fiber sprouting (6), particularly around the larger DRG cells. The modulating effects of satellite glial cells in DRGs have recently been demonstrated. Aβ fibers undergo a phenotypic change (7) and express neurotransmitters associated with nociceptors, e.g., substance P (SP). Injury-induced C-fiber degeneration (8) may result allowing Aβ fibers to sprout 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, enhance dorsal-horn-neuron and primary afferent activity and excitability. Persistent nociceptive input results in the sensitization of wide dynamic range (WDR) dorsal horn neurons, (DHN; 11), excitation of adjacent neurons (central sensitization), and activation of glial cells. Glutamate-induced excitotoxicity reduces the number of inhibitory interneurons, augmenting excitation (12). Persistent pain initiates descending modulation, which in pathological states tends toward facilitation (13). (With permission from: Benoliel et al. 2015.)
change and they begin to express substance-P (Nitzan-Luques et al. 2011). Aβ fibers thus acquire the ability to induce painful sensations in response to peripheral stimulation partially explaining the phenomenon of allodynia.

Novel Sensitivity to Catecholamines
During periods of stress or anxiety, which are accompanied by increased sympathetic activity, patients may report increased pain. This may be due to upregulation of α-adrenoreceptors in the dorsal root ganglion and the site of injury that induce sensitivity to circulating catecholamines. Additionally, sensory-sympathetic interactions can be amplified by basket-like sprouting of sympathetic fibers around large neuronal cell bodies within the dorsal root ganglion. This phenomenon has not been detected in the trigeminal ganglion and may explain the relative rarity of sympathetically maintained craniofacial pain (Benoliel et al. 2001).

Central Sensitization
The barrage of activity from primary afferents that is transmitted to dorsal horn neurons (DHN) may trigger central changes or plasticity. Repeated input from primary nociceptive afferent increasingly depolarizes DHNs leading to amplified responses (“wind up”). Prolonged DHN depolarization results in sensitization of the NMDA receptor (NMDAr). NMDAr is a calcium channel normally blocked by magnesium ion. Upon activation, the magnesium ion blocking the NMDAr is removed allowing calcium ions influx to the DHN and initiating a variety of intracellular events. Activation of NMDAr is thought to contribute to central sensitization by enhancing neuronal activity. Additionally, repeated nociceptive afferent input leads to activation of other calcium channels (L-, P-, and N-type) resulting in increases in intracellular calcium and DHN hypersensitivity, which manifests as hyperalgesia and/or allodynia.

In the presence of prolonged hypersensitivity, adjacent DHNs may be activated directly (possibly by diffusion of neurotransmitters) or by unmasking of silent inter-DHN connections. Activation of adjacent DHNs increases the receptive field leading to perception of pain in areas not normally innervated by the involved peripheral nerve. The increase in receptive field can be detected clinically as sensitivity in the uninjured areas in the vicinity of the injury, termed secondary hyperalgesia. The phenomenon of central sensitization accounts for increased pain and spread of pain to adjacent structures in patients with severe facial pain. The early neuronal excitability responds well to treatment as it is activity dependent. However, prolonged stimulation and long-term changes originating in the DRG and DHNs involve modified gene expression and down-regulation of repressor mechanisms that lead to further excitability. Central sensitization characterized by hyperalgesia, temporal summation, and abnormal sensation may develop following a minor injury such as third molar extraction (Juhl et al. 2008). Some months after nerve injury, neuronal death occurs (mainly C-fibers) and sprouting of Aβ fibers from deeper lamina follows as injured C-fiber terminals are removed from lamina I/II. The sprouting of Aβ fibers results in increased pain induced by light touch (Tan et al. 2011). Excitotoxic cell death induced by nerve damage is thought to deplete inhibitory interneurons and increase pain, although this does not seem necessary for development of persistent pain (Polgar et al. 2005). Supraspinal modification of peripheral signals is an essential part of balanced nociception. Increased facilitation with decreased inhibition is frequently observed in inflammatory or neuropathic pain states.

The above events are characteristic of the progressive malfunctioning of the nervous system establishing conditions for chronic pain and increasing the difficulty of therapeutic interventions. Increasingly, evidence shows that unmanaged, ongoing pain results in sensitization with changes in the peripheral and central nervous system that may promote establishment of chronic pain.

Glial and Satellite Glial Cells
Spinal cord glial cells have been implicated in normal development, connectivity, and plasticity of the central nervous system (Salter and Beggs 2014). Glia have been shown to play an important
role in the initiation and maintenance of chronic pain as well as pain modulation. They express receptors and transporter proteins for many neurotransmitters and are able to release excitatory molecules such as, pro-inflammatory cytokines, glutamate, nitric oxide, and prostaglandins, in response to neuronal signals leading to the strengthening of DHN hyperexcitability and neurotransmitter release from primary afferents (Salter and Beggs 2014; Vallejo et al. 2010). Glial cells can be activated by bacteria and viruses, which may explain the pain and allodynia associated with some systemic infections. Glial cells are an attractive therapeutic target because they participate in pathological pain and not in acute nociceptive responses. Additionally, peripheral satellite glial cells (in sensory ganglia such as trigeminal ganglion) may interact with neurons and thus influence changes occurring following nerve injury (Dublin and Hanani 2007; Hanani 2005).

Contribution of Macrotrauma

In macrotrauma, peripheral nerves may be damaged as a result of direct penetrating injuries around the face and scalp and may lead to PTTN. Musculoskeletal pain may develop as a result of direct damage to the temporomandibular joints and regional muscles. Accelerating-decelerating injuries and blunt blows to the cranium exert widespread shearing within the CNS that may result in extensive axonal injury, commonly known as diffuse axonal injury (Inglese et al. 2005; Povlishock and Katz 2005).

Pain Attributed to a Lesion or Disease of the Glossopharyngeal Nerve

Introduction

Glossopharyngeal neuralgia (GN) also known as vagoglossopharyngeal neuralgia (Kandan et al. 2010) is a rare condition that affects the throat or preauricular area corresponding to the distribution of auricular and pharyngeal branches of the vagus and glossopharyngeal nerves (Blumenfeld and Nikolskaya 2013; Rey-Dios and Cohen-Gadol 2013). GN patients often seek help from medical specialists such as otorhinolaryngologists based on the characteristic pain location. The clinical presentation of GN is similar to that of TN (Headache Classification Subcommittee of the International Headache Society (IHS) 2018), but it is characterized by milder natural history with majority of patients going into remission. Diagnosis of GN is very difficult (Table 14) due to its location and features frequently resulting in a delay in adequate treatment (Patel et al. 2002). High-quality studies on predictive value of special tests are not available due to the relatively low prevalence of GN.

Epidemiology

GN is extremely rare with the estimated prevalence of 0.2–0.4/100,000 patient years (van Hecke et al. 2014) and is more common in males. Most patients (57%) are older than 50 years of age, although GN may also occur in younger patients.

Classification

GN is now subclassified if there is access to imaging and special tests, with a similar approach to that taken for TN. Classical GN develops without apparent cause other than neurovascular compression (Fig. 13); secondary GN is that usually caused by neck trauma, multiple sclerosis, tonsilar or regional tumors, cerebello-pontine angle tumors, and Arnold-Chiari malformation. Finally, idiopathic GN has the same clinical phenotype with no evidence either of neurovascular compression or of causative underlying disease.

Imaging of the head and neck to rule out pathology is indicated and will allow subclassification. Preoperative magnetic resonance tomographic angiography is recommended to locate possible neurovascular contacts.

Clinical Features

The pharyngeal branches (IXth) together with the vagal (Xth) afferents innervate the base of the
tongue, tonsil, and soft palate. Therefore, GN pain is localized to the posterior part of the tongue, tonsillar fossa, pharynx, and the angle of the lower jaw and/or the ear (Teixeira et al. 2008) (Table 14). Two types of GN, pharyngeal and tympanic, have been described based on the location and referral patterns of pain. In pharyngeal-GN, pain is usually located in the pharynx, tonsil, soft palate, or posterior tongue-base. The pain can radiate upwards to the inner ear or the angle of the

Table 14 Diagnostic criteria for glossopharyngeal neuralgia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
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<tr>
<td>A</td>
<td>Recurring paroxysmal attacks of unilateral pain in the distribution of the glossopharyngeal nerve and fulfilling criterion B</td>
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<tr>
<td></td>
<td>May co-occur with classical trigeminal neuralgia (CTN). In the distributions of the auricular and pharyngeal branches of the vagus nerve as well as branches of the glossopharyngeal nerve. Prior to its development, unpleasant sensations can be experienced in affected areas for weeks to several months</td>
</tr>
<tr>
<td>B</td>
<td>Pain has all of the following characteristics:</td>
</tr>
<tr>
<td></td>
<td>1. Lasting from a few seconds to 2 min</td>
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<td></td>
<td>2. Severe intensity</td>
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<td></td>
<td>3. Electric shock-like, shooting, stabbing or sharp in quality</td>
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<td></td>
<td>4. Precipitated by swallowing, coughing, talking or yawning</td>
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<tr>
<td></td>
<td>Less severe than CTN. In rare cases, attacks of pain are associated with vagal symptoms such as cough, hoarseness, syncope, and/or bradycardia. Some distinguish between pharyngeal, otalgic, and vagal subtypes of neuralgia, and suggested using the term vagoglossopharyngeal neuralgia when pain is accompanied by asystole, convulsions, and syncope</td>
</tr>
<tr>
<td>C</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
<tr>
<td></td>
<td>When imaging shows neurovascular compression of the glossopharyngeal nerve, this would be termed classical glossopharyngeal neuralgia</td>
</tr>
<tr>
<td></td>
<td>There are reports of secondary glossopharyngeal neuropathy caused by neck trauma, multiple sclerosis, tonsillar or regional tumors, cerebello-pontine angle tumors, and Arnold-Chiari malformation</td>
</tr>
</tbody>
</table>
mandible; it may also affect the eye, nose, maxilla, or shoulder and the tip of the tongue. In tympanic-GN, pain is confined to or predominates in the ear with potential radiation to the pharynx, posing serious differential diagnosis dilemmas vis-à-vis geniculate neuralgia. Bilaterality is more common in GN than in TN (Patel et al. 2002).

GN pain is described as sharp, stabbing, shooting, or lancinating. Scratching or sensation of a foreign body in the throat has also been reported. However, an atypical, predominantly burning and long-lasting pain attacks have been reported in GN cases. Usually, the GN attacks are not preceded by warning signs, but some cases report preattack discomfort in the throat or ear. Intensity of GN attacks varies from typical mild to excruciating, and features of pain attacks are stereotyped within patients.

GN trigger areas are typically located in the tonsillar region and posterior pharynx and are activated by swallowing, chewing, talking, coughing, and/or yawning (Minagar and Sheremata 2000; Olesen et al. 2004). Pain may also be triggered during sneezing, clearing the throat, touching the gingiva or oral mucosa, nose blowing, and rubbing the ear or around it (Minagar and Sheremata 2000). Triggering and pain may be eliminated by topical analgesia applied to trigger areas.

Paroxysmal pain attacks occur at a rate of 5–12 per waking hour; however, up to 200 attacks per day have been reported. Pain attacks are usually short lasting from 8 to 50 s (Blumenfeld and Nikolskaya 2013) but may continue for a few minutes (4–40 minutes). Cases with longer lasting attacks of continuous series of paroxysms have also been described. A refractory period occurs following the pain attack in which additional stimuli are incapable of inducing pain.

A cluster of attacks lasting from weeks to months is usually followed by relapse for up to a number of years and 74% of GN patients experienced spontaneous remissions. Approximately, 17% of GN patients had no periods of pain relief. The average annual pain episode recurrence rate is low (3.6%), and in two-thirds of cases, there may be only one attack.

Excessive activation of the vagal nerve leading to bradycardia, syncope, and even cardiac arrest may occur in 10% of GN patients (Blumenfeld and Nikolskaya 2013; Esaki et al. 2007). Additional signs include uncontrollable coughing (8% of cases) and disturbed salivation during the pain-paroxysms. Lacrimation is rare and occurs when pain radiates to the eye.

**Differential Diagnosis**

TN co-occurs with GN in 10–12% of GN patients. The co-occurrence of TN with GN makes TN the most common differential diagnosis especially when pain of GN spreads to trigeminal dermatomes. Cluster headache could be another differential diagnosis particularly in the presence of bradycardia and clustering of attacks with a very rare spread to the eye with lacrimation.

**Pathophysiology**

The exact causes of GN are uncertain; however, it is probably secondary to compression of the nerve root by a blood vessel. Nerve compression has been identified in GN patients (MRI and on surgical exposure) (Rey-Dios and Cohen-Gadol 2013; Xiong et al. 2012; Fischbach et al. 2003), and variable myelin damage with patches of demyelinated axons was observed during nerve biopsy (Devor et al. 2002c). The described above morphological changes associated with GN are similar to those of TN patients suggesting shared pathophysiology. The new classification enables cases to examine with and without nerve compression to further elucidate its pathophysiology.

**Treatment**

Therapy for GN is modelled on successful treatments for TN. Cardiac pacing may be required when life threatening arrhythmias occur. An
electrocardiogram should be performed prior to and after treatment.

**Pharmacological**
Carbamazepine is usually successful (Singh et al. 2013) with baclofen, oxcarbazepine, gabapentin, lamotrigine, and phenytoin as alternatives (Rozen 2004).

**Surgical**
Surgery is indicated when GN patients become resistant to anticonvulsants (Martinez-Gonzalez et al. 2011). Microvascular decompression (MVD) and gamma knife surgery (Pollock and Boes 2011) have been successfully applied to patients with GN (Gaul et al. 2011; Rey-Dios and Cohen-Gadol 2013; Stieber et al. 2005; Xiong et al. 2012). MVD induced immediate and complete relief of pain in 80–95% of GN patients with stable long-term results (Patel et al. 2002; Sampson et al. 2004)

Rare (≈10%), permanent neurological deficits include mild hoarseness and/or dysphagia, or facial nerve paresis. Also, section of the glossopharyngeal nerve, the upper rootlets of the vagus nerve and of the fifth cranial nerve (if TN was also present) has provided pain relief in over 50% of GN patients (Rey-Dios and Cohen-Gadol 2013). GN patients who are not good neurosurgical candidates (e.g., older patients) may be treated with glycerol injections (Yue and Zhang 2013).

**Secondary Glossopharyngeal Neuralgia**
GN has been significantly associated with MS (Minagar and Sheremata 2000). Regional infectious or inflammatory processes may cause GN like symptoms. GN may be caused by tonsillar carcinoma invading the parapharyngeal space and other regional tumors (tongue, oropharyngeal). Posttraumatic GN is relatively rare but has been reported (Webb et al. 2000). Cerebellopontine angle or pontine lesions may resemble GN like symptoms (Huynh-Le et al. 2004).

**Pain Attributed to a Lesion or Disease of Nervus Intermedius**
The intermedius nerve carries parasympathetic fibers to the lacrimal, submandibular/sublingual, and nasopalatine glands and transmits sensory information from concha of the auricle, a small area behind the ear and over the mastoid process, to the outer layer of the tympanic membrane and part of the wall of the external auditory canal (Tubbs et al. 2013; Guinto and Guinto 2013). This distribution allows herpetic vesicles to be identified in the ear when a viral infection affects the geniculate ganglion, where the cell bodies of the nerve reside. Hence the alternative term for nervus intermedius neuralgia (NIN) has been “geniculate neuralgia.” Special sensory information from the taste receptors located in the anterior two-thirds of the tongue, floor of the mouth, and part of the palate also travel in fibers of this nerve.

**Nervus Intermedius Neuralgia**
Painful neuropathic pain affecting the nevus intermedius (facial nerve) may take the form of a neuralgia. With the current ICHD approach, NIN may be subdivided into classical when associated with a neurovascular contact, secondary when caused by an underlying disease and idiopathic when these are absent.

**Clinical Features**
NIN is extremely rare. Pain associated with NIN is often felt deep within the ear (Headache Classification Subcommittee of the International Headache Society (IHS) 2018; Pulec 2002) and lasts seconds to minutes (Table 15). NIN is paroxysmal and is described as sharp and stabbing. NIN cases with gradual onset and persistent nature of pain have also been reported (Headache Classification Subcommittee of the International Headache Society (IHS) 2018; Pulec 2002). Although difficult to verify, trigger points may be present and are located in the posterior wall of the auditory canal.
Nonspecific myelin sheath delamination has been documented in NIN patients (Pulec 2002). It has been suggested that NIN may be secondary to neurovascular contact (Saers et al. 2011). Although attractive, this theory is not yet firmly established or accepted (Alfieri and Strauss 2011). The nervus intermedius is a small diameter nerve with a variable course. These will hamper the establishment of neurovascular contact with diagnostic imaging. More experimental studies are needed to confirm this neurovascular compression theory. When presenting with facial palsy, ipsilateral loss of taste and herpetic vesicles in the auditory canal, NIN is “nervus intermedius neuropathy attributed to herpes zoster” (see below) (Headache Classification Subcommittee of the International Headache Society (IHS) 2018).

Anticonvulsant pharmacotherapy has been indicated (Tubbs et al. 2013). Surgery is suggested in cases resistant to pharmacotherapy or with intolerable side effects. In patients with clear evidence of neurovascular contact, MVD may provide relief (Tubbs et al. 2013). Combined nerve section and MVD is used to treat NIN patients with symptoms suggestive of TN and/or GN. Excision of the nervus intermedius and geniculate ganglion has been shown to be an effective and definitive treatment for intractable geniculate neuralgia that can be routinely performed without causing facial paralysis (Pulec 2002). The greater petrosal nerve is usually sectioned so that the ipsilateral eye remains tearless (Pulec 2002).

### Painful Nervus Intermedius Neuropathy

Painful nervus intermedius neuropathy associated with herpes zoster may appear in the acute form as “painful nervus intermedius neuropathy attributed to herpes zoster” (Ramsay Hunt Syndrome) or in the chronic “postherpetic neuralgia of nervus intermedius”.

### Painful Nervus Intermedius Neuropathy Attributed to Herpes Zoster

Herpes-zoster virus infection is responsible for Ramsay Hunt Syndrome (RHS) (also known as Herpes Zoster Oticus). RHS occurs when a herpes virus-3 infection affects the geniculate ganglion and spreads to the facial nerve and to the adjacent

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**Table 15** Diagnostic criteria for nervus intermedius neuralgia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Paroxysmal attacks of unilateral pain in the distribution of nervus intermedius and fulfilling criteria B</td>
</tr>
<tr>
<td></td>
<td>Pain is located in the auditory canal, auricle, in the region of the mastoid process and occasionally the soft palate, and may sometimes radiate to the temporal region or the angle of the mandible</td>
</tr>
<tr>
<td>B</td>
<td>Pain has all of the following characteristics:</td>
</tr>
<tr>
<td></td>
<td>1. Lasting from a few seconds to minutes</td>
</tr>
<tr>
<td></td>
<td>2. Severe in intensity</td>
</tr>
<tr>
<td></td>
<td>3. Shooting, stabbing or sharp in quality</td>
</tr>
<tr>
<td></td>
<td>4. Precipitated by stimulation of a trigger area in the posterior wall of the auditory canal and/or periauricular region</td>
</tr>
<tr>
<td></td>
<td>In view of the complex and overlapping innervation of the external ear, deriving from trigeminal (auriculotemporal), facial (nervus intermedius), glossopharyngeal, vagus and second cranial nerves, attribution of neuralgias to a single nerve may not be easy in this body region, particularly when a specific neurovascular contact cannot be visualized</td>
</tr>
<tr>
<td>C</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
<tr>
<td></td>
<td>When imaging shows neurovascular compression of the nervus intermedius the diagnosis would be classical nervus intermedius neuralgia</td>
</tr>
<tr>
<td></td>
<td>There are single reports of secondary nervus intermedius neuralgia caused by multiple sclerosis or tumour. In the latter case, neurological deficits arising from damage to other nerves in close proximity tend to dominate the clinical presentation. Herpes zoster typically usually leads to painful nervus intermedius neuropathy attributed to herpes zoster</td>
</tr>
</tbody>
</table>

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The syndrome is characterized by unilateral facial paralysis, severe ear pain ipsilateral to the infection side, tinnitus, and vertigo (Table 16). Additionally, herpetic blistering rash or vesicles occur on the pinna, external canal, and sometimes on the roof of the mouth in the distribution of the sensory branch of the facial nerve (Kim et al. 2010; Shim et al. 2011), although other cranial nerves may be involved (Ko et al. 2000). Some degree of meningeal inflammation may also be present (Ko et al. 2000). RHS most frequently affects the elderly and otherwise immunocompromised individuals (Goldani et al. 2009).

Prompt treatment with antiviral medication (e.g., acyclovir and famciclovir) in combination with corticosteroids improves the recovery for RHS patients (Kinishi et al. 2001; Morrow 2000; de Ru and van Benthem 2011). Some degree of hearing loss or facial paralysis may remain permanently but prognosis is improved when treatment is initiated within 3 days of onset (Morrow 2000). Complications may occur during recovery when the injured nerve grows back to the wrong areas (synkinesis) causing inappropriate responses, such as tearing when laughing or chewing (crocodile’s tears) or blinking when talking or eating.

### Table 16  Diagnostic criteria for painful nervus intermedius neuropathy attributed to herpes zoster

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Unilateral continuous or near-continuous pain in the distribution of nervus intermedius and fulfilling criterion C</td>
</tr>
<tr>
<td></td>
<td>Pain is located in the auditory canal, auricle, in the region of the mastoid process and occasionally the soft palate, and may sometimes radiate to the temporal region or the angle of the mandible</td>
</tr>
<tr>
<td>B</td>
<td>One or more of the following:</td>
</tr>
<tr>
<td></td>
<td>1. Herpetic eruption has occurred in the distribution of nervus intermedius</td>
</tr>
<tr>
<td></td>
<td>2. Varicella zoster virus (VZV) has been detected in the CSF by polymerase chain reaction (PCR)</td>
</tr>
<tr>
<td></td>
<td>3. Direct immunofluorescence assay for VZV antigen or PCR assay for VZV DNA is positive in cells obtained from the base of lesions</td>
</tr>
<tr>
<td></td>
<td>Brief paroxysms may be superimposed, but are not the predominant pain type</td>
</tr>
<tr>
<td></td>
<td>Due to viral spread, other cranial nerves may become affected</td>
</tr>
<tr>
<td>C</td>
<td>Pain developed in temporal relation to the herpes zoster</td>
</tr>
<tr>
<td></td>
<td>The diagnosis is confirmed clinically in the acute stages by detection of vesicles on the tympanic membrane, auditory canal, auricle and/or skin overlaying the mastoid process. They may also be seen in the anterior third of the tongue, which the virus has reached via chorda tympani, or on the hard palate, supplied by a vestigial remnant branch of the facial nerve</td>
</tr>
<tr>
<td>D</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
<tr>
<td></td>
<td>Pain can precede the herpetic eruption</td>
</tr>
</tbody>
</table>

### Postherpetic Neuralgia of Nervus Intermedius

There are sparse data on the natural course of “painful nervus intermedius neuropathy” attributed to herpes zoster; however, when the pain continues for more than 3 months, it should be classified as “postherpetic neuralgia of nervus intermedius” (Table 17). Pain in postherpetic neuralgia of the nervus intermedius is unilateral and distributed in the auditory canal, auricle, and/or region of the mastoid process (distribution of nervus intermedius). There must be a temporal history of pain and herpes zoster infection. In most cases, pain will have developed while the infection is still active but may occasionally develop later.

### Occipital Neuralgia

Most frequently occipital neuralgia (ON) arises as a result of trauma or irritation of the major, and/or lesser or third occipital nerves. No data are available on the prevalence or incidence of this condition. Cervical spine imaging is necessary to exclude underlying pathology.
Clinical Features

Pain associated with ON may be unilateral or bilateral. It occurs in the suboccipital region radiating over the vertex and posterior part of the scalp in the dermatomes of the major and/or lesser or third occipital nerves (Table 18). ON pain may reach the fronto-orbital area through trigeminocervical interneuronal connections in the trigeminal spinal nuclei (Mason et al. 2004). In most (90%) ON patients, the major occipital nerve is the source of pain. The minor occipital nerve is involved in 10% and both nerves are involved in 8.7% of ON cases (Vanelderen et al. 2010).

ON pain is described as shooting or stabbing (Vanelderen et al. 2010) and is paroxysmal with constant pain persisting between the paroxysms in some patients. Trigger points may be identified at the emergence of the greater occipital nerve or in the area of distribution of C2 (Vanelderen et al. 2010).

Tenderness to pressure over the course of the occipital nerves and a positive Tinel’s sign (pain upon percussion over the nerve) can be present. Additionally, ON may be accompanied by diminished sensation or dysesthesia in the affected area. Vision impairment/ocular pain occurs in 67% of ON patients, tinnitus (33%), dizziness (50%), nausea (50%), and nasal congestion (17%) due to connections with cranial nerves VIII, IX, X, and cervical sympatheticus (Kuhn et al. 1997).

Pain arising from the atlantoaxial or upper zygapophyseal joints or from tender trigger points in neck muscles or their insertions may mimic that of ON. Congenital anomalies associated with Arnold-Chiari malformation, tumors, and infection should be ruled out. Pain arising from structures such as the upper cervical facet joints (C2-C3), osteoarthritis of the atlanto-occipital or atlantoaxial joint, giant cell arteritis, and tumors of the cervical spinal column may mimic ON-associated pain. When ON is accompanied by nausea and nasal congestion, it can easily be mistaken for migraine (may be comorbid (Sahai-Srivastava and Zheng 2011)) or cluster headache and in milder attacks, even paroxysmal hemicrania.

Table 17  Diagnostic criteria for postherpetic neuralgia of nervus intermedius

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A  Unilateral pain in the distribution of nervus intermedius, persisting or recurring for &gt;3 months and fulfilling criterion C</td>
<td>Pain is located in the auditory canal, auricle, in the region of the mastoid process and occasionally the soft palate, and may sometimes radiate to the temporal region or the angle of the mandible</td>
</tr>
<tr>
<td>B  Nervus intermedius herpes zoster infection has occurred</td>
<td>Usually, pain will have developed while the infection was still active, but on occasion later</td>
</tr>
<tr>
<td>C  Pain developed in temporal relation to the herpes zoster infection</td>
<td>When imaging shows neurovascular compression of the nervus intermedius the diagnosis would be classical nervus intermedius neuralgia</td>
</tr>
<tr>
<td>C  Not better accounted for by another ICHD-3 diagnosis</td>
<td>There are single reports of secondary nervus intermedius neuralgia caused by multiple sclerosis or tumour. In the latter case, neurological deficits arising from damage to other nerves in close proximity tend to dominate the clinical presentation. Herpes zoster typically usually leads to painful nervus intermedius neuropathy attributed to herpes zoster</td>
</tr>
</tbody>
</table>

Treatment

A single infiltration of the nerves with local anesthetic and corticosteroids is suggested as initial treatment (Ashkenazi and Levin 2004). The infiltration sites of the nervous occipitalis major and minor are determined by external landmarks (Vanelderen et al. 2010). A 22-gauge needle is
introduced till bone contact or paresthesia is obtained. Subsequently, the needle is slightly withdrawn, and the local anesthetic and corticosteroid are injected (Vanelderen et al. 2010).

When there is no lasting pain relief following injection of local anesthetic and corticosteroid, various alternatives are available including pulsed radiofrequency treatment of the occipital nerves and subcutaneous occipital nerve stimulation. Botulinum toxin A injections have also been used in treatment of ON, but its effectiveness is unclear. There is no supportive evidence for pulsed radio-frequency treatment of the C2 dorsal root ganglia.

### Neck Tongue Syndrome

Neck Tongue Syndrome (NTS) is considered extremely rare with an estimated prevalence of 0.22% (Wig et al. 2009; Sjaastad and Bakketeig 2006). There are around 50 cases in the literature, slightly more females and an average onset age in the early 20s (Hu and Dougherty 2016; Gelfand et al. 2017).

NTS is characterized by occipital and/or upper neck pain associated with an abnormal sensation on the ipsilateral side of the tongue (Gelfand et al. 2017) (Table 19). Pain follows head rotation, usually to one side, and lasts some minutes (Sjaastad and Bakketeig 2006; Hu and Dougherty 2016; Gelfand et al. 2017). The quality is usually sharp or stabbing and pain may radiate to the occipital, cervical, and lingual regions (Elisevich et al. 1984; Lance and Anthony 1980). In the tongue, paresthesia, dysesthesia, or anesthesia may be reported lasting from a few seconds to about 2 minutes (Sjaastad and Bakketeig 2006), which may or may not be preceded by tongue pain (Lance and Anthony 1980; Chedrawi et al. 2000). More rarely motor symptoms are reported in the tongue (Gelfand et al. 2017). Patients may describe radicular symptoms and display restricted neck movements (Sjaastad and Bakketeig 2006).

Table 18: Diagnostic criteria for occipital neuralgia

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Unilateral or bilateral pain in the distribution(s) of the greater, lesser and/or third occipital nerves and fulfilling criteria B–D</td>
</tr>
<tr>
<td>B</td>
<td>Pain has at least two of the following three characteristics: 1. Recurring in paroxysmal attacks lasting from a few seconds to minutes 2. Severe in intensity 3. Shooting, stabbing or sharp in quality</td>
</tr>
<tr>
<td>C</td>
<td>Pain is associated with both of the following: 1. Dysesthesia and/or allodynia apparent during innocuous stimulation of the scalp and/or hair 2. Either or both of the following: (a) Tenderness over the affected nerve branches (b) Trigger points at the emergence of the greater occipital nerve or in the distribution of C2</td>
</tr>
<tr>
<td>D</td>
<td>Pain is eased temporarily by local anesthetic block of the affected nerve(s)</td>
</tr>
<tr>
<td>E</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>
that pass from the ansa hypoglossi (ansa cervicalis) to the C2 ventral ramus (Lance and Anthony 1980). Surgical findings confirm C2 nerve compression by the atlantoaxial joint (Elisevich et al. 1984). With limited published cases, the most appropriate management is unclear. Spinal immobilization (soft collar), atlantoaxial fusion or resection of the C2 spinal nerve may be needed; in uncomplicated cases, spinal manipulation and exercise may help (Gelfand et al. 2017; Elisevich et al. 1984; Borody 2004; Fortin and Biller 1985).

### Burning Mouth Syndrome

**Introduction**

Burning mouth syndrome (BMS) is characterized by a burning mucosal pain with no clinical signs. The term “oral dyesthesia” is also used for this condition and this is covered in greater detail in a separate chapter on the topic titled ▶ Oral Dyesthesia. It is a poorly understood pain condition that is most likely neuropathic with a central component. Currently, there are BMS diagnostic criteria, but they should be field tested, validated, and adapted (Table 20). BMS consists of burning oral pain or dyesthesia with no major paroxysmal character that is of >3 months duration or of a recurrent pattern. Symptoms are present during most of the day and clinical and/or radiographic examination do not reveal any obvious cause.

### Table 19  Diagnostic criteria for neck tongue syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least two episodes fulfilling criteria B–D</td>
</tr>
<tr>
<td>B</td>
<td>Sharp or stabbing unilateral pain in the upper neck and/or occipital region with concurrent abnormal sensation and/or posture of the ipsilateral tongue. Pain may or may not be accompanied by dysesthesia. Motor changes occur but are less common</td>
</tr>
<tr>
<td>C</td>
<td>Precipitated by sudden turning of the neck. Occipital neuralgia must be distinguished from occipital referral of pain arising from the atlantoaxial or upper zygapophyseal joints or from tender trigger points in neck muscles or their insertions</td>
</tr>
<tr>
<td>D</td>
<td>Lasting from seconds to several minutes</td>
</tr>
<tr>
<td>E</td>
<td>Not better accounted for by another ICHD-3 diagnosis</td>
</tr>
</tbody>
</table>

Two subclasses of BMS have been identified: “primary BMS” or essential/idiopathic BMS for which a neuropathological cause (local or systemic) is likely (Rhodus et al. 2003a) and “secondary BMS” resulting from local or systemic pathological conditions (Scala et al. 2003). The secondary causes of BMS also need reevaluation under rigorous scientific conditions.

**Epidemiology**

The exact prevalence of BMS is unclear due to vague diagnostic criteria. The reported BMS prevalence rates in general population vary from 0.7% to 15% with postmenopausal women being most frequently affected (Zakrzewska et al. 2005b). In the United States, 0.7% of all adults aged 18 and older report BMS-like symptoms; 0.8% in women and 0.6% in men. In middle aged and elderly women, BMS was reported by 4.6%.

The estimates of BMS prevalence in Europe are higher (13–15%) (Femiano 2002a); however, in one study, approximately half of the patients had an oral disease that could cause BMS like symptoms. No BMS was reported in male patients under the age of 40 nor in female patients under the age of 30 (Bergdahl and Bergdahl 1999).

**Clinical Features**

The burning sensation is usually localized to the anterior two-thirds of the tongue (Netto et al.
2011; Amos et al. 2011). However, multiple sites are usually affected including the hard palate, lips, and gingivae. The quality of pain is usually described as burning or hot. Pain intensity is mild to severe with the VAS scores ranging from 3 to 7. It usually increases from the morning to the evening and may reach 8–10 (Amos et al. 2011; Danhauer et al. 2002; Gremeau-Richard et al. 2004; Petruzzi et al. 2004; Forssell et al. 2012). BMS pain is typically of spontaneous onset and lasts from months to several years (Rhodus et al. 2003a; Zakrzewska et al. 2005b; Rhodus et al. 2003b). Pain follows a chronic unremitting pattern, but some patients report intermittent pain (Forssell et al. 2012). Although remission is rare, 3% of BMS patients were reported to experience this spontaneously about 5 years after onset (Sardella et al. 2006; Rodriguez-de Rivera-Campillo and Lopez-Lopez 2013).

In more than two-thirds of BMS cases, the burning sensation is accompanied by altered taste (dysguesia), often described as metallic. Gastrointestinal problems may also be present and these should be treated early (Netto et al. 2011). Additionally, BMS in postmenopausal women has been associated with anxiety, depression, and personality disorders (Scala et al. 2003); however, it remains to be determined if pain initiated the psychological disorder or vice versa (Al Quran 2004; Maina et al. 2005). Psychosocial profiles of BMS patients revealed that approximately 21% of patients exhibited significant psychologic distress requiring evaluation (Carlson et al. 2000). However, no evidence of significant clinical depression, anxiety, and somatization have been identified in BMS patients as a group, and they report fewer disruptions in normal activities due to associated pain compared to other chronic pain patients (Carlson et al. 2000). These reports suggests that while a small proportion of BMS patients may present with significant distress, the vast majority cope better than many chronic pain patients (Carlson et al. 2000). This despite the significant impact of BMS on quality of life (Ni Riordain et al. 2010). When compared to healthy controls, BMS patients showed significantly higher adverse early life experiences, depression, anxiety, cancer phobia, gastrointestinal problems, and chronic fatigue (Lamey et al. 2005). Additionally, BMS patients report sleep disturbances possibly related to levels of depression and anxiety (Adamo et al. 2013; Chainani-Wu et al. 2011).

Secondary BMS (SBMS) is defined as oral and perioral burning sensation that accompanies local or systemic factors or diseases (Scala et al. 2003).

### Table 20: Diagnostic criteria for burning mouth syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Oral pain fulfilling criteria B and C Usually bilateral and of fluctuating intensity</td>
</tr>
<tr>
<td>B</td>
<td>Recurring daily for &gt;2 h per day for &gt;3 months There is a high menopausal female prevalence, and some studies show comorbid psychosocial and psychiatric disorders</td>
</tr>
<tr>
<td>C</td>
<td>Pain has both of the following characteristics: 1. Burning quality 2. Felt superficially in the oral mucosa The most common site is the tip of the tongue. Subjective dryness of the mouth, dysesthesia, and altered taste may be present. Concomitant complaints may include dry mouth, paresthesia, and taste disturbance</td>
</tr>
<tr>
<td>D</td>
<td>Oral mucosa is of normal appearance and clinical examination including sensory testing is normal Erosive or ulcerative mucosal diseases commonly induce burning sensory abnormalities may be detected using advanced techniques but are not usually clinically apparent</td>
</tr>
<tr>
<td>E</td>
<td>Not better accounted for by another ICHD-3 diagnosis Subjective dryness of the mouth, dysesthesia and altered taste may be present. Whether secondary burning mouth syndrome attributed to a local (candidosis, lichen planus, hyposalivation) or systemic disorder (medication induced, anemia, deficiencies of vitamin B12 or folic acid, Sjogren's syndrome, diabetes) should be considered as an entity is a matter for debate. Current evidence does not justify inclusion even in the appendix</td>
</tr>
</tbody>
</table>
Local factors and diseases historically associated with SBMS include oral candidosis, galvanism, lichen planus, allergies, hyposalivation, and xerostomia (Vitkov et al. 2003). Systemic disorders associated with SBMS include hormonal changes, nutritional abnormalities (e.g., vitamin B12, folic acid, or iron deficiencies), diabetes mellitus, drugs (directly or indirectly), autoimmune diseases, and emotional stress (Scala et al. 2003). These “causal” associations have not been rigorously tested. Indeed, it remains unclear if treatment aimed at the primary disease will resolve the burning sensation in all SBMS patients (Danhauer et al. 2002).

Pathophysiology

BMS is considered a neuropathic pain state; however, hormonal (Femiano 2002b) and psychosocial factors may contribute to its pathophysiology. Various regional and local phenomena such as reduced parotid gland function (Pinto et al. 2003), altered salivary composition (Ko et al. 2012), and epithelial changes in the tongue (Silvestre-Rangil et al. 2011) have been associated with idiopathic BMS. Greater vasoreactivity observed in BMS patients suggests the involvement of the autonomic nervous system (Heckmann et al. 2012).

BMS may be a common clinical phenotype for variable dysfunctions affecting the peripheral and central nervous systems. A decreased tolerance to heat pain and increased detection thresholds to warming and heat pain have been found in BMS patients, suggesting that BMS is a neuropathic pain condition (Ko et al. 2012; Femiano et al. 2004a; Femiano and Scully 2002; Carbone et al. 2009; Cavalcanti and da Silveira 2009; Lopez-Jornet et al. 2009).

Based on the currently available evidence, two mechanisms have been suggested to contribute to the pathophysiology of BMS: a sensory neuropathy that is probably peripheral and central or a neuropathic imbalance between the gustatory and sensory systems.

BMS and Taste

The chorda tympani nerve (a branch of the facial nerve) supplies taste sensation to the anterior two-thirds of the tongue whereas mechanical and thermal sensations are supplied by the lingual nerve (a branch of the mandibular division of the trigeminal nerve). Thus, a “sensory balance” in the tongue is thought to be maintained by the inhibitory influences of the two systems. Damage to the chorda tympani could disinhibit the somatosensory system, intensifying trigeminal nerve sensations, including pain, which is perceived by the patient as a constant burning sensation (Nasri-Heir et al. 2011; Eliav et al. 2007; Bartoshuk et al. 2005). Electrical stimulation to the tongue can induce sensation of tingling or taste. BMS patients have been shown to have significantly higher electric taste/tingling ratio and taste detection thresholds compared to healthy controls, indicating a dysfunction of Aδ fibers of the chorda tympani (Nasri-Heir et al. 2011; Eliav et al. 2007). Additionally, increased electric taste/tingling detection threshold ratio was observed in patients with prolonged BMS indicating progressive neural damage.

BMS patients are likely to be “supertasters” (able to taste the bitter compound phenylthiocarbamide). Supertasters have a larger number of fungiform papillae mostly (75%) innervated by the trigeminal nerve and partly (25%) by the chorda tympani nerve (Femiano 2004). Supertasting in BMS patients may be caused by damage to the chorda tympani resulting in loss of central inhibition and subsequent hyperactivity of the sensory component of the trigeminal nerve (Femiano 2004). Supertasting in BMS patients may be caused by damage to the chorda tympani resulting in loss of central inhibition and subsequent hyperactivity of the sensory component of the trigeminal nerve (Femiano 2004; Grushka et al. 2003; Eliav et al. 2007). BMS patients are characterized by higher sweet taste detection threshold and lower intensity ratings to salt and sweet stimuli indicating altered taste sensation and damage to the taste pathway (Formaker and Frank 2000).
BMS as a Painful Neuropathy

Significantly, higher sensory thresholds in tongues of BMS patients compared to controls suggest that BMS is a neuropathy. BMS patients are characterized by heterogeneous sensory profiles suggesting different mechanisms in different patient populations and results from QST suggest a loss of small fibers in some BMS patients (Forssell et al. 2002; Ito et al. 2002). BMS patients have a significantly lower density of epithelial nerve fibers in the anterior two-thirds of the tongue with some correlation to disease duration (Lauria et al. 2005; Yilmaz et al. 2007; Beneng et al. 2010). Epithelial and subpapillary nerve fibers showed diffuse morphological changes reflecting axonal degeneration suggesting a trigeminal small-fiber sensory neuropathy (Lauria et al. 2005).

Sensory assessment in BMS patients reveals reduced thermal pain tolerance, elevated pain detection thresholds, significantly elevated thermal sensory thresholds, decreased pain scores for tonic heat pain, and an increased level of somatization (Granot and Nagler 2005). Additionally, following mechanical stimulation, BMS patients perceived significantly more pain that lasts longer and is more intricately described compared to controls (Ito et al. 2002). Several subgroups have been described in BMS patients based on QST data and altered blink reflex recordings (Forssell et al. 2002; Jaaskelainen et al. 1997). Taken together, these data suggest the presence of sensory nerve dysfunction.

BMS patients are characterized by central dysfunction of pain modulatory system and are characterized by presynaptic dysfunction of the nigrostriatal dopaminergic system (involved in central pain modulation) (Hagelberg et al. 2003a). The nigrostriatal dopaminergic system is protected by physiological levels of estrogens and their decline with menopause may partly explain the age and gender predilection BMS (Gajjar et al. 2003). Nociceptive responses may be modulated by estrogen receptors found in trigeminal neurons that may further explain the preponderance of BMS in females (Puri et al. 2005).

Brain hypoactivity has been suggested to be an important feature in the pathophysiology of BMS. Greater signal changes in the right anterior cingulate cortex and bilateral precuneus have been reported in BMS patients compared to controls (Albuquerque et al. 2006) and less volumetric activation throughout the entire brain was observed in BMS patients compared to controls. Overall, brain activation patterns observed in BMS patients resemble those of patients with other neuropathic pain conditions and appear to process thermal painful stimulation to the trigeminal nerve in a manner that is qualitatively and quantitatively different than in pain-free individuals.

In summary, the symptoms BMS may reflect variable underlying pathophysiology. It has been suggested that BMS can be divided into three subgroups (Jaaskelainen 2012). The first (50–65%) is characterized by peripheral small diameter fiber neuropathy of intraoral mucosa. The second (20–25%) consists of patients with subclinical lingual, mandibular, or trigeminal system pathology that can be dissected with careful neurophysiologic examination but is clinically indistinguishable from the other two subgroups. The third (20–40%) fits the concept of central pain related to hypofunction of dopaminergic neurons in the basal ganglia.

Treatment

BMS is characterized by resistance to a wide range of treatments and is one of the most challenging conditions in the field of orofacial pain. Very few evidence-based treatments are available for BMS. Due to the elusive pathophysiology of BMS, patients may seek help from numerous clinicians and undergo many, largely unsuccessful therapies. There is no one accepted treatment for BMS; however, this condition should be treated as neuropathic pain and the outcomes should be assessed across a wide range of measures (Dworkin et al. 2005).

In elderly and medically compromised patients, topical medications may be effective in relieving pain. Topical clonazepam (“sucking and spitting” 1 mg three times daily for 2 weeks) was shown to effectively reduce pain intensity in a
subgroup of BMS patients, with some carry over effects observed at 6 months (Gremeau-Richard et al. 2004). Additionally, stimulation of salivary flow may be effective in some patients (de Souza et al. 2012). Mouthwashes containing benzydamine or lactoperoxidase are ineffective in BMS patients (Femiano 2002b), and topical anesthetics provide unpredictable effects.

Benzodiazepines or low dose of tricyclic antidepressants (TCAs) were shown to provide pain relief (Pinto et al. 2003; Ko et al. 2012; Silvestre-Rangil et al. 2011). There is some evidence supporting systemic clonazepam (Ko et al. 2012; Heckmann et al. 2012). Additionally, combination of systemic and topical (“sucking and swallowing” 0.5 mg × 3/day) clonazepam provided promising results (Amos et al. 2011). The effectiveness of a 2 month course of 600 mg daily of alpha lipoic acid in treatment of BMS provided contradictory results with some studies showing its effectiveness (Femiano et al. 2004a; Femiano and Scully 2002) and others not (Carbone et al. 2009; Cavalcanti and da Silveira 2009; Lopez-Jornet et al. 2009).

Systemic capsaicin (0.25% capsule 3/day for 30 days) was shown to be effective in reducing BMS pain intensity; however, significant gastric pain was observed in over 30% of cases (Petruzzi et al. 2004). Amisulpride (atypical antipsychotic drug), paroxetine, and sertraline (the selective serotonin reuptake inhibitors (SSRIs)) were shown to be equally effective treatments for BMS (Maina et al. 2002). However, amisulpride was shown to have a shorter response time and was associated with better compliance within the first week of treatment compared to SSRIs (Maina et al. 2002).

Cognitive behavioral therapy (CBT) was shown to be beneficial in BMS patients with underlying psychological distress that are therapy resistant. CBT has been successfully supplemented with alpha lipoic acid (Femiano et al. 2004b).

Depending on the treatment modalities used, 42–60% of BMS patients may experience some pain relief (Rodriguez-de Rivera-Campllllo and Lopez-Lopez 2013). Evidence-based management of BMS is based on topical clonazepam, systemic SSRI, alpha lipoic acid, and CBT (Moraes et al. 2012; Buchanan and Zakrzewska 2016). Widespread clinical practice for BMS and for neuropathic pains would support a trial for selected cases using topical therapies such as lidocaine, doxepin, or capsaicin. Similarly, systemic therapies would include TCAs, selective noradrenaline and serotonin reuptake inhibitors, anti-convulsants, opioids, and benzodiazepines.

**Persistent Idiopathic Facial Pain**

**Introduction**

Persistent idiopathic facial pain (PIFP) is defined as “persistent facial and/or oral pain, with varying presentations but recurring daily for more than 2 hours per day over more than 3 months, in the absence of clinical neurological deficit” (Headache Classification Subcommittee of the International Headache Society (IHS) 2018). This rather loose definition allows for the classification of a large number of chronic facial pain disorders. PIFP has historically been termed atypical facial pain (AFP) and atypical odontalgia (AO). The diagnosis of AFP was used when no other diagnosis was feasible and has therefore tended to include a heterogeneous group of patients.

With increasing knowledge and diagnostic skills, many PIFP cases would now be better classified as chronic myofascial pain, traumatic neuropathy, pre- or atypical trigeminal neuralgia, facial migraine, or neurovascular orofacial pain.

The prevalent theory is that PIFP is a disproportionate reaction to a mild injury, but the exact pathophysiology is still unclear.

**Epidemiology**

Based on existing studies, the estimated lifetime prevalence of PIFP is around 0.03% (Mueller et al. 2011), and the incidence rate is 4.4 per 100,000 person years (Koopman et al. 2009). Most patients that present for care are female with a mean onset age in the mid-40s (Maarbjerg et al. 2017). Often PIFP may coexist with other...
chronic orofacial pain syndromes such as chronic myalgia (Evans and Agostoni 2006).

**Clinical Features**

Pain onset in PIFP is often associated with minor surgical or other invasive dental or otorhinolaryngologic procedures (Nobrega et al. 2007); these may be reported as the initiating event or as an attempt to manage the pain (Israel et al. 2003; Mc and Horton 1947). However, many patients cannot reliably recall the sequence of events. Is their pain the result of treatment or was pain present before treatment was initiated and subsequently worsened?

Although there should be no clinically evident neurosensory deficits in PIFP (Headache Classification Subcommittee of the International Headache Society (IHS) 2018), hypoesthesia has been reported in studies using quantitative sensory testing (QST) (Siqueira et al. 2013; Baad-Hansen et al. 2013c; Forssell et al. 2007) (Table 21). Patients with a neuropathic type pain following surgery or other trauma with neurosensory changes should be diagnosed as painful traumatic trigeminal neuropathy (PTTN), as defined by the IHS (Headache Classification Subcommittee of the International Headache Society (IHS) 2018; Benoliel et al. 2012). These changes in inclusion criteria, both in classification systems and in published cases and case series, must be taken into account when interpreting the data on the clinical profile and indeed management protocols. (Siqueira et al. 2013; Maarbjerg et al. 2017; Baad-Hansen et al. 2013c; Forssell et al. 2007; Pfaffenrath et al. 1993).

Pain in PIFP is usually deep but can be superficial as well (Headache Classification Subcommittee of the International Headache Society (IHS) 2018). It is poorly localized, radiating, and mostly unilateral although up to 40% of cases may describe bilateral pain (Maarbjerg et al. 2017). PIFP is commonly described as aching, burning, throbbing, and often stabbing (Headache Classification Subcommittee of the International Headache Society (IHS) 2018; Siqueira et al. 2013; Maarbjerg et al. 2017; Baad-Hansen et al. 2013c; Forssell et al. 2007; Pfaffenrath et al. 1993; Lang et al. 2005). Severity, usually mild to severe (rated 7 on an 11-point VAS), may be aggravated by emotional stress (Headache Classification Subcommittee of the International Headache Society (IHS) 2018; Maarbjerg et al. 2017). PIFP patients with severe pain often demonstrate a disparity between their apparent calm emotional and physical state and the reported pain severity. Most PIFP patients report persistent, long lasting (years) daily pain (Maarbjerg et al. 2017) that tends to spread, in a nondermatomal pattern, with time (Headache Classification Subcommittee of the International Headache Society (IHS) 2018). Typically, pain characteristics, location, and associated features change over time. Rarely, some PIFP patients report pain free or remission periods (Maarbjerg et al. 2017). Often PIFP may coexist with other chronic orofacial pain or headache syndromes (Maarbjerg et al. 2017).

Psychiatric and psychosocial disability have often been associated with PIFP (Taiminen et al. 2011), although one study on 14 PIFP patients found no significant comorbid psychiatric disorders compared to controls (Lang et al. 2005). Increased scores for anxiety and depression are common especially in PIFP patients reporting higher pain intensity (Brailo and Zakrzewska 2015), indicating that a psychiatric screening should be performed (Zakrzewska 2016). Systematic screening revealed that 41.3% of patients suffering from PIFP or BMS had an axis I disorder (major depression was the most frequent) before the onset of orofacial pain. Therefore, the authors conclude “that psychiatric morbidity, and comorbidity to other chronic pain conditions, in chronic idiopathic orofacial pain can be best understood in terms of shared vulnerability to both chronic pain and specific psychiatric disorders” (Taiminen et al. 2011). We conclude that an interdisciplinary approach is needed for the diagnosis and management of PIFP (Hals and Stubhaug 2011).

**Pathophysiology**

The large number of PIFP patients presenting with a history of mild trauma and subclinical sensory changes has led to the suggestion that PIFP and
PTTN may represent extremes of a spectrum of clinical presentations. As such, PIFP would therefore be considered a neuropathic pain syndrome. In support, studies of PIFP patients reveal increased neuronal excitability at the brainstem level (Forssell et al. 2007; Lang et al. 2005; Jaaskelainen et al. 1999), disturbed inhibitory function of the prefrontal cortex (Derbyshire et al. 1994), and alterations in the dopamine systems associated with either/both pain transmission and its modulation (Hagelberg et al. 2003b). Additionally sensory changes consistent with a neuropathy or neuropathic pain have been shown employing QST in patients with PIFP (Siqueira et al. 2013; Baad-Hansen et al. 2013c; Forssell et al. 2007). The data seem to indicate that PIFP is indeed a neuropathic pain syndrome. One study (Forssell et al. 2007) highlighted the need for detailed neurophysiologic and quantitative sensory examinations as a consequence of their study comparing neurophysiological findings in PIFP and trigeminal neuropathic pain. The authors were the initial proponents that PIFP might be a heterogeneous entity representing one extreme of a continuum that ranges from definitive neuropathic pain syndromes to idiopathic pains with an unclear “neuropathic” involvement (Forssell et al. 2007).

However, unchanged somatotopy of the somatosensory cortex (by magnetoencephalography) and inconsistent changes in the blink reflex in a group of PIFP patients indicate no significant alterations in the trigeminal somatosensory pathways, suggesting that PIFP may not always be a neuropathic pain syndrome (Lang et al. 2005). In these same patients, the QST profile other than thresholds for warm and heat pain was not significantly different to that in controls. These findings, if duplicated, suggest the existence of subtypes of PIFP, neuropathic, and “other.”

### Treatment

The lack of a clear pathophysiological basis precludes the establishment of a treatment protocol.
The approach to the management of PIFP patients should consider patients’ beliefs on pain and the consequences of the pain disorder on their personal lives (Galli et al. 2010). Considering the psychiatric comorbidity, chronic course of disease in many patients, and the lack of drug treatment RCTs, a multidisciplinary approach encompassing the comorbidities is suggested comparable to treatment concepts in other chronic headaches (Gaul et al. 2016). Considering the chronicity and resulting distress, behavioral interventions are indicated. Accumulating evidence suggesting that PIFP may be a type of painful neuropathy underlies the preferential use of medications known to have an effect in painful neuropathies, i.e., antidepressants and antiepileptic drugs. Patient education is needed to clarify the diagnosis and certainly the patient should be discouraged from any further invasive interventions aimed at pain relief in the absence of clear associated pathology.

Therapeutic trials of PIFP (and AFP) have been reported as efficient but the trials are not all randomized or controlled. Case series using tricyclic antidepressants (Guler et al. 2005), an open study on duloxetine (Nagashima et al. 2012), a randomized controlled trial on venlafaxine (Forssell et al. 2004), and open studies on anticonvulsants (Volcy et al. 2006; Delvaux and Schoenen 2001) and low-level laser therapy (Yang and Huang 2011) have all shown beneficial effects but other than one study, the level of evidence is clearly low. Similarly, based on the premise that PIFP is neuropathic, high-frequency repetitive transcranial magnetic stimulation (rTMS) on the right secondary somatosensory (S2) cortex in patients with neuropathic orofacial pain induced significant pain relief compared to stimulation of the somatosensory (S1/M1) cortex and sham stimulation (Lindholm et al. 2015). The right S2 cortex is therefore a promising new target for the treatment of neuropathic orofacial pain and possibly PIFP using high-frequency rTMS.

Some authors claim success with treatments aimed at the regional musculoskeletal system, but no convincing evidence is available. Occipital nerve blocks have not been effective in PIFP patients (Jurgens et al. 2012). Often the clinician is at a loss when all accepted treatments have failed.

There are no contraindications to non-interventional novel therapies (e.g., based on virtual reality) (Won and Collins 2012) or complementary and alternative medicine (Nguyen and Wang 2013), and these may be beneficial. Hypnosis might be a promising approach for therapy (Abrahamsen et al. 2008). However, the evidence for psychosocial interventions is limited due to the lack of controlled studies (Aggarwal et al. 2011). When all treatments fail, some have suggested pulsed radiofrequency treatment of the sphenopalatine ganglion (Bayer et al. 2005), but this is based on an open trial in a small number of patients and there is no high level evidence for this or any other neurosurgical type of intervention (Rahimpour and Lad 2016; Maniam et al. 2016). We do not recommend invasive procedures as these always carry the risk for inducing a traumatic neuropathy and therefore may end up increasing pain.

Available evidence for any of the treatments is limited and randomized clinical trials are missing. It is therefore recommend a conservative, multidisciplinary approach based on experiences with comparable chronic headache disorders including medications, relaxation training, psychological interventions, and physiotherapy (Gaul et al. 2016).

**Atypical Odontalgia**

According to the International Association for the Study of Pain, atypical odontalgia (AO) is defined as a severe throbbing pain in the tooth without major pathology and is considered a subentity of PIFP. AO has been referred to as phantom toothache indicating a neuropathic etiology (Baad-Hansen et al. 2006; Melis et al. 2003; Vickers and Cousins 2000). It is also possible that various studies included some heterogeneous groups of patients with localized neuropathic or neurovascular syndromes. Repeated dental interventions aimed at pain relief in neurovascular or undiagnosed orofacial pain cases may lead to nerve injury and PTTN. This theory is supported
by findings that chronic orofacial pain patients undergo extensive but often misguided surgical interventions (Israel et al. 2003; Merrill 2004) that are known to exacerbate pain in 55% of patients. About 5% of AO patients that are misdiagnosed, suffer the consequences of serious sequelae and delay of necessary treatment (Israel et al. 2003).

Due to the ambiguity in the terminology, it has been suggested that AO should not be used (Benoliel 2013), similar to the way that AFP is no longer advocated. Patients with neuropathic pain following surgery or other trauma should be diagnosed as PTTN. However, in clinical reality, a number of patients with intraoral pain do not neatly fit any diagnostic category. These patients usually have persistent pain in the dentoalveolar region and have been grouped into a diagnosis of “primary persistent dentoalveolar pain” (PDAP) (Durham et al. 2013; Nixdorf et al. 2012). Since this seems to be an intraoral representation of PIFP, the term “persistent idiopathic dentoalveolar pain” seems very suitable (Fig. 14).

Central Causes of Facial Pain

Damage to the central nervous system, whether direct (stroke or spinal cord trauma) or indirect, may result in central pain. The indirect damage is a damage secondary to centrally occurring diseases such as epilepsy, Parkinson’s disease, and multiple sclerosis (MS). Pain resulting from lesions to the nervous system is associated with decreased sensation and is termed anesthesia dolorosa, also known as deafferentation pain. Painful peripheral traumatic neuropathies involve central mechanisms but are not strictly speaking central pain.

Central Neuropathic Pain

Central Poststroke Pain

Central poststroke pain (CPSP) is characterized by constant or paroxysmal pain accompanied by sensory abnormalities such as decreased perception and frequently allodynia (Table 22). Severity of CPSP may be underestimated as many post-stroke patients are unable to self-report their pain (Smith et al. 2013b).

Epidemiology

CPSP occurs in 2.7–11% of all stroke patients and 25% of brainstem infarct patients within 6–12 months (Nicholson 2004; Hansen et al. 2012; O’Donnell et al. 2013). Women and younger patients seem to be at higher risk of CPSP following stroke (Hansen et al. 2012). CPSP is commonly located in the upper extremity in (37.9%), the lower extremity (20.7%), and in both upper and lower extremities (10.3%). Pain is rarely in the head (16.0%) and in both head and lower extremity (3.4%) in CPSP. The entire side of the body is affected in around 10% of cases (Hansen et al. 2012; Klit et al. 2007).

Clinical Features

Pain associated with brainstem lesions, particularly lateral medullary infarcts is localized to the face and is usually unilateral (Fitzek et al. 2001). Facial pain is mostly reported periorbitally. The quality of CPSP is most frequently described as burning or hot, aching, pricking, stinging, lacerating, and pressure like (Klit et al. 2007). Patients with thalamic stroke frequently describe the quality of pain as lacerating. CPSP is usually of moderate to severe intensity and is exacerbated by external stimuli, most commonly movement, light touch, and cold (Fitzek et al. 2001).

According to IHS criteria, symptoms must occur within 6 months of a stroke to be classified as CPSP (Table 22). The onset of pain is usually within 1 month (range 3–6 months), although it may take up to 6 years and a gradual onset of CPSP has been reported (Klit et al. 2007). Although usually constant, around one quarter of CPSP patients reported persistent pain with superimposed attacks and 42% reported paroxysmal pain lasting seconds to minutes (Fitzek et al. 2001).

Motor impairment and a variety of sensory symptoms may occur, depending on the extent and location of the lesion. Symptoms include unilateral pain and/or dysesthesia associated with loss of sensation to pin-prick, temperature, and/or
Constant or evoked dysesthesia is the most common abnormal sensation (Nicholson 2004). Thermal sensory impairment has been reported in the majority of CPSP cases and sensory dysfunction that correlates with the presence of pain occurs in over half of cases (Fitzek et al. 2001). About 60% of CPSP patients present with muscle spasticity.

**Pathophysiology**

The exact pathophysiology of CPSP is unclear. It is thought to result from ectopic activity in damaged circuits and an imbalance in facilitatory and inhibitory pathways induced by the stroke. Because, CPSP is often associated with lesions of the ventrocaudal thalamic nuclei and particularly within the ventroposterior inferior nucleus, it was initially thought to be induced by a damage to pain pathways in the thalamus and was alternatively called thalamic pain. Spinothalamic pathways and cortical processing have also been implicated in CPSP (Frese et al. 2006). However, many patients with poststroke damage to spinothalamic pathways do not develop pain, suggesting that other factors must contribute to the pathophysiology of CPSP.

**Treatment**

The antidepressant, amitriptyline, as well as the anticonvulsant, lamotrigine, are effective in the treatment of CPSP and should be considered first-line therapy (Saarto and Wiffen 2005; Frese et al. 2006; Vestergaard et al. 2001). Gabapentin is a good second choice drug (Frese et al. 2006). Additionally, intravenous lidocaine or propofol may provide a short-term pain relief (Frese et al. 2006).

**Table 22** Diagnostic criteria for central poststroke pain

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>A Facial and/or head pain fulfilling criterion C</td>
<td>Diagnosis is often made retrospectively in a patient with a history of stroke and facial pain that started afterwards</td>
</tr>
<tr>
<td>B Ischemic or hemorrhagic stroke has occurred</td>
<td>CPSP is attributed to a lesion of the ascending projections of the trigeminal nuclei. Cervical spinothalamic pathways and cortical processing may also play a significant role. Therefore, symptoms may also involve the trunk and limbs of the affected side.</td>
</tr>
<tr>
<td>C Evidence of causation demonstrated by both of the following: 1. Pain has developed within 6 months after the stroke 2. Imaging has demonstrated a vascular lesion in an appropriate site</td>
<td>Cranio-cervical pain following a thalamic lesion is part of a hemisyndrome. With lateral medullary lesions, hemifacial pain may occur in isolation but is more often accompanied by crossed hemidysesthesia.</td>
</tr>
<tr>
<td>D Not better accounted for by another ICHD-3 diagnosis</td>
<td>Pain and sensory disturbance are resistant to therapy. Imaging is usually MRI.</td>
</tr>
</tbody>
</table>

A patient with a history of extensive dental treatments including multiple extractions and root canal treatments who was ultimately diagnosed with persistent idiopathic dentoalveolar pain. (Image courtesy of Clinical Associate Professor Ramesh Balasubramaniam, Perth Oral Medicine & Dental Sleep Centre, Perth WA, Australia)
Tricyclic antidepressants may be contraindicated in some CPSP patients and a medical consult should be obtained. Alternatively, anticonvulsants may be employed (Finnerup et al. 2005).

Conclusions and Future Directions

Neuropathic pains all arise as a direct consequence of a lesion or disease affecting the somatosensory system, and indeed they often share clinical features. Nevertheless, the natural history, management, and prognosis are extremely variable. There is a lack of efficient drugs, and those currently employed may have debilitating side effects. At best we are offering mediocre management for most of our patients with neuropathic pain. More translational research is required to change this. There is a need for new efficient drugs with minimal side effects. For this to occur, integration of basic preclinical experimental research, genetic and clinical studies is necessary. One must understand why, after injury or disease, certain patients develop chronic pain and others do not. Functional imaging studies in humans have gone far in elucidating CNS areas involved in registering, interpreting, modulating, and reacting to incoming noxious stimuli. Further advances in this area are expected, including the mapping of the connections between relevant CNS areas (the “connectome”). Ultimately, there is a need to integrate all this knowledge and leverage this to design better targeted drugs and timely interventions.

Cross-References

- Biopsychosocial Aspects of Orofacial Pain
- Clinical Evaluation of Orofacial Pain
- Headache
- Neurophysiology of Orofacial Pain
- Neurosensory Disturbances Including Smell and Taste
- Neurovascular Orofacial Pain
- Oral Dysesthesia

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