Review Article

Idiopathic Facial Pain Syndromes

An Overview and Clinical Implications

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Summary

Background: Idiopathic facial pain syndromes are relatively rare. A uniform classification system for facial pain became available only recently, and many physicians and dentists are still unfamiliar with these conditions. As a result, patients frequently do not receive appropriate treatment.

Methods: This article is based on pertinent publications retrieved by a selective search in PubMed, focusing on current international guidelines and the International Classification of Orofacial Pain (ICOP).

Results: The ICOP subdivides orofacial pain syndromes into six major groups, the first three of which consist of diseases of the teeth, the periodontium, and the temporomandibular joint. The remaining three groups (non-dental facial pain) are discussed in the present review. Attack-like facial pain syndromes most closely resemble the well-known primary headache syndromes, such as migraine, but with pain located below the orbitomeatal line. These syndromes are treated in accordance with the guidelines for the corresponding types of headache. Persistent idiopathic facial pain (PIFP) is a chronic pain disorder with persistent, undulating pain in the face and/or teeth, without any structural correlate. Since this type of pain tends to become chronified after invasive procedures, no dental procedures should be performed to treat it if the teeth are healthy; rather, the treatmentis similar to that of neuropathic pain, e.g., with antidepressant and anticonvulsive drugs. Neuropathic facial pain is also undulating and persistent. It is often described as a burning sensation, and neuralgiform attacks may additionally be present. Trigeminal neuralgia is a distinct condition involving short-lasting, lancinating pain of high intensity with a maximum duration of two minutes. The first line of treatment is with medications; invasive treatment options should be considered only if pharmacotherapy is ineffective or poorly tolerated.

Conclusion: With the aid of this pragmatic classification system, the clinician can distinguish persistent and attack-like primary facial pain syndromes rather easily and treat each syndrome appropriately.

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Facial pain patients seek care from a variety of medical disciplines with diverse diagnostic and therapeutic competencies. Because of their pain history and the location, many facial pain patients consult a dentist initially and also during their further healthcare journey (1, 2). In most patients, the facial pain is of dental origin and expert dentists are either the right healthcare contact or can refer patients with other morphological findings to the appropriate specialist in an adjacent discipline, e.g. to an ear, nose and throat (ETN) specialist in case of chronic sinusitis. As with headache, this type of facial pain is by definition a secondary pain and as such a warning symptom pointing to an underlying pathology. A common feature of these syndromes is that they often require interventional treatment.

However, despite very similar or even identical symptoms, in some patients all diagnostic attempts to reveal a definite physical intra- or extraoral pain correlate remain unsuccessful. This type of pain lacks the warning function and is, by itself, the actual health problem (primary pain). These patients should primarily be treated conservatively. As an example, the *Table* shows demographic and clinical characteristics of 411 facial pain patients (mean age 52 ± 15.3 years, 72% female) of the Headache and Facial Pain Outpatient Clinic of the University Medical Center Hamburg-Eppendorf in Hamburg, Germany.

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TABLE

Characterization of 411 facial pain patients of the Headache and Facial Pain Outpatient Clinic of the University Medical Center Hamburg-Eppendorf*

Diagnoses	
Persistent idiopathic facial pain (PIFP)	32.4%
Trigeminal neuralgia	27.0%
Neuropathic facial pain	20.9%
Other (e.g. facial headaches)	19.7%
Number of physician contacts solely for facial pain in the last 12 months	
> 10	49.6%
1–10	37.5%
0	12.7%
Which doctors were consulted for facial pain?	
Dentist	87.8%
General practitioner	77.9%
Neurologist	76.6%
ENT specialist	59.6%
Pain therapist	35.0%
Previous interventions for pain	
Extractions of teeth	45.3%
Root canal treatment	50.0%
Apicoectomy	32.2%
Other (e.g. splint therapy, replacement of dental prostheses, grinding)	39.0%
Costs paid privately	
Yes	59.7%
No	40.3%
Estimated amount paid privately	
Mean	7 360.90 Euro
Median	3 000 Euro
Minimum–Maximum	100–200 000 Euro

* Selection of multiple items allowed

Even though a correct diagnosis is an essential requirement for successful treatment as well as prevention of unnecessary interventions, identifying these patients can be challenging in clinical practice. Despite the fact that it is possible to establish a diagnosis by asking only a few questions in the patient's history *(Figure)*, dentists are in a difficult position because there are only few experts in the management of non-dental facial pain locally available to them whom they could contact directly.

The introduction of the first internationally recognized facial pain classification system, the International Classification of Orofacial Pain (ICOP), early in 2020 (3) is meant to support a standardized scientific reappraisal of facial pain syndromes and to pave the way to a deeper understanding of these disorders in the future. The classification's structure and contents closely follows the successful international classification of headache disorders (ICHD-3) (4). The ICOP distinguishes between six subgroups of facial pain (*Box 1*).

In the following, we summarize the most common facial pain syndromes of clinical importance in the ICOP groups 4–6.

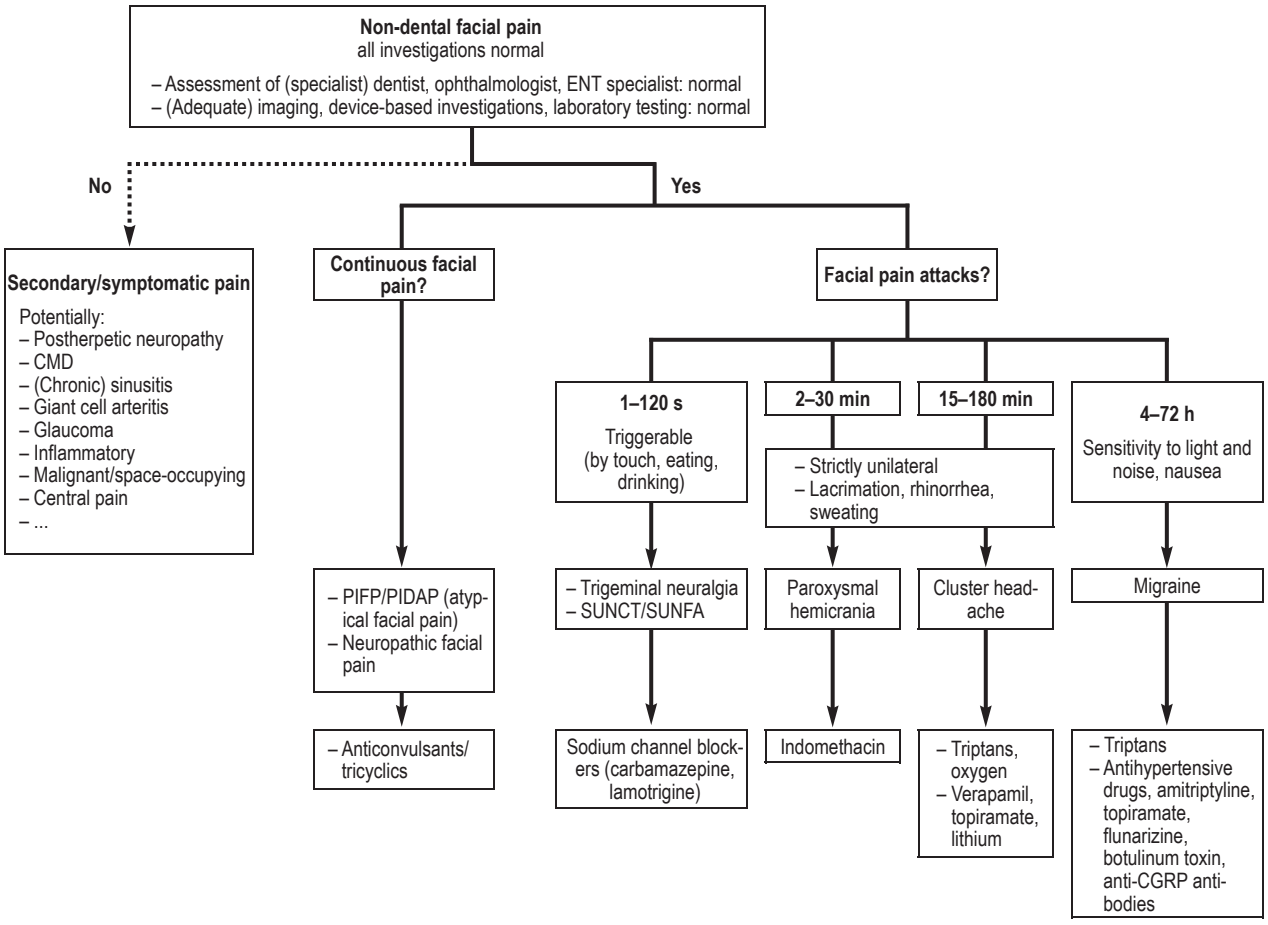
Attack-like facial headache syndromes

Primary headache syndromes, such as cluster headache and migraine (5), are well known. Less known is a group of facial pain syndromes which create diagnostic and therapeutic uncertainty in clinical practice, i.e. the facial variants of primary headaches (6, 7). Characteristically, these rare pain syndromes present solely in an area of the face, such as the cheek or lower jaw, below the orbitomeatal line (8). Otherwise, they closely resemble the corresponding headache types, such as migraine or cluster headache, in their pattern of occurrence, their concomitant symptoms and their management. Thus, facial migraine presents, besides the typical attack duration of 4 to 72 hours, also with associated vegetative symptoms, while, for example, facial cluster attacks last between 15 minutes and 3 hours and occur with typical autonomic symptoms. The new ICOP classification has dedicated a separate chapter to them (3). Important and common representatives of this type of syndromes include facial migraine (2.3% of all migraine patients) and facial cluster headache (14.8% of all cluster headache patients) (6). In principle, however, all primary headache syndromes, including rare trigeminal autonomic cephalgias and primary stabbing headache, can also or even solely present as facial pain (9, 10). In our own patient population, the proportion of patients with pain radiating to the face is about 10% *(Table)*.

Affected patients characteristically report attacks of pain in the teeth, the upper jaw or the lower jaw. The key criterion is that the facial pain occurs in attacks and corresponds in its duration to, for example, that of migraine (4–72 hours) or cluster headache (30–180 minutes). Most patients present with the same concomitant symptoms as patients with the corresponding headache; however, patients with facial migraine virtually never experience an aura and associated trigeminal autonomic symptoms are significantly less intense in patients with facial cluster attacks (6).

Whether facial pain syndromes presenting solely with pain attacks are a headache disorder "shifted" to the second and third branches of the trigeminal nerve or actually distinct syndromes remains unclear (11). What is certain is that some differences between the head variant and the face variant of the pain disorder apparently exist and that a facial pain location is rare, but possible. As a rule of thumb for clinicians, the management of these syndromes should follow the management of the corresponding headache and, with this approach, the treatment is usually effective (6) (*Figure, Box 2*).

FIGURE



Flowchart for diagnostic history in patients with primary/idiopathic facial pain

CMD, craniomandibular dysfunction; CGRP, calcitonin gene-related peptide; ENT specialist: ear, nose and throat specialist; PIFP: persistent idiopathic facial pain; PIDAP: persistent idiopathic dentoalveolar pain; SUNCT: short-lasting unilateral pain attacks with conjunctival injection and tearing; SUNFA: short-lasting unilateral pain attacks with autonomic symptoms

Persistent idiopathic facial pain

Unlike the facial pain attacks described above, persistent idiopathic facial pain (PIFP) is a chronic pain disorder. The underlying mechanisms causing PIFP are poorly understood (12). The disorder is characterized by continuous pain of the face and/or teeth, sometimes varying in intensity throughout the day, with no objectively identifiable neurological deficits. PIFP was formerly known as *atypical facial pain*. The term "atypical" was first used in 1924 to distinguish the condition from trigeminal neuralgia with its "typical" lancinating pain attacks (13). Even though only limited epidemiological data are available, it appears likely that PIFP is a rare disease. According to a Dutch study, the incidence of PIFP is 4.4 (95% confidence interval: [3.2; 5.9])/100 000 person-years (14). A population-based study from Essen, Germany, found a lifetime prevalence of 0.03% (15). Overall, women are significantly more frequently affected than men and account for about 75% to 90% of cases (14, 16). Most cases are between 30 and 60 years of age at the time of first diagnosis (16).

Clinical presentation of persistent idiopathic facial pain

Most patients with PIFP experience pain throughout the day. Only few patients report that their pain ceases for longer periods of time. At night, sleep is usually undisturbed by the pain and some patients report that they experience a brief pain-free period upon waking in the morning before the pain recurs (typically ≤ 30 minutes). While initially only one side of the face is affected, patients may suffer from bilateral pain later in the course of the disease, with the maximum pain intensity being experienced mostly in the cheeks and the upper jaw. The pain may also radiate into the lower jaw, occiput, ear, shoulder or arm, but this is rather unusual (16). The pain fluctuates during the day with usually

BOX 1

International Classification of Orofacial Pain (first edition)

The International Classification of Orofacial Pain (ICOP) categorizes the diagnoses into six groups (3). The first three main groups represent disorders of the masticatory system in its broadest sense and are treated by dentists. The fourth to sixth groups comprise orofacial pain syndromes where the pain is not explained by a morphological correlate of the teeth, dentoalveolar structures or temporomandibular joint. These patients suffer from non-dental orofacial pain and should be treated with conservative pain therapy.

1. **Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures**
   - 1.1 Dental pain
   - 1.2 Oral mucosal, salivary gland and jaw bone pains
2. **Myofascial orofacial pain**
   - 2.1 Primary myofascial orofacial pain
   - 2.2 Secondary myofascial orofacial pain
3. **Temporomandibular joint (TMJ) pain**
   - 3.1 Primary temporomandibular joint pain
   - 3.2 Secondary temporomandibular joint pain
4. **Orofacial pain attributed to lesion or disease of the cranial nerves**
   - 4.1 Pain attributed to lesion or disease of the trigeminal nerve
   - 4.2 Pain attributed to lesion or disease of the glossopharyngeal nerve
5. **Orofacial pains resembling presentations of primary headaches**
   - 5.1 Orofacial migraine
   - 5.2 Tension-type orofacial pain
   - 5.3 Trigeminal autonomic orofacial pain
   - 5.4 Neurovascular orofacial pain
6. **Idiopathic orofacial pain**
   - 6.1 Burning mouth syndrome (BMS)
   - 6.2 Persistent idiopathic facial pain
   - 6.3 Persistent idiopathic dentoalveolar pain

medium and, less frequently, strong intensity. Unlike the facial pain attacks described above, PIFP patients do not experience concomitant autonomic symptoms. Additional discrete attacks or neuralgic components are also not present. PIFP differs from neuropathic facial pain in that it is not associated with sensory negative symptoms (hypoesthesia, anesthesia); however, some patients report a sensation of swelling, usually experienced in the nasolabial region of the affected side of the face. Atypical odontalgia, now referred to as persistent idiopathic dentoalveolar pain (PIDAP), is a subtype of PIFP with identical symptoms as described above, but which remains strictly limited to one or two teeth and moreover does not spread (3).

In everyday clinical practice, PIFP is a diagnosis of exclusion in the absence of any pathology. Very often, the onset of PIFP is preceded by a recent minor (in most cases dental) procedure performed in the affected area (12). However, it often remains unclear whether the procedure was performed because of the pain or whether it triggered the pain (17). It remains to be said that most patients in our outpatient clinic had teeth extracted later, as part of pain therapy.

In particular, the collaboration with dentists and maxillofacial surgeons is of fundamental importance. However, other specialists, such as ENT specialists, should additionally be consulted on a case-by-case basis. It is very common that patients see a dentist with the explicit wish for dental treatment of the supposedly affected area or tooth. While dental procedures frequently induce temporary local improvements, symptoms subsequently reoccur at other teeth and may later reoccur at the original locations as well. This frequently triggers a vicious cycle of further invasive procedures which—driven by the patient's wish and the dentist's good intentions—leads to additional tooth extractions. In the course of such patient careers, these patients may lose multiple healthy teeth (*Figure*) and still experience pain in the entire orofacial region.

Management of persistent idiopathic facial pain

The first rule is: No further surgical procedures in patients with healthy dental status! In general, invasive procedures tend to result in pain chronification or spreading of the pain to another branch of the trigeminal nerve or even the contralateral side (12). For this

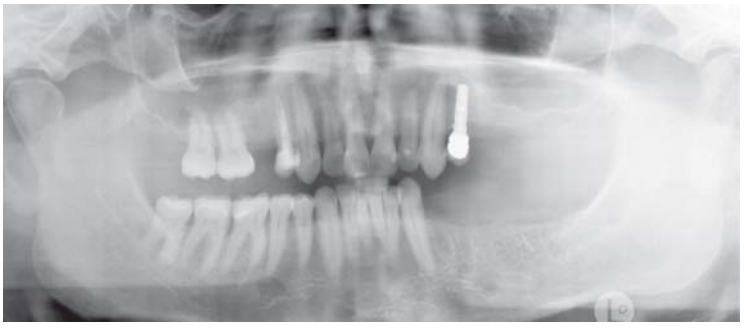


Figure: 48-year-old patient who had teeth extracted because of left facial pain . The pain started on the upper left side of the face (in the territory of second branch of CN-V) and spread after root canal treatment, root removal and finally tooth extraction initially to the adjacent tooth and later to the ipsilateral lower jaw (III branch of CN-V). Non-surgical pain management has now been started.

reason, the S1 guideline of the German Society of Neurology recommends to avoid dental procedures and to only perform interventions which are absolutely necessary (18). Disorders of the teeth or disorders of dentoalveolar and/or adjacent structures as comorbidities in PIFP patients represent a therapeutic dilemma for dentists, pain therapists and patients alike. In such cases, it is important to evaluate the significance of the respective comorbid condition, while continuing to pursue a conservative strategy.

Since no randomized controlled trials on the pharmacotherapy of PIFP have yet been conducted, all recommendations are made at the S1 standard level (expert opinion-based management recommendations). Essentially, the pharmacotherapy for PIFP is similar to that for neuropathic pain. Of special importance are antidepressants, such as amitriptyline 10–150 mg, duloxetine 60 mg and doxepin 10–150 mg, as well as anticonvulsants, such as gabapentin 1200–2400 mg and pregabalin 150–300 mg (18). As with the management of neuropathic pain, combination therapy may be useful (19) *(Box 2)*. Behavioral therapy is an important component of interdisciplinary multimodal pain therapy which primarily aims at providing better adapted pain management and a realistic assessment of the pain (20). The latter refers to understanding that the pain will not simply disappear with yet another dental treatment. Early involvement of specialists in pain psychology is advisable and should be sought on a regular basis.

Neuropathic facial pain

The clinical presentation of neuropathic facial pain is almost identical with that of PIFP, but the pain is of a burning quality and additional neuralgiform attacks may occur (21). The key clinical differentiation from PIFP is the presence of a nerve lesion: typically in the form of permanent hypoesthesia, dysesthesia or allodynia in the region of the pain. Neuropathic facial pain may also occur after facial injuries or procedures for facial tumors. Additional prominent examples of non-traumatic disorders include herpes zoster and trigeminal neuralgia. For the management of neuropathies, reference is made here to an excellent review by Binder and Baron (22). In the following, only trigeminal neuralgia will be discussed as here several important changes have occurred in the last two to three years. The burning mouth syndrome (23, 24) which is often listed under neuropathic facial pain syndromes (result of an underlying primary disease, vitamin deficiency) is also not covered here.

Trigeminal neuralgia

Trigeminal neuralgia (TN) is certainly the most prominent representative of neuropathic facial pain syndromes. It is characterized by attacks of extremely intense, shooting, stabbing pain lasting for (fractions of) seconds. The lifetime prevalence is estimated to be 0.16% to 0.3% (15, 25) and the mean age at the time of first diagnosis falls in the sixth decade of life (25). The

BOX 2

Pharmacologic treatment options for facial pain syndromes

The primary treatment options for the facial pain syndromes described in this article are listed below. The list is, where possible, based on existing and cited guidelines or, in the case of facial migraine and facial cluster headache, on the cited case series and the DGN/DMKG guideline on treatment of headache.

- **Facial migraine**
  - **Acute**
    NSAIDs, triptans
  - **Prophylactic**
    Antihypertensive drugs (beta blocker, candesartan), amitriptyline, topiramate, flunarizine; second choice: botulinum toxin and anti-CGRP (R) antibodies
- **Facial cluster headache**
  - **Acute**
    Oxygen, triptans
  - **Prophylactic**
    Verapamil, topiramate, lithium
- **Persistent idiopathic facial pain**
  - Combination of antidepressants and anticonvulsants (e.g. amitriptyline and/or gabapentin)
- **Neuropathic facial pain**
  - Combination of antidepressants and anticonvulsants (e.g. amitriptyline and/or gabapentin)
- **Trigeminal neuralgia**
  - **Pharmacotherapy**
    Anticonvulsants (carbamazepine, oxcarbazepine; second-line lamotrigine or gabapentin);
    With multiple sclerosis, misoprostol is also an option
  - **Interventional**
    Microvascular decompression; second choice: neuroablative procedures (mechanical, thermal, radiosurgery)

DGN, Deutsche Gesellschaft für Neurologie (German Society of Neurology);
DMKG, Deutsche Migräne und Kopfschmerzgesellschaft (German Migraine and Headache Society);
NSAIDs, non-steroidal anti-inflammatory drugs; CGRP-(R), calcitonin gene-related peptide (receptor)

BOX 3

Trigeminal neuralgia

The International Classification of Orofacial Pain (ICOP) categorizes trigeminal neuralgia as follows (3):

- **Classical trigeminal neuralgia (TN; neurovascular contact with displacement or atrophy of the trigeminal nerve)**
  - Classical TN, purely paroxysmal
  - Classical TN, with concomitant continuous pain
- **Idiopathic TN**
  - Idiopathic TN, purely paroxysmal
  - Idiopathic TN, with concomitant continuous pain
- **Secondary TN (due to underlying disease)**
  - Secondary TN due to underlying multiple sclerosis
  - Secondary TN due to space-occupying lesion
  - Secondary TN due to other causes

territory of the second trigeminal branch is primarily affected, while the third branch is less frequently and the first branch very rarely involved (25, 26).

The criteria of the classifications mentioned at the beginning (3, 4) require that the attacks are strictly unilateral, and, indeed, bilateral occurrence is a clinical rarity. However, ipsilateral involvement of multiple territories is certainly possible (27, 28). Another characteristic features is that attacks do not only occur spontaneously, but can be triggered by touch, eating and drinking (29); consequently, triggerability is now regarded a diagnostic criterion (3). Unfortunately, this criterion is also a typical pitfall since not every attack of facial pain which can be triggered is a neuralgia and not every neuralgia can be trigged. More critical for the diagnosis of neuralgia is the neuralgiform electric shock-like occurrence of the attacks lasting for seconds.

It is often disregarded that in many patients TN is characterized by episodic occurrence or even spontaneous remission. However, TN differs from primary headache disorders, such as cluster headache (30) and migraine (31), in that the presentation over time is unpredictable (25).

In addition to the eponymous neuralgic pain component, about half of the patients report continuous pain in the affected area of the face (32). In some patients, this pain component even precedes the onset of typical TN attacks—a condition known as pre-trigeminal neuralgia (33). Thus, especially in neurosurgery, episodic (type 1) TN and continuous (type 2) TN are distinguished (3). However, ultimately the classification of TN based on the neurovascular contact (NVC) between small blood vessels and the trigeminal nerve (CN-V) at its entrance into the brainstem and exit at the cerebellopontine angle proved useful and was generally adopted (34). Today, it is differentiated between classic TN with a NVC identified by magnetic resonance imaging or perioperatively, causing morphological changes in the nerve root, and idiopathic TN. The latter presents with the same clinical picture, but shows no NVC (*Box 3*) (3, 4). These two types of TN have to be distinguished from secondary TN due to an underlying primary disease, such as a tumor or multiple sclerosis. An important insight gained in the last few years is that the existence of an NVC is not the key factor determining the clinical presentation or the indication for surgical treatment, but rather the extent of the resulting damage to the nerve (35): A severe NVC (with displacement and/or atrophy of the root of the nerve) was detected significantly more frequently on the affected side and is a predictor of the effectiveness of surgical treatment (27).

Trigeminal neuralgia work-up

Since the subgroups of TN mentioned above cannot be differentiated based on the patient's clinical history and it is consequently impossible to rule out a symptomatic etiology, high-resolution magnetic resonance imaging is recommended for all patients (36, 37).

Management of trigeminal neuralgia

The European and national guidelines recommend pharmacotherapy as the first-line treatment. Only if this treatment fails or a patient is intolerant to it, surgical management is indicated (36, 37) *(Box 2)*.

Carbamazepine as treatment of first choice is a proven, well established strategy, showing an initial response rate of 90% and 50% of patients show good responses even in the long term (37). Oxcarbazepine appears to offer better tolerability with a similarly high level of effectiveness, but only few studies on it have yet been conducted (37).

Other anticonvulsants, such as lamotrigine and gabapentin, were evaluated in small studies. However, because of the limited data available, only a "weak recommendation" for these drugs alone and/or as add-on therapy can be made, based on the available "low-grade evidence" (36). As a special case, the possible off-label use of misoprostol, a prostaglandin analogue, to treat secondary TN due to multiple sclerosis should be mentioned (37, 38). Acute exacerbations of TN may require hospitalization of patients and treatment with intravenous phenytoin (36, 37) or lidocaine (36); however, the available evidence in support of this treatments is of a low grade.

In patients with classical trigeminal neuralgia, i.e. with displacement and/or atrophy of the nerve root, microvascular decompression (as proposed by Jannetta) should be performed if the attacks cannot be controlled with conservative measures (36). Neuroablative procedures (mechanical, thermal, radiosurgery) on the ganglion of the trigeminal nerve are also effective, but considered second choice because of their adverse event profile (36).

Outlook

With the exemption of trigeminal neuralgia, research, especially into primary/idiopathic facial pain, is still in its infancy. The great hope is that the new facial pain classification will help to better align the scientific efforts and, in doing so, contribute to advances in the treatment of facial pain over the next decades. Currently, a special focus should be on the interdisciplinary collaboration of pain therapists, in particular dentists and maxillofacial surgeons (18, 37).

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