Drugs (2023) 83:1269–1292
https://doi.org/10.1007/s40265-023-01927-z

REVIEW ARTICLE

Pharmacological Management of Orofacial Pain

Marcela Romero-Reyes[1,2] · Sherwin Arman[3] · Antonia Teruel[4] · Satish Kumar[5] · James Hawkins[6] · Simon Akerman[2]

Accepted: 26 July 2023 / Published online: 26 August 2023

Abstract
Orofacial pain is a category of complex disorders, including musculoskeletal, neuropathic and neurovascular disorders, that greatly affect the quality of life of the patient. These disorders are within the fields of dentistry and medicine and management can be challenging, requiring a referral to an orofacial pain specialist, essential for adequate evaluation, diagnosis, and care. Management is specific to the diagnosis and a treatment plan is developed with diverse pharmacological and non-pharmacological modalities. The pharmacological management of orofacial pain encompasses a vast array of medication classes and approaches. This includes anti-inflammatory drugs, muscle relaxants, anticonvulsants, antidepressants, and anesthetics. In addition, as adjunct therapy, different injections can be integrated into the management plan depending on the diagnosis and needs. These include trigger point injections, temporomandibular joint (TMJ) injections, and neurotoxin injections with botulinum toxin and nerve blocks. Multidisciplinary management is key for optimal care. New and safer therapeutic targets exclusively for the management of orofacial pain disorders are needed to offer better care for this patient population.

1 Introduction

Orofacial pain is the dental specialty that involves the evaluation, diagnosis, and management of pain disorders of the head, face, jaw, mouth, and neck [1]. Perhaps for the reader, the first thing that comes to mind when dentistry and orofacial pain is mentioned, is dental pain. Pains of odontogenic origin can be the most excruciating pain experiences, and fortunately they are relieved once the dental or periodontal pathology is resolved. However, there are other types of pains in this region that are of non-odontogenic origin and can become chronic. The focus of this narrative review is to discuss these orofacial pain disorders and their pharmacological management. Our search, within PubMed, focused on the last 10 years of orofacial pain and headache literature and included international classifications, guidelines, consensus, systematic and meta-analysis reviews, narrative reviews, prospective and retrospective studies, basic science studies and, when available, clinical trials. Some older references were also included because they were considered of key importance to our topic.

Orofacial pain (OFP) disorders are complex conditions that impact dramatically the quality of life of the patient [2]. Their prevalence varies between studies, but it has been reported that up to a quarter of the population may report orofacial pain and 11% may be chronic [2–5]. OFP comprises disorders of different etiology and pathophysiology, from musculoskeletal to neuropathic and neurovascular in nature, including the temporomandibular disorders (TMDs), neuropathic pains such as trigeminal neuralgia, as well as headache disorders [1, 6]. The interrelated anatomy and physiology of the region adds to the complexity of these disorders, presenting to the clinician a diagnostic and a

✉ Marcela Romero-Reyes
mromero@umaryland.edu

1 Brotman Facial Pain Clinic, School of Dentistry, University of Maryland, 650 W. Baltimore St, 1st Floor, Baltimore, MD 21201, USA

2 Department of Pain and Neural Sciences, School of Dentistry, University of Maryland, 650 W. Baltimore St, 8th Floor, Baltimore, MD 21201, USA

3 Orofacial Pain Program, Section of Oral Medicine, Oral Pathology and Orofacial Pain, University of California, Los Angeles, School of Dentistry, Los Angeles, CA, USA

4 Head Pain Institute, Scottsdale, AZ, USA

5 Department of Periodontics, Arizona School of Dentistry and Oral Health, A.T. Still University, Mesa, AZ, USA

6 Naval Postgraduate Dental School, Naval Medical Leader and Professional Development Command, Uniformed Services University of the Health Sciences Postgraduate Dental College, Baltimore, MD, USA

Key Points

Orofacial pain disorders are complex and can be quite challenging to diagnose and manage. The orofacial pain specialist is trained to diagnose and manage these conditions.

The management plan is individualized and may include different pharmacological and non-pharmacological modalities.

Orofacial pain disorders are within the realms of dentistry and medicine. Multidisciplinary management is key for optimal care.

Novel and safer therapeutic targets exclusively for the management of trigeminal mediated pain and the development of evidence-based guidelines and protocols for the management of the different orofacial pain disorders are greatly needed, to offer better care and reassurance to this patient population.

management challenge. In persistent pain disorders of idiopathic etiology such as burning mouth syndrome and persistent idiopathic facial and dentoalveolar pains, diagnosis is further challenging as it has to be made by exclusion of other pain disorders [7, 8]. Moreover, another layer of complexity is the psychological burden that these disorders inflict on the individual, which impact greatly on management [2, 9, 10].

The heterogeneous nature of these disorders requires a management plan tailored exclusively to the patient following the biopsychosocial framework and diagnosis. Management may include different pharmacological and non-pharmacological approaches, as well as trial of different medications and modalities. An orofacial pain specialist is key for the evaluation, diagnosis, and management of these disorders, but management is multidisciplinary, and it is necessary that a team of health professionals from different fields, including but not limited to neurology, pain medicine, psychiatry, psychology, otolaryngology, and physical therapy are involved for effective management.

The intent of this review is to examine the most common orofacial pain disorders and their management. The focus is on pharmacological approaches; however, non-pharmacological approaches are key in the management plan of this patient population, so they will be briefly discussed.

2 Temporomandibular Disorders

Temporomandibular disorders (TMDs) are a number of disorders affecting the muscles of mastication, the temporomandibular joint (TMJ), and contiguous structures [1]. After chronic lower back pain, these disorders are the most common musculoskeletal disorders that cause pain and disability [11]. According to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), the most common pain-related TMDs are myalgia, local myalgia, myofascial pain, myofascial pain with referral, arthralgia and headache attributed to TMDs; and the most common intraarticular disorders are disc displacement with reduction, disc displacement with reduction and intermittent locking, disc displacement without reduction with or without limitation at opening, degenerative joint disease, and subluxation [12]. The etiology of TMDs is still ambiguous but diverse factors including history of trauma to the masticatory structures, parafunctional habits, and genetic and psychosocial factors may contribute to the onset, perpetuation, and predisposition of TMDs [1, 13]. The presence of behaviors known as parafunctional habits, such as clenching and grinding included in the broad term of bruxism do not usually result in TMD symptoms but in some individuals may be contributing factors [14–16]. However, further research is still necessary to clarify this relationship [17]. The International Classification of Orofacial Pain (ICOP) distinguishes two main diagnostic categories of TMD that include myofascial orofacial pain and TMJ pain [18]. Primary myofascial orofacial pain and TMJ pain could be acute (<3 months) or chronic (≥3 months). Secondary myofascial orofacial pain is caused by myositis, muscle spasm, or tendonitis. Secondary TMJ pain is caused by arthritis, degenerative joint disease, disc displacement, or subluxation [1, 18]. Overall, the most prevalent painful TMD is of muscular origin. Myofascial pain is estimated to be the most prevalent with 45% or higher prevalence [19–21]. TMJ disorders such as TMJ disc displacements are highly prevalent in the population. A systematic review and meta-analysis reported their prevalence to be high, at 25.9% for adults and elderly [22]. The main indicator of this alteration in condyle-disc function is clicking or popping sounds, which are usually non-painful (non-painful TMD) but sometimes can be accompanied by pain (arthralgia) and with limited mouth opening during condylar movement, such as in the cases of disc displacement without reduction [23].

Migraine, lower back pain, fibromyalgia, irritable bowel syndrome, anxiety and depression, sleep disorders, vulvodynia, and chronic fatigue are more prevalent among TMD patients and are considered comorbid disorders [24–26]. In addition, anxiety and depression have been reported to affect

about 40–65% of patients with TMD [27] and is noted in particular in patients with myofascial orofacial pain [28].

Accurate diagnosis of TMD conditions is essential for effective management. Signs and symptoms include pain located in the preauricular area or muscles of mastication, difficulty in mouth opening, TMJ noises such as clicking, popping, crepitus, intensified by jaw activities such as chewing, eating, talking, yawning, and smiling, among others [29]. Complexity in diagnosing specific TMDs lies in the fact that referred pain from associated muscles of mastication, as in the case of myofascial pain, may be present at a different site, such as a toothache or a headache, masking the actual source of pain. Palpation of the TMJ and muscles of mastication to verify pattern of referral, and diagnostic tests, such as trigger point injections in the suspected muscle source of pain are essential to confirm the diagnosis.

2.1 Management

TMD symptomatology tends to improve over time [10, 30] and therefore management should be conservative and reversible and based on evidence-based therapeutics [31]. Management is within the biopsychosocial framework whereby behavioral approaches are included in the management plan [1, 32]. When a TMD is chronic, for some patients, management can be quite challenging, greatly affecting their quality of life [33].

Several modalities are currently used for the management of TMDs and a management plan including different modalities is tailored to diagnosis and patient needs. These modalities include conservative and non-invasive approaches (patient education and self-management, physical therapy, pharmacological management, and oral appliances), minimally invasive approaches (intra-articular injections), and surgical interventions (e.g., arthrocentesis) [34]. The clinical outcomes expected with these therapies include pain relief and improvement of function. The medications used in the management of TMDs include non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, anticonvulsants, antidepressants, and corticosteroids. While high quality evidence such as randomized controlled trials are lacking for most drugs in specific TMD diagnoses, observational studies, preclinical and clinical studies have documented their efficacy.

2.1.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Oral NSAIDs are supported to be used as first line to alleviate acute muscle and joint pain [35]. NSAIDs such as ibuprofen, naproxen, celecoxib, and diclofenac sodium have been shown to reduce TMD-related pain and improve mouth opening. Both systemic intake and topical formulations of NSAIDs have been shown to be helpful in the management of TMDs. However, high quality evidence is lacking on specific NSAIDs and the dosage and duration of treatment for different TMDs [36, 37]. NSAIDs are usually prescribed short term and should be avoided in patients with active gastrointestinal disorders and kidney disease. Caution should also be exercised in cardiovascular disease with risk of endothelial injury [38].

2.1.2 Muscle Relaxants

Muscle relaxants such as cyclobenzaprine, baclofen, and tizanidine are helpful in the management of myofascial orofacial pain [39]. Cyclobenzaprine is the most studied drug in this category with supporting evidence [40]. Side effects include sedation, so it is usually prescribed short term at lower doses of 5–10 mg at bedtime for the management of myofascial orofacial pain [6, 29, 41].

2.1.3 Antidepressants

Tricyclic antidepressants (TCAs) and selective norepinephrine and serotonin reuptake inhibitors (SNRIs) have been effective in pain management. Examples of these drugs include amitriptyline, nortriptyline, duloxetine, and venlafaxine [1]. Amitriptyline has been reported to provide a reduction of pain and discomfort in patients with chronic TMD [42], in addition to being useful in patients with headache attributed to TMD and tension-type headache [6].

2.1.4 Anticonvulsants

Gabapentin and pregabalin are two commonly prescribed medications for neuropathic pain and there have been reports of use for the management of myofascial orofacial pain as well [43]. However, these are not first-line management approaches, and there is limited data to support their use, and so they are not normally used in TMD management. Gabapentin may be considered as an alternative for patients who do not respond to TCAs [44].

2.1.5 Trigger-Point Injections—Local Anesthetics, Botulinum Toxin

Myofascial trigger points are hypersensitive spots located within taut bands of the skeletal muscles, which can cause pain locally or at distant sites when compressed or stretched [45]. Intramuscular injections have been used for the management of myofascial orofacial pain, usually with local anesthetics, corticosteroids (tendinitis), or botulinum toxin, as well as dry needling without any injection drugs. Limited evidence has shown the beneficial effects of trigger-point injections with local anesthetics [46, 47] and dry needling [48]. The use of botulinum toxin A (BTX) is approved for

the management of chronic migraine [49]. BTX has shown superiority over placebo in reducing TMD symptomatology, although data are still unclear [50, 51], and it currently does not have FDA approval for use in TMD management. However, BTX is useful in patients with myogenous TMD refractory to conventional therapy and in patients with significant parafunctional behaviors, such as bruxism [51–53]. More randomized controlled trials (RCT) are necessary to support standardized protocols of care and it should not be used as a first line of management.

2.1.6 Temporomandibular Joint (TMJ) Injections

Intra-articular injections are indicated for joint pain, limited mouth opening, and inflammatory and degenerative joint diseases. There are several advantages for the use of TMJ injections in addition to being a conservative therapy with very low risk of complications. These advantages are direct local drug delivery into the TMJ, increased bioavailability of the drug in the joint, and lower systemic effects and toxicity. All of these ultimately result in a lower dose of medication needed to achieve a therapeutic effect [54]. TMJ injections appear to be a good choice for cases where conservative measures have failed, in cases that are not yet in need of surgical intervention, or for patients that do not wish to undergo surgery as a supportive therapy.

2.1.6.1 TMJ Injections—Corticosteroids Systemic corticosteroids are only prescribed short term for acute episodes of painful arthralgia and inflammation, and when NSAIDs have been not effective. Oral methylprednisolone is commonly used at a starting dosage of 4 mg in a 6-days course for acute management [6, 55]. Corticosteroid injections are indicated for inflammatory conditions affecting the TMJ to decrease pain and improve function. They are also helpful for patients that are not responding to usual self-management strategies and/or oral anti-inflammatory medications, or for those patients with gastro-esophageal reflux (GERD) or gastritis. Several steroids can be used for injections in the TMJ, namely, tenoxicam [56], betamethasone [57], and methylprednisolone [58, 59]. Triamcinolone is a steroid that is commonly used, and which is usually injected in the superior joint space in a 10–20 mg dose and mixed with an equal amount of local anesthetic, such as lidocaine or bupivacaine [55]. Although corticosteroid injections are considered a safe treatment modality with low risk of morbidity, some complications are reported with its use [60, 61]. Major limitations of intra-articular corticosteroids include a short duration of effect and limited frequency of use due to safety reasons [54]. The general guideline for steroid use recommends injecting the TMJ no more than three times in a 12-months period [55].

2.1.6.2 TMJ Injections—Hyaluronic Acid Hyaluronic acid (HA), a natural glycosaminoglycan that is found in the synovial fluid and is produced by synovial cells [62], aids in joint stabilization, nutrition, elasticity, and viscosity of the synovial fluid. HA has been used as a viscosupplementation of TMJ to help in the management of internal derangement and osteoarthritis. HA injections are usually indicated for patients who only responded temporarily or partially to intra-articular corticosteroid injections. These injections have been shown to improve TMJ pain and jaw motion by decreasing inflammation, and to have a moderate success rate in patients with new-onset osteoarthritis with crepitation [63, 64]. Additionally, HA has been shown to be effective in treating patients with anterior disc displacement with or without reduction [65, 66]. HA injections appear to improve jaw function and induce condylar reparative remodeling in patients with ADD associated with osteoarthritis [67]. The usual practice for HA is a series of three injections once a month [55]. In osteoarthritis and anterior disk displacement with or without reduction, HA treatment when used alone has been shown to be effective in pain reduction compared with placebo or other therapies in many studies. However, HA, when combined with arthrocentesis, has not been shown to be effective compared with arthrocentesis alone. There is no single universal clinical protocol with a specific molecular weight, dose and concentration of HA, and number of applications, and this has created a heterogenous and equivocal body of evidence [68].

2.1.6.3 TMJ Injections—Platelet-Rich Plasma Platelet-rich plasma is an orthobiological agent comprising a concentrate of platelets derived from the patients' own blood. Due to its high concentration of growth factors, it possesses anti-inflammatory and analgesic properties and hence aids in the healing of bones, muscles, tendons, and cartilage [69]. PRP is produced by centrifuging whole autologous blood with an anticoagulant and separating the platelets from the other contents of the blood and diluting them to the ideal concentration [70]. The duration of this process varies by system used. There is increasing evidence that intra-articular injection of PRP is a promising treatment modality for degenerative conditions of the joints such as osteoarthritis and disc displacement with osteoarthritic lesions [71]. The benefits of PRP in degenerative TMDs may result from its capacity to restore HA in the joint, trigger the synthesis of glycosaminoglycans from chondrocytes, and provide a scaffold for the stem cells [72]. Clinical studies for the treatment of osteoarthritis of the TMJ have shown PRP to be beneficial in preventing the recurrence of pain and joint sounds and improvement of mandibular opening in comparison with HA and corticosteroids in long-term follow-ups [73]. Similarly, PRP may be more effective long term in decreasing pain and increasing mandibular function in comparison with HA for

patients with osteoarthritis of the TMJ [71]. Moreover, PRP effectiveness has been studied for the treatment of internal derangements. Intra-articular injection of PRP in patients with anterior disc displacement with reduction resulted in decreased pain levels and joint sounds and increases in mandibular opening in comparison with arthrocentesis [74]. A systematic review compiled nine studies (443 patients) that investigated HA, corticosteroids, and/or autologous blood products in patients with temporomandibular joint osteoarthritis. They concluded that all of these injectables along with arthrocentesis were effective in reducing pain and improving maximum mouth opening [75].

2.1.6.4 Prolotherapy Prolotherapy involves injection of hypertonic dextrose into the joint space and has been shown to be helpful in the management of TMD pain as well as subluxation and hypermobility [76]. The mechanism of action is unclear and has been attributed to a transient inflammatory response and tissue proliferation. A systematic review compiled ten randomized control trials, of which five trials were combined in a meta-analysis. Hypertonic dextrose prolotherapy was found to be better than placebo injections in improving TMJ pain symptoms at 12 weeks. However, dextrose prolotherapy did not provide additional benefits in maximum inter-incisal mouth opening and disability scores [77].

2.1.7 Surgical Therapy

The decision to perform a surgical intervention is made carefully and for very specific cases and depends on the degree of intraarticular pathology and adaptation. From the surgical interventions available, arthrocentesis and arthroscopy reduce pain and improve joint function by reducing the inflammatory mediators in the joint space. These are minimally invasive surgical procedures. Surgical interventions, according to the American Association of Oral and Maxillofacial Surgeons, should be reserved to intractable cases after non-invasive options have been tried and failed [78].

3 Neuropathic Orofacial Pain

Neuropathic pains are caused by a lesion or disease of the somatosensory system [79]. In the orofacial region, neuropathic pains can occur as a consequence of sensitization from nerve injury secondary to dental procedures, facial trauma, injury associated with inflammation, infection or neoplasia, and due to some metabolic disorders [80–82]. Pre-clinical and clinical evidence support that this maladaptive response to peripheral and central sensitization is associated with multiple mechanisms involved in neuroplastic changes in the nervous system, leading to a dysregulation in descending pain modulation, favoring pain facilitation and maintenance [83–87].

Trigeminal neuralgia is the most common neuropathy in the orofacial region. Less common conditions include disorders affecting the glossopharyngeal nerve such as glossopharyngeal neuralgia, and the facial nerve in the case of nervus intermedius neuralgia. As with any other neuropathic pain in other body regions, allodynia and hyperalgesia are present as well as other signs that accompany nerve injury such as paresthesia and dysesthesia. The pain can be continuous or episodic, spontaneous, and triggered by touch. These types of pain are accompanied by significant psychosocial burden affecting the quality of life of the patients, impairing activities such as eating, talking, kissing, smiling, and social interactions [88–90].

It is very important to highlight that these pains, in the trigeminal distribution and their branches, can be reported by the patient as a toothache, and therefore they have the potential risk of being misdiagnosed as being of dental origin. Unfortunately, misdiagnosis is not uncommon, leading to unnecessary dental procedures in an attempt to alleviate the symptomatology, with the potential to exacerbate the pain and cause more suffering [90, 91]. Therefore, a careful differential diagnosis performed by an orofacial pain specialist to differentiate between odontogenic and non-odontogenic pain is necessary.

Thanks to the International Classification of Headache Disorders (ICHD-3) [92] and, more recently, the International Classification of Orofacial Pain (ICOP) [18], a diagnostic criteria for the different neuropathic orofacial pain disorders is now available. The use of opioids in orofacial pain management is not supported by the literature and the risks for the development of hyperalgesia, tolerance, and physical dependence outweigh any benefit [93, 94]. The management of orofacial neuropathic pain is based on the guidelines and recommendations for the management of other neuropathic pain disorders of other areas of the body [95]. However, evidence-based sources and guidelines with the focus on trigeminal and other orofacial neuropathic pains are becoming more available [1, 96]. Research focusing exclusively on craniofacial neuralgias and trigeminal neuropathic pains is greatly needed.

We have divided the following sections of neuropathic orofacial pains into episodic and continuous disorders according to their temporal features [1]. Episodic disorders are characterized by their intermittent patterns of pain and their characteristic presence of painful paroxysms (neuralgic pain), while continuous disorders are characterized by unremitting, constant patterns of pain and occasionally they may also present episodes of painful paroxysms. Information about common oral medications used for trigeminal neuralgia and other trigeminal neuropathic pains including dosages and side effects are summarized in Table 1. Topical

Table 1 Medications used for trigeminal neuropathic pains [1, 94, 96, 102–105]

Medication class	Starting dose	Dose titration	Maximum dose	Duration of adequate trial	Adverse events	Precautions and contraindications
Sodium channel blockers						
Carbamazepine	100–200 mg/d	Increase as tolerated by 100–200 mg every third day	1200 mg/d or 1800 mg/d in a divided-dose regimen, bid–qid	At least 4 weeks A beneficial effect is usually present within hours to a couple of days	Dizziness, tiredness, drowsiness, nausea, ataxia, leucopenia, aplastic anemia	Hepatotoxicity, myelosuppression Monitor: liver function test; complete (full) blood count (CBC) and urea and electrolytes Screening of HLA-A*31:01 and HLA-B*15:02 is recommended (SJS) Decreases plasma concentration of warfarin and oral contraceptives Do not combine with monoamine oxidase inhibitors Caution when used with multiple anticholinergic drugs Contraindicated in atrioventricular block
Oxcarbazepine	150 mg, bid	Increase dose as tolerated up to 300–600 mg bid Increase by 300 mg every 3 days	2400 mg/d	At least 6 weeks	Dizziness, tiredness, drowsiness, nausea, ataxia, headache, double vision, hyponatremia	Hyponatremia Monitor: sodium levels; screening for HLA-B*1502 is recommended (SJS). Might decrease plasma concentration of oral contraceptives. Caution when used with multiple anticholinergic drugs
Lamotrigine	25 mg qd for 2 weeks	Increase dose to 50 mg daily for 2 weeks, then 100 mg, 200 mg, 300 mg and 400 mg for 1 week at each dose level. Can be taken qd or bid	400 mg/d	2–8 weeks	Rash, headache, pain, dizziness, fatigue, nausea	Rash severity varies but includes a risk for SJS. Other serious adverse effects include multi-organ sensitivity, hemophagocytic lymphohistiocytosis, blood dyscrasias, suicidal behavior/ideations, aseptic meningitis, status epilepticus, and sudden unexplained death in epilepsy
Calcium channel ligands						
Gabapentin	100–300 mg at bedtime or 100–300 mg, tid	Increase by 100–300 mg tid every 3–7 days	3600 mg/d	3–8 weeks, minimum 2 weeks at effective dose	Sedation, dizziness, peripheral edema and weight gain	Reduce dose in patients with renal insufficiency
Pregabalin	50 mg, tid or 75 mg, bid	3–7 days, followed by 150 mg/d every 3–7 days	600 mg/d as 200 mg, tid or 300 mg, bid	4 weeks	Sedation, dizziness, peripheral edema and weight gain	Reduce dose in patients with renal insufficiency

Table 1 (continued)

Medication class	Starting dose	Dose titration	Maximum dose	Duration of adequate trial	Adverse events	Precautions and contraindications
Tricyclic antidepressants						
Tertiary amine: amitriptyline Secondary amine: nortriptyline	10 mg at bedtime	Start 10 mg HS and increase by 10–25 mg/d every 3–7 days until therapeutic effect reached or adverse symptoms present	150 mg/d	6–8 weeks with at least 2 weeks at maximum tolerated dosage	Somnolence, anticholinergic effects, and weight gain	Cardiac disease, glaucoma, prostatic adenoma and seizure High doses should be avoided in adults >65 years of age
SNRIs						
Duloxetine	30 mg/d	Increase to 60 mg/d after 1 week	60 mg, bid	4 weeks	Nausea, abdominal pain, and constipation	Hepatic disorder, hypertension Use of serotonergic medications
Venlafaxine	37.5 mg once or twice daily	Daily after 1 week Increase by 75 mg each week	225 mg/d	4–6 weeks	Nausea and hypertension	Cardiac disease and hypertension Use of serotonergic medications
Skeletal muscle relaxants						
Baclofen	10 mg, tid	Increase by 5 mg every third day	70 mg (15–70 mg)	Variable	Nausea, somnolence, gastrointestinal symptoms	Abrupt discontinuation of may cause seizures and hallucinations Seizure disorder, kidney disorders, reduce lung function, cerebrovascular disease, psychiatric disease
Neurotoxins						
Botulinum toxin type A	No standardized dose for neuropathic pain	May increase dose subsequent treatments	TN, PTTN and PHN, studies report 17–200 units	2 weeks to experience therapeutic effect	Pain at injection site, antibody formation, esthetic considerations	Known hypersensitivity and infection of the painful area

bid twice daily, *PHN* post-herpetic neuralgia, *PTTN* post-traumatic trigeminal neuropathy, *qd* one a day, *qid* four times daily, *SJS* Stevens-Johnson syndrome, *SNRIs* serotonin reuptake inhibitors, *tid* three times daily, *TN* trigeminal neuralgia, *HS* take at bedtime

agents commonly used in neuropathic orofacial pains are summarized in Table 2.

3.1 Episodic Disorders

3.1.1 Trigeminal Neuralgia

Trigeminal neuralgia (TN) (ICOP 4.1.1; ICHD 13.1.1) is the most characteristic episodic neuropathic pain disorder and the most common neuralgia in the orofacial region [97]. The average onset is in the sixth decade of life; it is more prevalent in women and has an incidence of 12.6–27.0 per 100,000 person-years [96]. It is characterized by episodic unilateral and severe sharp, shooting, electrical-like paroxysmal pain localized in the distribution of one or more of the divisions of the trigeminal nerve, usually the maxillary (V2) and the mandibular (V3) divisions, where trigger areas can be localized intraorally and extraorally. Therefore, it is important to highlight that in the case of an intraoral trigger zone, a differential diagnosis to rule out dental pathology is necessary. The paroxysmal pain can be triggered but it can also present spontaneously. When it is triggered it can be elicited by innocuous stimuli and daily life activities, such as teeth brushing, washing the face, shaving, applying makeup, a cool breeze touching the face, eating, and talking [1, 98]. The duration of the pain can usually be from seconds to 2 min and can present periods of remission lasting days, to months to years in which minimal or no pain is appreciated. A distinctive characteristic of TN is that when the pain subsides, it presents a refractory period between attacks in which the pain is not elicited [1]. Pathophysiology may involve axonal demyelination and possible gain of function mutations of voltage-gated sodium channels (NaV) [96].

During the differential diagnosis of TN, it is critical to explore the cause further; therefore, imaging of the brain is necessary (e.g., magnetic resonance imaging/MRI). The ICHD-3 and the ICOP categorize TN into classical, where the cause is a neurovascular compression; secondary, where it is caused by an underlying disease including multiple sclerosis, an occupying lesion (e.g., cerebellum-angle tumor), or arteriovenous malformation; and lastly idiopathic, where no abnormalities in brain imaging or electrophysiological tests have been found [18, 92]. TN can present purely paroxysmal or also with concomitant continuous pain. Moreover,

Table 2 Topical agents used in neuropathic orofacial pains [138–142, 207]

Topical agent	Mechanism	Location of activity	Pain conditions used for management
Lidocaine 5%	Sodium channel blockade TRPA1 blockade	Aδ-fibers C-fibers	Post-herpetic neuralgia Post-traumatic neuropathy
Ketamine 0.5–5% 0.5%	NMDA receptor blockade with reduction of glutamate production	Aδ-fibers C-fibers	Post-herpetic neuralgia Post-traumatic neuropathy
Baclofen 2–5%	GABA-B receptor agonist	C fibers	Neuropathic pain related to acromegaly, radicular pain Muscle spasm
Capsaicin 8% patch Capsaicin 0.025–0.075% used in a compounded medication: intraorally or extraorally	TRPV1 channel agonist	Aδ-fibers C-fibers	Post-herpetic neuralgia Post-traumatic trigeminal neuropathy
Clonazepam rinse, 0.5 mg/mL solution (5 mL)	GABA-A receptor agonist	PNS CNS Post-synaptic neuron	Burning mouth syndrome
Diclofenac 1.5%	Topical inflammation Topical antinociception: TRPV1, TRPA1	Superficial tissues Aδ-fibers C-fibers	Post-herpetic neuralgia
Antidepressants:			
Amitriptyline 1–10%	Blockade of Na^+, K^+, Ca^{2+} channels Muscarinic, cholinergic, nicotinic receptors H^+, alpha-2, adenosine and NMDA receptors	Aδ-fibers C-fibers	Post-herpetic neuralgia Post-traumatic neuropathic pain Peripheral neuropathy
Clonidine 0.1%	α2-adrenergic receptor agonist I2 imidazoline receptor agonist	Aδ-fibers C-fibers Peripheral α-adrenergic activity	Sympathetic mediated pain

TRPA1 transient receptor potential A1, *TRPV1* transient receptor potential vanilloid 1, *NMDA* N-methyl-D-aspartate, *GABA-B* gamma-aminobutyric acid-B, *GABA-A* gamma-aminobutyric acid-A, *PNS* peripheral nervous system, *CNS* central nervous system

in some cases TN may present mild autonomic features and therefore the possibility of a trigeminal autonomic cephalgia or trigeminal autonomic orofacial pain should be explored during interview and examination. Short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache with autonomic symptoms (SUNA), or short-lasting unilateral neuralgiform facial pain attacks with cranial autonomic symptoms (SUNFA) [18, 99] should be considered in the differential diagnosis when autonomic symptomatology is more profound. As in TN, SUNFA can be localized in V2 and V3, but SUNCT and SUNA are localized in the ophthalmic division (V1). Another distinction is that unlike TN, these disorders do not have a refractory period [99, 100].

3.1.1.1 Management The medication class used for the management of TN is antiepileptics and the only medication that is approved by the FDA for both TN and glossopharyngeal neuralgia is carbamazepine (see Table 1). Other medications such as oxcarbazepine, gabapentin, pregabalin, lamotrigine, baclofen, duloxetine, and topiramate are used too, but their use is off label [101]. Carbamazepine and oxcarbazepine are generally used as first line of management with specific recommendations [94, 96, 102–104]. When carbamazepine and oxcarbazepine are ineffective or patients present poor tolerability, other options such as gabapentin, pregabalin, baclofen, lamotrigine, anesthetic blocks, and botulinum toxin should be considered as an addition or monotherapy [94, 105, 106]. Other medications such as topiramate and duloxetine, an SNRI, have been reported in the use of TN but with unclear effectiveness and a lack of controlled studies to confirm their efficacy [101, 107, 108]. The use of carbamazepine needs to be monitored with complete blood count (CBC) and differential and liver function tests since there is a risk of hepatotoxicity and myelosuppression [109]. Screening of human leucocyte antigen (HLA) allele HLA-B*15:02 and HLA-A*31:01 is recommended when prescribing carbamazepine to avoid the risk for toxic epidermal necrolysis/Steven-Johnson syndrome (SJS), which even though rare, has been shown to be a greater risk in populations of Southeast Asian and Japanese descent [110, 111]. Serum sodium levels need to be monitored while using oxcarbazepine to avoid hyponatremia, and genetic testing for HLA-B*15:02 is recommended since it can also cause SJS [112].

It is not uncommon that TN symptomatology may present sudden exacerbations while a medication regimen has provided stability. Steroid administration is effective in the acute management of flare ups, and it may also potentially reduce the likelihood of surgical intervention [113]. Type of steroid, rescue dosages and length of treatment may vary (e.g., IV dexamethasone 20–40 mg to higher) in the emergency room setting [113, 114]. TN secondary to multiple sclerosis may also benefit from the use of steroid therapy; in addition, the use of prostaglandin-E1-analogue misoprostol (600 μg/day) has been shown to be effective in refractory cases [115, 116].

As described above, pharmacotherapy is the first line of management for TN. However, neurosurgical options need to be discussed when pain is refractory to management or side effects arise causing poor tolerability [105]. Unfortunately, there is no protocol that indicates how many medications the patient should try before surgery is discussed, but carbamazepine and oxcarbazepine should be tried in combination as well as the other options discussed above before surgery is offered [96, 117].

3.2 Continuous Disorders

3.2.1 Trigeminal Postherpetic Neuralgia

Post-herpetic neuralgia (PHN) (ICOP 4.1.2.2; ICHD-3 13.1.2.2) is a persistent and refractory pain condition present for 3 months or more following an outbreak of acute herpes zoster, known as shingles. PHN is more common in the elderly and immunocompromised populations and is associated with the reactivation of the dormant varicella zoster virus. The herpes zoster infection induces changes in the peripheral nervous system impairing all sensory fiber groups as well as changes in the central nervous system somatosensory processing. The pain experience is variable and described as a constant deep, aching, burning pain, and can present episodes of lancinating pain [118, 119].

3.2.1.1 Management PHN is an extremely complex drug-resistant neuropathic pain. Medications including anticonvulsants, tricyclic antidepressants, opiates, topical capsaicin and lidocaine, botulinum toxin injections, and nerve blocks are used for its management [120, 121]. The use of opioids for orofacial pain is not supported by the literature and the risks for the development of hyperalgesia, tolerance, and physical dependence outweigh any benefit. See Tables 1 and 2 for summary.

3.2.2 Post-Traumatic Trigeminal Neuropathic Pain/Painful Post-Traumatic Trigeminal Neuropathy

Post-traumatic trigeminal neuropathic pain (PTTN) (ICOP 4.1.2.3)/painful post-traumatic trigeminal neuropathy (ICHD 13.1.2.3) can arise after injury to the trigeminal nerve and its branches and cause severe dysfunction. PTTN can occur after third molar extraction, local anesthetic blocks, root canal therapy, dental implant surgery, orthognathic surgery, as well as after ablation procedures for trigeminal neuralgia [92, 122, 123]. The prevalence in development can range from 3 to 5% [89, 124]. Pain is reported as continuous and variable in intensity, and can be described as burning,

pricking, tingling, and accompanied by electric-like paroxysms of pain. In addition, positive somatosensory symptoms such as allodynia, and negative symptoms such as hypoesthesia and hypoalgesia may be present [125].

3.2.2.1 Management Management of PTTN is based on evidence and guidelines associated with neuropathic pain management in other parts of the body and of different etiologies [94, 102]. Pharmacological therapy is the first line of management and comprises antidepressants and anticonvulsants [126]. These include tricyclic antidepressants such as amitriptyline and nortriptyline, which are often used as first-choice management, SNRIs such as venlafaxine and duloxetine, or anticonvulsants such as gabapentin or pregabalin [1, 127–129]. For summary, see Tables 1 and 2. Microsurgery can be recommended for PTTN when the injury involves the inferior alveolar nerve and/or the lingual nerve and when non-surgical options have been ineffective. However, these procedures carry their risks and challenges. Different variables (location, severity of injury, and pain characteristics and duration) need to be taken into account to select the right candidate for these procedures [89, 123].

3.3 Idiopathic Orofacial Pains

Idiopathic orofacial pains are a group of disorders where there is absence of any other obvious etiology. They may present somatosensory changes or not, as determined by qualitative and quantitative sensory testing [18, 130], and they may possibly be of nociplastic nature. Persistent idiopathic facial pain (PIFP), persistent idiopathic dentoalveolar pain (PIDAP) and burning mouth syndrome (BMS) will be briefly discussed. Diagnosis of these conditions is by exclusion where clinical and radiological exams are normal. A more comprehensive definition and criteria are listed in the ICOP [18].

PIFP (ICOP 6.2; ICHD-3 13.1.2.5 idiopathic painful trigeminal neuropathy), previously known as atypical facial pain, has an incidence estimated at 4.4 per 100,000 person-years and is more prevalent in women [131, 132]. It is characterized by a dull, aching, deep or superficial diffuse pain, is poorly localized, may not follow neuroanatomical distributions, and sometimes may present sensory abnormalities with considerable overlap with trigeminal neuropathic pain [18, 130, 133]. PIDAP (ICOP 6.3), previously known as atypical odontalgia, phantom tooth pain and primary dentoalveolar pain disorder (PDAP) [18], is presented as persistent tooth or teeth pain or pain over a dentoalveolar site in the absence of any detectable pathology during a radiological and clinical exam, and with no history of precipitating event/dental procedure for the last 6 months or more. PIDAP/PDAP can be comorbid with TMD and may be considered a chronic overlapping pain condition (COPC) [134]. BMS (ICOP 6.1; ICHD-3 13.11) may have some elements of neuropathic pain but it is still poorly understood. It is more prevalent in menopausal women and is characterized by an intraoral burning with fluctuating intensity that usually is bilateral with a common site such as the tongue. In BMS it is necessary to rule out any other secondary cause including candida infection, oral mucosa lesions, tobacco chewing, autoimmune and endocrine disorders, nutritional deficiencies, medication side effects, and chemotherapy [1, 8, 18].

3.3.1 Management

There are few RCTs for the pharmacological management of these disorders and there is not a standardized protocol. Management is multidisciplinary and should include pharmacological and non-pharmacological modalities, such as cognitive behavioral therapy and psychological support [128, 135]. See Tables 1 and 2 for more details. Pharmacological modalities include TCAs, SSNRIs (duloxetine), anticonvulsants (gabapentin, pregabalin), and for BMS, management options are even more limited—not only due to the incomplete understanding of its etiology and pathophysiology, but also for the appearance of side effects such as dry mouth with the use of some medications like TCAs that may exacerbate symptoms in some individuals. In addition to cognitive behavioral therapy, topical clonazepam, topical capsaicin, alpha-lipoic acid, and laser therapy appear to be beneficial in some patients [8, 127, 135]. Moreover, a couple of case reports show potential promise with the use of low-dose naltrexone (LDN) with a positive response decreasing BMS symptomatology as well as pain associated with other comorbidities present in these patients [136, 137].

3.4 Topical Medications, Botulinum Toxin and Nerve Blocks in the Management of Neuropathic Orofacial Pains

In addition to management with oral systemic medications (Table 1), other pharmacological modalities can be implemented as adjunct topical therapy and in specific cases as monotherapy if there is a contraindication to systemic medications.

3.4.1 Topical Agents

Topical agents offer safety, lower side effect profile, and rapid onset of action [138–140]. They are very useful in the case of peripheral neuropathies where during neurosensory testing complete pain relief is reported using a topical anesthetic or local anesthetic block, as well as in cases of centralized neuropathies where during neurosensory

testing there is significant decrease in allodynia. Different compound formulations can be tailored for the patient and depending on the preparation and pain localization, they can be applied intraorally in the oral mucosa and extraorally in the skin as creams or patches. When they are indicated to be applied in the oral mucosa, a stent (neurosensory stent) is fabricated to help retain the topical agent in place covering the affected area [6]. Anesthetics such as lidocaine 5% and benzocaine 20% are commonly used intraorally as well as vanilloid agents such as capsaicin in a concentration of 0.025%–0.075%. When capsaicin is used, it needs to be used with caution as it can cause burning. Therefore, it is recommended that it is mixed with lidocaine or benzocaine to avoid this. Other preparations may include anticonvulsants (carbamazepine), tricyclic antidepressants (amitriptyline), antispasmodics (baclofen), NSAIDs (ketoprofen), N-methyl-D-aspartate (NMDA) antagonists (ketamine), and sympathomimetic agents (clonidine) [138, 139]. For BMS specifically, a clonazepam rinse, 0.5-mg/mL solution (5 mL) has been found beneficial [141, 142] (see Table 2).

3.4.2 Botulinum Toxin Type A Injection, Nerve and Sphenopalatine Ganglion Blocks

Evidence is growing supporting the use of botulinum toxin type A as an effective therapy approach for the management of TN and other trigeminal neuropathic pains [96, 143–145]. There is no current standardized protocol, but this approach could be used as adjunct therapy or monotherapy in some cases when oral systemic medications have not been effective or present poor tolerability. The injection approach could be extraoral as well as intraoral, localized in the area of trigger or pain. Approach, dosage units, and volumes vary [143, 146]. See Table 1.

3.4.3 Peripheral Nerve Blocks and Sphenopalatine Ganglion (SPG) Block

Peripheral nerve blocks are valuable as adjunct therapy in orofacial pain such as in the case of cranial neuralgias, and headache disorders. The most common anesthetic agents are lidocaine and bupivacaine in a variety of concentrations and volumes. Usually in clinical practice, nerve blocks are provided in infiltration series and based on the response of the first block. They include supratrochlear, supraorbital, infraorbital, auriculotemporal and greater occipital and lesser occipital injections [147–149]. In a retrospective study, occipital blocks were reported to be useful for trigeminal neuralgia and trigeminal neuropathic pain but not for persistent idiopathic facial pain [150]. This functional inhibition provided by the occipital nerve block on trigeminal nociceptive responses may be explained due to the converging of C2 and trigeminal inputs in the trigeminocervical complex before being processed in higher centers [151]. See Table 3 for summary.

Sphenopalatine ganglion (SPG) anesthetic block is useful in migraine and cluster headache and in some cases of facial pain such as trigeminal neuralgia [152–154]. Anesthesia of the SPG can be performed with a transnasal approach with topical application of local anesthesia to the mucosa of the lateral wall of the nasal cavity. This can be done with the use of an intranasal catheter or a long cotton-tipped applicator saturated with 4% lidocaine that is inserted intranasally [155].

Table 3 Common targets for peripheral nerve blocks in the management of orofacial pain

Sensory nerve/ganglion name	Nerve system	Description
Sphenopalatine ganglion	Parasympathetic: trigeminal sensory nerves (V2) and sympathetic fibers travel through but do not synapse within ganglion	Parasympathetic fibers provide secretomotor function to the lacrimal glands, nasal glands, palatine glands, and pharyngeal glands
Greater occipital nerve	C2	Cutaneous innervation of the upper neck, scalp
Lesser occipital nerve	C2 and C3	Cutaneous innervation of the lateral scalp, posterior to ear
Supraorbital nerve	V1	Cutaneous innervation of forehead, eyelid, conjunctiva of the upper eyelid, vertex, frontal sinus
Supratrochlear nerve	V1	Cutaneous innervation of the forehead, eyelid and conjunctiva
Infraorbital nerve	V2	Cutaneous innervation of the lower eyelid, medial cheek, upper lip, mucosa of the nasal septum and mucosa and vermilion of the upper lip
Auriculotemporal	V3	2 roots. The superior root carries sensory information from the auricle of the ear, external auditory meatus, part of tympanic membrane, cutaneous region of the temporal region and the TMJ

TMJ temporomandibular joint

3.5 Considerations for the Management of Neuropathic Orofacial Pains

Due to the different presentations and etiologies of neuropathic orofacial pain disorders, a careful diagnosis is critical. In addition, a combination of different management approaches may be implemented for the same individual in an effort to provide adequate pain relief. Some considerations for patients with trigeminal neuralgia and continuous trigeminal neuropathic pains are provided. These provide guidance and do not pretend to be exhaustive. Protocols may vary in different care provider settings.

3.5.1 Considerations for the Management of Trigeminal Neuralgia (TN)

Step 1

- TN may mimic dental pain; therefore, during differential diagnosis and more so if pain is localized intraorally, it is important to consider a dental examination and imaging to rule out possible odontogenic causes.
- Do not confuse TN with TMD. The symptomatology is different, however, patients with TN may also present myofascial pain as a secondary muscle co-contraction or protective muscle co-contraction in response to the paroxysm of TN pain.
- When odontogenic causes and TMD are ruled out, conduct brain imaging to identify if TN is classical, secondary, or idiopathic.
- Prepare a plan that includes pharmacological and non-pharmacological modalities. Consider consultation/referral with other health providers.

Step 2

- Start with carbamazepine or oxcarbazepine as first line. Screen for HLA-B*15:02 and HLA-A*31:01. Order laboratory tests: liver function test; complete (full) blood count (CBC) as baseline and to monitor during therapy with carbamazepine.
- Gabapentin (or pregabalin) may be chosen as an alternative in case of side effects as well as to prevent possible medication interactions that may exclude the use of carbamazepine.
- Alternatives to carbamazepine are to switch to oxcarbazepine or the addition of baclofen in cases when it is being effective but side effects arise.
- Trigger areas may benefit from adjunct therapy with the use of anesthetic blocks or botulinum toxin type A.

Step 3

- If no or inadequate pain relief, lamotrigine can be tried.
- Gabapentin, pregabalin, baclofen, lamotrigine and botulinum toxin should be considered as an addition or monotherapy.

Step 4

- If pain is refractory or side effects are intolerable after different trials of combination therapy, surgical options should be discussed.

3.5.2 Considerations for the Management of Continuous Trigeminal Neuropathic Pains

Step 1

- Establish the diagnosis. In the case of idiopathic or 'atypical' facial pains, diagnosis could be even more challenging. Include in your differential diagnosis possible musculoskeletal sources of pain such as TMD, inflammation of the stylohyoid ligament (eagle syndrome) and neurovascular sources, either orofacial pain resembling primary headache disorders or secondary headaches. In the case of possible BMS, carry out a thorough examination and medical history to rule out possible secondary sources.
- Prepare a plan that includes pharmacological and non-pharmacological modalities. Consider consultation/referral with other health providers.

Step 2

- Management can be initiated with first-line medications using TCA (e.g., amitriptyline, nortriptyline) or an SNRI (duloxetine, venlafaxine). Anticonvulsants such as gabapentin and pregabalin can also be used.
- In cases of BMS, initiate treatment with clonazepam rinse, TCA, or gabapentin. Symptomatology may require the use of more than one of these medications. If dry mouth due to the use of TCA is present, consider the use of venlafaxine.
- In cases of post-traumatic trigeminal neuropathy, if the patient reports continuous pain accompanied by paroxysms of sharp, shooting electrical pain, similar to TN, consider the use of anticonvulsants starting with calcium channel blockers.
- In cases of peripheral neuropathic pain/intraoral pain, consider the use of topical medication, anesthetic blocks and/or botulinum toxin A injection.
- During neurosensory testing, if the anesthetic block does not completely relieve the chief pain complaint (centralized) but a pain reduction is reported, the use of topical medications should be considered in the treatment plan as an adjunct therapy to oral pharmacology.
- The addition of more than one oral medication may be necessary for optimal management. Consider including anesthetic blocks and botulinum toxin A injections if side effects arise to provide substantial pain relief.

Step 3

- If pain relief is not optimal, consider the use anticonvulsants including carbamazepine, oxcarbazepine, or lamotrigine.

Step 4

- If trials of first-line medication, combination treatment, and adjunct therapy is still not optimal, consider referral to a multidisciplinary pain center for other management options.

4 Headache and Orofacial Pain

Patients with TMD can also report headache symptomatology, with dull, aching, sore, or tension-type pain in the head region. This pain is aggravated by TMJ biomechanics and/or parafunctional habits such as clenching or grinding. The ICHD-3 categorizes this type of head pain as headache secondary to TMD [92]. This headache may be ipsilateral to the area of TMD symptomatology or bilateral and may also refer to the temple area. TMD and primary headache disorders, particularly migraine and chronic daily headache, can be comorbid [156, 157], in that they are more likely than chance to occur together. The shared anatomical and physiological relationship of the craniofacial structures are likely a factor in this comorbidity; both are mediated by the trigeminal nociceptive system. However, calcitonin gene-related peptide (CGRP), a neuropeptide thought to be integral to migraine mechanisms and an established therapeutic target, is also involved in TMD pathogenesis and may be a potential therapeutic target [158–160]. Lastly, the presence of TMD, particularly chronic TMD, in migraine patients is a significant risk factor to accelerate progression to chronic migraine [161]. A further concern is that the presence of TMD in migraine patients significantly impacts migraine therapeutic management, making it much more challenging [157, 162–166]. Current recommendations are for each disorder to be managed simultaneously [25, 159, 167]. However, perhaps in the future for certain cases, protocols targeting an overlapping mechanism, such as CGRP as a monotherapy, when this comorbidity is present, may offer an effective avenue for management [159].

Primary headache disorders are most commonly localized in the frontal, temporal, parietal, and occipital areas, behind the eye (V1 distribution) or the neck (C1–C2 distribution) [17, 92]. However, they can also be localized in the mid-facial region, classified as 'orofacial pains resembling presentations of primary headaches' [18]. It is known that stimulation of the dura mater can induce pain that resembles a migraine phenotype, not only in the ophthalmic division [168, 169], but through all three divisions of the trigeminal nerve [170, 171]. Moreover, the convergence of inputs in the trigeminocervical complex from all three trigeminal divisions, the upper cervical regions [172], as well as the trigeminal autonomic reflex and the interactions with higher centers, may explain this clinical presentation [173]. Orofacial pains that resemble characteristics and features of primary headache disorders may present a challenge during diagnosis and therefore management. This is especially the case when the clinician is not aware of this presentation. It is imperative during differential diagnosis, in addition to ruling out odontogenic and other types of musculoskeletal or neuropathic orofacial pains, that there is screening for red flags and potential sources of secondary headache disorders. Consultation and collaboration with neurology and headache medicine is essential.

Within the ICHD-3 there is mention of '*facial migraine*' under the subcategory of migraine without aura [92]. However, the ICOP provides a more thorough diagnostic criteria of '*orofacial pains resembling presentations of primary headache*', including orofacial migraine, tension type orofacial pain, trigeminal autonomic orofacial pain, and neurovascular orofacial pain [18]. For example, in the case of an orofacial migraine, the use of migraine therapeutics will be indicated, and in the case of paroxysmal hemifacial pain (trigeminal autonomic orofacial pain), a response with therapeutic doses of indomethacin is indicated to confirm diagnosis and for management.

Migraine management involves pharmacotherapy including medications, nerve blocks, and the onabotulinum toxin A protocol for chronic migraine, as well as non-pharmacological approaches that include neuromodulatory devices and behavioral approaches. More comprehensive discussions about headache therapeutics can be found elsewhere, including consensus updates for integrating newer migraine treatments provided by the American Headache Society [174–176], and summarized in Table 4 (acute treatments) and Table 5 (preventive treatments).

It is worth noting that this is an exciting new era in headache management with new specific medications that target CGRP and its receptor, as well as non-pharmacological approaches such as non-invasive neuromodulation [174]. Alongside established acute treatment approaches, including NSAIDs, over-the-counter analgesics, and triptans, there are the newer small molecule CGRP receptor antagonists, gepants, including rimegepant, ubrogepant [177], and the newly approved nasal spray, zavegepant [178]. Lasmiditan, a 5HT-1F receptor agonist, is also approved for the acute management of migraine [177]. There are four approved monoclonal antibodies for migraine prevention that directly target CGRP (fremanezumab, eptinezumab, and galcanezumb) or the CGRP receptor complex (erenumab) [179]. Two gepants (atogepant and rimegepant) are also now approved for the prevention of episodic migraine [180]. For treatment options for tension-type headache and trigeminal autonomic

Table 4 Commonly used acute migraine treatments [208–211]

Medication class	Treatment	Dose range	Adverse effects
Initial therapy			
Oral NSAIDs	Aspirin	500–900 mg	Esophageal or gastric irritation
	Diclofenac	50–100 mg	
	Ibuprofen	200–800 mg	
	Naproxen	500 mg–1 g	
	Tolfenamic acid	200 mg	
	Ketorolac	30–60 mg	
OTC analgesics	Acetaminophen (if NSAIDs are contraindicated)	500–1000 mg	
Combination	Acetaminophen/aspirin/caffeine	500/500/130 mg	Esophageal or gastric irritation
Failed NSAIDs/analgesic (≥3 consecutive attacks with no/insufficient response)			
Triptans (po)	Sumatriptan	50–100 mg	Warmth, tightness, discomfort in torso, head and neck, sedation, nausea (DHE) Arterial ischemia in patients with coronary disease (rare)
	Rizatriptan	5–10 mg	
	Almotriptan	6.25–12.5 mg	
	Eletriptan	20–40 mg	
	Zolmitriptan	2.5–5 mg	
	Naratriptan	1–2.5 mg	
Slower effect	Frovatriptan	2.5 mg	
	Dihydroergotamine (DHE)	0.5–2 mg nasal spray	
Ergot derivatives Headache recurrence	Combination triptan/NSAID (sumatriptan + naproxen)	85 mg/500 mg	
Insufficient response to triptans (≥3 consecutive attacks with no/insufficient response to all triptans (plus naproxen)			
Gepants (po)	Rimegepant	75 mg	Dry mouth, dizziness
	Ubrogepant	50–100 mg	
	Zavegepant (nasal spray)	10 mg	
Ditans (po)	Lasmiditan	50–200 mg	Sedation, dizziness, impaired driving for 8 hours
Non-pharmacological options			
Neuromodulation	Single-pulse transcranial magnetic stimulation (sTMS) Non-invasive vagus nerve stimulation (nVNS) Remote electrical neurostimulation (RENs) Trigeminal nerve stimulation (TNS)		All devices report local discomfort. TMS, (dizziness), VNS (hoarseness), TNS (sedation)

Ditans 5-HT1F receptor agonists, *Gepants* small molecule CGRP receptor antagonists, *NSAIDs* non-steroidal anti-inflammatory drugs, *OTC* over-the-counter, *Triptans* 5-HT1B/1D receptor agonists, *po* oral

cephalalgias, readers are referred to these detailed review papers [181, 182].

5 General Pearls in Orofacial Pain Management

5.1 Comprehensive Medical History

Obtaining a complete description of the pain (onset, frequency, duration, quality, and intensity) is necessary in the diagnostic process in order to determine etiology and subsequently in the treatment planning process. Pain associated with function and TMJ biomechanics may indicate the possibility of a TMD, pain associated with migrainous symptoms or autonomic phenomena may indicate the possibility of an orofacial migraine or trigeminal autonomic orofacial pain. A history of persistent dental pain, history of trauma, vesicles indicating probable viral origin (PHN), and systemic symptoms indicating possible rheumatologic disease or a neurologic demyelinating process will be crucial in directing the provider to the appropriate diagnostic tests to order, and to determine which tests are not necessary.

Table 5 Preventive migraine treatments [208–212]

Treatment	Dose	Adverse events
β-blockers – FDA approved		
Propranolol	40–100 mg, bid	Reduced energy, tiredness, hypotension, postural symptoms. Contraindicated in asthma
Metoprolol	25–100 mg, bid	
Timolol	10–30 mg	
Anticonvulsants – FDA approved		
Valproate (valproic acid)	400–600 mg, bid	Drowsiness, weight gain, tremor, hair loss, teratogenicity, hematological/liver abnormalities, teratogenicity
Topiramate	50–200 mg, qd	Paresthesia, cognitive dysfunction, weight loss, taste perversion, angle closure glaucoma, teratogenicity
Anti-depressants – FDA approved		
Amitriptyline	25–75 mg, qd	Drowsiness, dry mouth, urinary retention, tachycardia, weight gain
Nortriptyline	25–75 mg, qd	
Venlafaxine	75–150 mg, qd	As above, plus erectile dysfunction, nausea, insomnia, tremor
CGRP and CGRP receptor monoclonal antibodies – FDA approved		
Eptinezumab	100 mg or 300 mg (IV) quarterly	All: injection site irritation, brief upper respiratory infection-like symptoms Erenumab: constipation, elevated blood pressure
Fremanezumab	225 mg monthly or 675 mg (SC) quarterly	
Galcanezumab (all CGRP mAbs)	240 mg (SC) loading dose then 120 mg monthly)	
Erenumab (CGRP receptor mAb)	70 mg or 140 mg (SC) monthly	
Small molecule CGRP receptor antagonists		
Rimegepant	75 mg, alt daily (every other day)	Dry mouth, dizziness
Atogepant	10 mg, 30 mg or 60 mg, daily	Nausea, constipation, and fatigue/somnolence
Botulinum toxin – FDA approved only for the prevention of chronic migraine		
Botulinum toxin	*Onabotulinumtoxin type A (155 U every 12 weeks)	Loss of brow furrow, neck pain
Angiotensin receptor blockers – use supported by at least one placebo-controlled RCT		
Candesartan	16 mg, qd	Dizziness, hypotension
Lisinopril	10–20 mg, qd	
Nutraceuticals – use supported by at least one placebo-controlled RCT		
Riboflavin (vitamin B2)	400 mg, qd	Orange urine
Coenzyme Q10	100 mg, tid	Gastrointestinal upset
Butterbur	50–75 mg, bid	Elevation of transaminases
Magnesium	400–800 mg	Gastrointestinal upset
Melatonin	3 mg at night	Morning tiredness
Neuromodulatory devices – with FDA clearance		
Single-pulse transcranial magnetic stimulation (sTMS)		Dizziness (sTMS), tinnitus, tingling, scalp irritation, local pain
Non-invasive vagus nerve stimulation (nVNS)		Lip/facial twitching, local neck/throat pain, hoarseness
Trigeminal nerve stimulation (TNS)		Drowsiness, uncomfortable scalp feeling
Remote electrical neurostimulation (RENs)		Local discomfort

bid twice daily, *CGRP* calcitonin gene-related peptide, *FDA* US Food and Drug Administration, *IV* intravenous, *OTC* over the counter, *PO* orally, *qd* once daily, *RCT* randomized controlled trial, *SC* subcutaneous, *tid* three times daily

5.2 Performing a Thorough Clinical Exam

The clinical exam serves to help the provider rule out secondary pathology as well as to identify the source of pain, pattern of referral, location of the symptoms and trigger zones. With the identification of trigger zones, incorporating topical management strategies can improve pain symptoms with minimal adverse effects. Diagnostic testing with trigger point injections, in cases of suspicious dental pains when dental pathology has been ruled out, is a great resource to identify possible myofascial pain and muscular source. In addition, for neuropathic pains, diagnostic testing with peripheral nerve blocks from topical anesthetics, local infiltration, and regional blocks will be invaluable in determining whether the symptoms are able to be modulated through peripheral versus systemic treatment modalities, or whether both should be considered.

5.3 Medication Interactions, Dosages, Titrating, and Tapering

Oral medications are considered first-line management. Review medical history for possible contraindications and interactions. Antidepressants or anticonvulsants are typically used for the management of primary neuropathic pain. However, these can also cause adverse effects and synergistic effects with other medications including serotonin syndrome. Medications may interact with current medications that can have an additive effect in terms of side effects. With tricyclic antidepressants, cardiac toxicity is a concern, and should be used with caution in patients with ischemic cardiac disease or ventricular conduction abnormalities. With the gabapentinoids, dosage reduction is recommended in patients with renal insufficiency, and dosage adjustments can be made in relation to creatinine clearance. It is recommended to titrate slowly to avoid the abrupt appearance of side effects. Increase dose until sufficient pain relief is attained, or intolerable side effects appear. While tapering dose, decrease the dosage to the lowest effective dose where the patient experiences pain relief or where intolerable side effects disappear, or tolerable side effects are present [105].

5.4 Pregnancy

Our knowledge about the impact of medications for the management of orofacial pain and headache during pregnancy is limited, and the use of topical medications and local anesthetic blocks should be considered. When a CNS-acting drug is used during pregnancy, careful follow-up during pregnancy and after childbirth is required. It is important to have a conversation with the patient about pregnancy plans and to establish a plan with the patient and other care providers. Regarding TMD, the use of acetaminophen as an analgesic is safe but non-pharmacological approaches in the management plan may be the focus to optimize care. For neuropathic pains, folic acid supplements are recommended from the prenatal stage for mothers using some antiepileptics to diminish the risk of neural tube defects [183]. The first trimester should be a period with minimum drug exposure if possible. Medications should be used at the minimum effective dose and monotherapy is preferable [184]. For headache management, triptans are considered safe, and the use of magnesium as well as neuromodulation devices can be added to the toolbox care of the patient [185, 186].

5.5 Team-Based Approach to Management

Patients seeking OFP care often have multiple comorbid health conditions that impact their prognosis. These include, but are not limited to, depression and anxiety, sleep disorders, and chronic overlapping pain conditions [10, 16, 33, 187–189]. In addition, in case of headache disorders or the possibility of red flags and secondary headache sources, it is essential to consult with neurology/headache medicine specialists. Therefore, optimal care necessitates a multidisciplinary management approach tailored to the individual patient [190] with a team of healthcare professionals. Modalities used in the management of neuropathic pain involve medications, interventions including somatic nerve blocks, autonomic nerve blocks (sphenopalatine and stellate ganglion), neuroablative procedures, surgical options (neurectomy), injection of botulinum toxin, and psychological management. When a multimodal approach is necessary, referral for evaluation and treatment to other providers should be made for optimal patient outcomes and improvement in quality of life.

6 Discussion

Orofacial pain disorders comprise a vast array of disorders with different etiologies and pathophysiological mechanisms supporting their complexity. These together with the interrelated anatomy and physiology of the craniofacial and cervical structures, may pose a challenge in diagnosis. In particular, when pain mimics dental pain or is localized intraorally, there is a risk of misdiagnosis followed by unnecessary dental procedures in efforts to relieve symptomatology. In order to diagnose and manage these disorders, specialty care by an orofacial pain specialist is required. In the United States, orofacial pain is a newly recognized dental specialty that

focuses on the evaluation, diagnosis, and evidence-based management of these complex disorders bridging the domains of dentistry and medicine.

Furthermore, after a correct diagnosis, these complex conditions may still be challenging to manage. It has been reported that pharmacological management may require different trials of medication protocols until a plan is built depending on the diagnosis and may include systemic and topical medications, trigger point injections, and nerve blocks. In addition to pharmacological management, the focus of this review, non-pharmacological approaches and a multidisciplinary team of care is essential, underscoring the importance of the biopsychosocial model of care [2].

The biopsychosocial framework assesses the multilayered interplay between a person's biological, psychological, and social health and how this may influence both the perception of, and response to, pain [191]. In the context of a biopsychosocial stratified care approach, a variety of therapeutic categories should be considered to target modifiable contributory factors. This approach may be chosen if a patient's pain is high impact and causes severe functional limitations, as it has been shown to produce better clinical outcomes and reduced disability [192].

Self-management approaches are particularly useful in TMD, and may include patient education, jaw relaxation and habit reversal, sleep optimization, healthy nutrition intake, physical activity, and breathing techniques [193, 194]. Oral parafunctional activities such as clenching or grinding the teeth, protruding or pressing the tongue to the palate, mandibular posturing, or other masticatory overuse activities, such as chewing gum, pose a physiologic risk to the trigeminal system and may increase the risk of head or face pain in a vulnerable individual [13, 195]. Therefore, modifying these habits and teaching jaw posture relaxation may play an essential role in recovery [196]. The use of oral appliances such as stabilization appliances can be utilized as part of the management plan even though RTC and systematic reviews have brought into question their efficacy, but other studies have shown favorable results improving myogenous and arthrogenous symptomatology [197].

Cognitive behavioral therapy (CBT) has been shown to be effective for several OFP conditions and should be strongly considered as part of the management strategy [198]. In addition, complementary modalities, such as acupuncture therapy, has demonstrated benefit for chronic pain in a large meta-analysis assessing over 20,000 patients [199], including showing benefit for some OFP patients [200–202]. As many studies question whether acupuncture benefit is derived from the procedure itself or a non-specific effect, further well-designed studies should explore the value of acupuncture in orofacial pain patients, but its safe and conservative nature warrant consideration as part of a management strategy.

New pharmacological and non-pharmacological approaches in the field of orofacial pain are greatly needed. Often, reaching the effective therapeutic dosage of pain control may originate the appearance of side effects, presenting the dilemma of relieving the pain that is affecting the quality of life of the patient with medications that also may greatly impact this quality. Efforts in understanding pain modulation and neuroplasticity in orofacial pain disorders in addition to identifying new and safer targets for management are essential. In particular, research that focuses exclusively on trigeminal neuropathic pains is needed since current therapeutic options are not optimal. CGRP is a neuropeptide involved in peripheral and central sensitization in the nervous system and a current therapeutic target for migraine that has shown not only efficacy, but safety [203]. Promising clinical research efforts are being geared towards exploring targeting CGRP as a management approach for OFP since evidence suggests that CGRP also has a role in TMD pathophysiology [158], as well as in trigeminal neuropathic pains [204]. Moreover, the use of LDN, a semisynthetic opioid that in higher dosages functions as an opioid antagonist, but in very low dosages (0.1–5 mg) acts as a glial modulator through the Toll-like receptor 4 (TLR4), has shown to induce antinociceptive and anti-inflammatory actions with a relatively low side effect profile [205, 206]. LDN may also be a promising new therapeutic approach for the management of chronic orofacial pain as is indicated by a couple of case reports supporting its use in BMS [136, 137, 206]. Further exploration of LDN, CGRP therapeutics, and the discovery of new potential targets in addition to other modalities of management for orofacial pain disorders, is greatly needed.

7 Conclusion

Orofacial pain disorders can be challenging to diagnose and manage. The orofacial pain specialist is trained to diagnose and manage these conditions. Pharmacological and non-pharmacological management in a multidisciplinary manner is the best approach to care for patients with these conditions. Research efforts on novel and safer pharmacotherapeutic targets for OFP management are essential to offer better care of this patient population.

Declarations

Funding No source of funding or financial assistance was used or received for the development of this manuscript.

Conflicts of Interest/Competing Interests Dr Marcela Romero: Reports personal fees and/or grant support from Amgen, Kallyope and the AHS unrelated to this work. Dr Sherwin Arman: There are no financial or non-financial interests to disclose relevant to this manuscript submitted for publication. Dr Antonia Teruel: There are no financial or non-financial interests to disclose relevant to this manuscript submitted for publication. Dr Satish Kumar: There are no financial or non-financial interests to disclose relevant to this manuscript submitted for publication. Dr James Hawkins: Government Disclaimer: The views in this article reflect the results of research conducted by the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, Uniformed Services University of the Health Sciences, nor the US Government. "I am a military service member or federal/contracted employee of the United States government. This work was prepared as part of my official duties. Title 17 U.S.C. 105 provides that 'copyright protection under this title is not available for any work of the United States Government.' Title 17 U.S.C. 101 defines a U.S. Government work as work prepared by a military service member or employee of the U.S. Government as part of that person's official duties." Neither I nor any member of my family have a financial arrangement or affiliation with any corporate organization offering financial support or grant monies for this research, nor do I have a financial interest in any commercial product(s) or service(s) I will discuss in the presentation or publication. Dr Simon Akerman: Reports personal fees and/or grant support from Amgen, Kallyope, at the AAOP, unrelated to this work.

Ethics Approval Not applicable.

Consent (Participation & Publication) Not applicable.

Author Contributions M.R.R. Developed the conception and design of the paper and led contribution in all sections. Led literature review and final review of all the sections with support and contribution from S.A. A.T, S.K, J.H and S.AK; S.A. contributed and assisted in developing the section of trigeminal neuropathic pains and tables; A.T., S.K developed section on TMD; J.H. contributed to section on TMD and non-pharmacological approaches integrated in discussion. S.AK. contributed to headache section and tables. All authors contributed to development of the clinical considerations and pearls.

Data Availability Statement Not applicable.

Code Availability Not applicable.

References

1. Klasser G, Romero-Reyes M. Orofacial pain guidelines for assessment, diagnosis, and management. 7th ed. Quintessence Publishing; 2023.
2. Haviv Y, Zini A, Etzioni Y, Klitinich V, Dobriyan A, Sharav Y, et al. The impact of chronic orofacial pain on daily life: the vulnerable patient and disruptive pain. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;123(1):58–66.
3. McMillan AS, Wong MC, Zheng J, Lam CL. Prevalence of orofacial pain and treatment seeking in Hong Kong Chinese. J Orofacial Pain Summer. 2006;20(3):218–25.
4. Lipton J, Ship J, Larach-Robinson D. Estimated prevalence and distribution of reported orofacial pain in the United States. J Am Dental Assoc. 1993;124(10):115–21 (**1993 October 1**).
5. Macfarlane TV, Blinkhorn AS, Davies RM, Kincey J, Worthington HV. Oro-facial pain in the community: prevalence and associated impact. Commun Dent Oral Epidemiol. 2002;30(1):52–60.
6. Romero-Reyes M, Uyanik JM. Orofacial pain management: current perspectives. J Pain Res. 2014;7:99–115.
7. Heir GM, Ananthan S, Kalladka M, Kuchukulla M, Renton T. Persistent idiopathic dentoalveolar pain: Is it a central pain disorder? Dental Clin North Am. 2023;67(1):71–83.
8. Tan HL, Smith JG, Hoffmann J, Renton T. A systematic review of treatment for patients with burning mouth syndrome. Cephalalgia. 2022;42(2):128–61.
9. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Diatchenko L, Dubner R, et al. Psychological factors associated with development of TMD: the OPPERA prospective cohort study. J Pain. 2013;14(12 Suppl):T75–90.
10. Fillingim RB, Slade GD, Greenspan JD, Dubner R, Maixner W, Bair E, et al. Long-term changes in biopsychosocial characteristics related to temporomandibular disorder: findings from the OPPERA study. Pain. 2018;159(11):2403–13.
11. Facial Pain. National Institute of Dental and Craniofacial Research 2018 July, 2018; Available from: http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/FacialPain/
12. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet J-P, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group. J Oral Facial Pain Headache. 2014;28(1):6–27.
13. Slade GD, Ohrbach R, Greenspan JD, Fillingim RB, Bair E, Sanders AE, et al. Painful temporomandibular disorder: decade of discovery from OPPERA studies. J Dent Res. 2016;95(10):1084–92.
14. Glaros AG, Burton E. Parafunctional clenching, pain, and effort in temporomandibular disorders. J Behav Med. 2004;27(1):91–100.
15. Glaros AG, Forbes M, Shanker J, Glass EG. Effect of parafunctional clenching on temporomandibular disorder pain and proprioceptive awareness. Cranio. 2000;18(3):198–204.
16. Ohrbach R, Fillingim RB, Mulkey F, Gonzalez Y, Gordon S, Gremillion H, et al. Clinical findings and pain symptoms as potential risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 2011;12(11 Suppl):T27–45.
17. Teruel A, Romero-Reyes M. Interplay of oral, mandibular, and facial disorders and migraine. Curr Pain Headache Rep. 2022. https://doi.org/10.1007/s11916-022-01054-6.
18. International Classification of Orofacial Pain. 1st edition (ICOP). Cephalalgia. 2020;40(2):129–221.
19. Kuć J, Szarejko KD, Gołębiewska M. The prevalence and overlaps of temporomandibular disorders in patients with myofascial pain with referral—a pilot study. Int J Environ Res Public Health. 2021;18(18):9842.
20. Golanska P, Saczuk K, Domarecka M, Kuć J, Lukomska-Szymanska M. Temporomandibular myofascial pain syndrome-aetiology and biopsychosocial modulation. A narrative review. Int J Environ Res Public Health. 2021;18(15):7807.
21. Liu F, Steinkeler A. Epidemiology, diagnosis, and treatment of temporomandibular disorders. Dent Clin North Am. 2013;57(3):465–79.
22. Valesan LF, Da-Cas CD, Réus JC, Denardin ACS, Garanhani RR, Bonotto D, et al. Prevalence of temporomandibular joint disorders: a systematic review and meta-analysis. Clin Oral Invest. 2021;25(2):441–53.
23. Okeson JP. Management of temporomandibular disorders and occlusion-E-book. Elsevier Health Sciences; 2019.
24. Kleykamp BA, Ferguson MC, McNicol E, Bixho I, Arnold LM, Edwards RR, et al. The prevalence of comorbid chronic pain

conditions among patients with temporomandibular disorders: a systematic review. J Am Dent Assoc. 2022;153(3):241–50 (**e10**).
25. Franco AL, Goncalves DA, Castanharo SM, Speciali JG, Bigal ME, Camparis CM. Migraine is the most prevalent primary headache in individuals with temporomandibular disorders. J Orofacial Pain. 2011;24(3):287–92.
26. Thomas DC, Khan J, Manfredini D, Ailani J. Temporomandibular joint disorder comorbidities. Dent Clin North Am. 2023;67(2):379–92.
27. Karamat A, Smith JG, Melek LNF, Renton T. Psychologic impact of chronic orofacial pain: a critical review. J Oral Facial Pain Headache. 2022;36(2):103–40.
28. Reis PHF, Laxe LAC, Lacerda-Santos R, Münchow EA. Distribution of anxiety and depression among different subtypes of temporomandibular disorder: a systematic review and meta-analysis. J Oral Rehabil. 2022;49(7):754–67.
29. De Leeuw RaK GD. Orofacial pain guidelines for assessment, diagnosis, and managment. 6th ed. Chicago: Quintessence Books; 2018.
30. Ohrbach R, Dworkin SF. Five-year outcomes in TMD: relationship of changes in pain to changes in physical and psychological variables. Pain. 1998;74(2–3):315–26.
31. Kandasamy S, Greene CS. The evolution of temporomandibular disorders: a shift from experience to evidence. J Oral Pathol Med. 2020;49(6):461–9.
32. Noma N, Watanabe Y, Shimada A, Usuda S, Iida T, Shimada A, et al. Effects of cognitive behavioral therapy on orofacial pain conditions. J Oral Sci. 2021;63(1):4–7.
33. Bair E, Gaynor S, Slade GD, Ohrbach R, Fillingim RB, Greenspan JD, et al. Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study. Pain. 2016;157(6):1266–78.
34. Van Bellinghen X, Idoux-Gillet Y, Pugliano M, Strub M, Bornert F, Clauss F, et al. Temporomandibular joint regenerative medicine. Int J Mol Sci. 2018;19(2):446. https://doi.org/10.3390/ijms19020446. PMID: 29393880; PMCID: PMC5855668.
35. Montinaro F, Nucci L, d'Apuzzo F, Perillo L, Chiarenza MC, Grassia V. Oral nonsteroidal anti-inflammatory drugs as treatment of joint and muscle pain in temporomandibular disorders: a systematic review. Cranio. 2022;7:1–10.
36. Kulkarni S, Thambar S, Arora H. Evaluating the effectiveness of nonsteroidal anti-inflammatory drug(s) for relief of pain associated with temporomandibular joint disorders: a systematic review. Clin Exp Dental Res. 2020;6(1):134–46.
37. Ta LE, Dionne RA. Treatment of painful temporomandibular joints with a cyclooxygenase-2 inhibitor: a randomized placebo-controlled comparison of celecoxib to naproxen. Pain. 2004;111(1–2):13–21.
38. Andre A, Kang J, Dym H. Pharmacologic treatment for temporomandibular and temporomandibular joint disorders. Oral Maxillofac Surg Clin North Am. 2022;34(1):49–59.
39. Häggman-Henrikson B, Alstergren P, Davidson T, Högestätt ED, Östlund P, Tranaeus S, et al. Pharmacological treatment of oro-facial pain—health technology assessment including a systematic review with network meta-analysis. J Oral Rehabil. 2017;44(10):800–26.
40. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004;28(2):140–75.
41. Herman CR, Schiffman EL, Look JO, Rindal DB. The effectiveness of adding pharmacologic treatment with clonazepam or cyclobenzaprine to patient education and self-care for the treatment of jaw pain upon awakening: a randomized clinical trial. J Orofacial Pain. 2002;16(1):64–70.
42. Rizzatti-Barbosa CM, Nogueira MT, de Andrade ED, Ambrosano GM, de Barbosa JR. Clinical evaluation of amitriptyline for the control of chronic pain caused by temporomandibular joint disorders. Cranio. 2003;21(3):221–5.
43. Kimos P, Biggs C, Mah J, Heo G, Rashiq S, Thie NM, et al. Analgesic action of gabapentin on chronic pain in the masticatory muscles: a randomized controlled trial. Pain. 2007;127(1–2):151–60.
44. Haviv Y, Rettman A, Aframian D, Sharav Y, Benoliel R. Myofascial pain: an open study on the pharmacotherapeutic response to stepped treatment with tricyclic antidepressants and gabapentin. J Oral Facial Pain Headache. 2015;29(2):144–51.
45. Müggenborg F, de Castro Carletti EM, Dennett L, de Oliveira-Souza AIS, Mohamad N, Licht G, et al. Effectiveness of manual trigger point therapy in patients with myofascial trigger points in the orofacial region-a systematic review. Life (Basel, Switzerland). 2023;13(2):336.
46. Machado E, Machado P, Wandscher VF, Marchionatti AME, Zanatta FB, Kaizer OB. A systematic review of different substance injection and dry needling for treatment of temporomandibular myofascial pain. Int J Oral Maxillofac Surg. 2018;47(11):1420–32.
47. Nouged E, Dajani J, Ku B, Al-Eryani K, Padilla M, Enciso R. Local anesthetic injections for the short-term treatment of head and neck myofascial pain syndrome: a systematic review with meta-analysis. J Oral Facial Pain Headache. 2019;33(2):183–98.
48. Tough EA, White AR, Cummings TM, Richards SH, Campbell JL. Acupuncture and dry needling in the management of myofascial trigger point pain: a systematic review and meta-analysis of randomised controlled trials. Eur J Pain. 2009;13(1):3–10.
49. Blumenfeld AM, Stark RJ, Freeman MC, Orejudos A, Manack AA. Long-term study of the efficacy and safety of OnabotulinumtoxinA for the prevention of chronic migraine: COMPEL study. J Headache Pain. 2018;19(1):13.
50. Awan KH, Patil S, Alamir AWH, Maddur N, Arakeri G, Carrozzo M, et al. Botulinum toxin in the management of myofascial pain associated with temporomandibular dysfunction. J Oral Pathol Med. 2019;48(3):192–200.
51. Delcanho R, Val M, Guarda Nardini L, Manfredini D. Botulinum toxin for treating temporomandibular disorders: What is the evidence? J Oral Facial Pain Headache. 2022;36(1):6–20.
52. Connelly ST, Myung J, Gupta R, Tartaglia GM, Gizdulich A, Yang J, et al. Clinical outcomes of Botox injections for chronic temporomandibular disorders: do we understand how Botox works on muscle, pain, and the brain? Int J Oral Maxillofac Surg. 2017;46(3):322–7.
53. Muñoz Lora VRM, Del Bel Cury AA, Jabbari B, Lacković Z. Botulinum toxin type A in dental medicine. J Dent Res. 2019;98(13):1450–7.
54. Wehling P, Evans C, Wehling J, Maixner W. Effectiveness of intra-articular therapies in osteoarthritis: a literature review. Therapeutic Adv Musculoskelet Dis. 2017;9(8):183–96.
55. Clark GT, Dionne RA. Orofacial pain: a guide to medications and management; 2013.
56. Gencer ZK, Özkiriş M, Okur A, Korkmaz M, Saydam L. A comparative study on the impact of intra-articular injections of hyaluronic acid, tenoxicam and betametazon on the relief of temporomandibular joint disorder complaints. J Cranio-Maxillo-Facial Surg. 2014;42(7):1117–21.
57. de Souza RF, Lovato da Silva CH, Nasser M, Fedorowicz Z, Al-Muharraqi MA. Interventions for the management of temporomandibular joint osteoarthritis. Cochrane Database Syst Rev. 2012;2012(4): Cd007261.

58. Isacsson G, Schumann M, Nohlert E, Mejersjö C, Tegelberg Å. Pain relief following a single-dose intra-articular injection of methylprednisolone in the temporomandibular joint arthralgia—a multicentre randomised controlled trial. J Oral Rehabil. 2019;46(1):5–13.
59. Yapici-Yavuz G, Şimşek-Kaya G, Oğul H. A comparison of the effects of Methylprednisolone Acetate, Sodium Hyaluronate and Tenoxicam in the treatment of non-reducing disc displacement of the temporomandibular joint. Medicina oral, patologia oral y cirugia bucal. 2018;23(3):e351–8.
60. Skármeta NP, Hormazábal FA, Alvarado J, Rodriguez AM. Subcutaneous lipoatrophy and skin depigmentation secondary to TMJ intra-articular corticosteroid injection. J Oral Maxillofac Surg. 2017;75(12):2540 (**e1-.e5**).
61. Schindler C, Paessler L, Eckelt U, Kirch W. Severe temporomandibular dysfunction and joint destruction after intra-articular injection of triamcinolone. J Oral Pathol Med. 2005;34(3):184–6.
62. Nitzan DW. The process of lubrication impairment and its involvement in temporomandibular joint disc displacement: a theoretical concept. J Oral Maxillofac Surg. 2001;59(1):36–45.
63. Guarda-Nardini L, Cadorin C, Frizziero A, Ferronato G, Manfredini D. Comparison of 2 hyaluronic acid drugs for the treatment of temporomandibular joint osteoarthritis. J Oral Maxillofac Surg. 2012;70(11):2522–30.
64. Iturriaga V, Bornhardt T, Manterola C, Brebi P. Effect of hyaluronic acid on the regulation of inflammatory mediators in osteoarthritis of the temporomandibular joint: a systematic review. Int J Oral Maxillofac Surg. 2017;46(5):590–5.
65. Korkmaz YT, Altıntas NY, Korkmaz FM, Candırlı C, Coskun U, Durmuslar MC. Is hyaluronic acid injection effective for the treatment of temporomandibular joint disc displacement with reduction? J Oral Maxillofac Surg. 2016;74(9):1728–40.
66. Fonseca R, Januzzi E, Ferreira LA, Grossmann E, Carvalho ACP, de Oliveira PG, et al. Effectiveness of sequential viscosupplementation in temporomandibular joint internal derangements and symptomatology: a case series. Pain Res Manage. 2018;2018:5392538.
67. Li C, Long X, Deng M, Li J, Cai H, Meng Q. Osteoarthritic changes after superior and inferior joint space injection of hyaluronic acid for the treatment of temporomandibular joint osteoarthritis with anterior disc displacement without reduction: a cone-beam computed tomographic evaluation. J Oral Maxillofac Surg. 2015;73(2):232–44.
68. Ferreira N, Masterson D, Lopes de Lima R, de Souza-Moura B, Oliveira AT, Kelly da Silvafidalgo T, et al. Efficacy of viscosupplementation with hyaluronic acid in temporomandibular disorders: a systematic review. J Cranio-Maxillo-Facial Surg. 2018;46(11):1943–52.
69. Dhillon MS, Behera P, Patel S, Shetty V. Orthobiologics and platelet rich plasma. Indian J Orthopaedics. 2014;48(1):1–9.
70. Zotti F, Albanese M, Rodella LF, Nocini PF. Platelet-rich plasma in treatment of temporomandibular joint dysfunctions: narrative review. Int J Mol Sci. 2019;20(2):277.
71. Bousnaki M, Bakopoulou A, Koidis P. Platelet-rich plasma for the therapeutic management of temporomandibular joint disorders: a systematic review. Int J Oral Maxillofac Surg. 2018;47(2):188–98.
72. Hegab AF, Ali HE, Elmasry M, Khallaf MG. Platelet-rich plasma injection as an effective treatment for temporomandibular joint osteoarthritis. J Oral Maxillofac Surg. 2015;73(9):1706–13.
73. Gokçe Kutuk S, Gökçe G, Arslan M, Özkan Y, Kütük M, Kursat AO. Clinical and radiological comparison of effects of platelet-rich plasma, hyaluronic acid, and corticosteroid injections on temporomandibular joint osteoarthritis. J Craniofac Surg. 2019;30(4):1144–8.
74. Hancı M, Karamese M, Tosun Z, Aktan TM, Duman S, Savaci N. Intra-articular platelet-rich plasma injection for the treatment of temporomandibular disorders and a comparison with arthrocentesis. J Cranio-Maxillo-Facial Surg. 2015;43(1):162–6.
75. Liapaki A, Thamm JR, Ha S, Monteiro J, McCain JP, Troulis MJ, et al. Is there a difference in treatment effect of different intra-articular drugs for temporomandibular joint osteoarthritis? A systematic review of randomized controlled trials. Int J Oral Maxillofac Surg. 2021;50(9):1233–43.
76. Zarate MA, Frusso RD, Reeves KD, Cheng AL, Rabago D. Dextrose prolotherapy versus lidocaine injection for temporomandibular dysfunction: a pragmatic randomized controlled trial. J Altern Complement Med. 2020;26(11):1064–73.
77. Sit RW, Reeves KD, Zhong CC, Wong CHL, Wang B, Chung VC, et al. Efficacy of hypertonic dextrose injection (prolotherapy) in temporomandibular joint dysfunction: a systematic review and meta-analysis. Sci Rep. 2021;11(1):14638.
78. Bouloux G, Koslin MG, Ness G, Shafer D. Temporomandibular joint surgery. J Oral Maxillofac Surg. 2017;75(8s):e195–223.
79. Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, et al. NeuPSIG guidelines on neuropathic pain assessment. Pain. 2011;152(1):14–27.
80. Eliav E MM. Management of neuropathic pain. In: Sessle B LG, Lund J, Dubner R, editors., editor. Orofacial pain From basic science to clinical management Chicago: Quintessence; 2008. p. 195–202.
81. Renton T. Persistent pain after dental surgery. Rev Pain. 2011;5(1):8–17.
82. Delcanho R, Moncada E. Persistent pain after dental implant placement: a case of implant-related nerve injury. J Am Dent Assoc. 2014;145(12):1268–71.
83. Mills EP, Keay KA, Henderson LA. brainstem pain-modulation circuitry and its plasticity in neuropathic pain: insights from human brain imaging investigations. Front Pain Res (Lausanne, Switzerland). 2021;2: 705345.
84. Sessle BJ. Chronic orofacial pain: models, mechanisms, and genetic and related environmental influences. Int J Mol Sci. 2021;22(13):7112.
85. Korczeniewska OA, Kohli D, Benoliel R, Baddireddy SM, Eliav E. Pathophysiology of post-traumatic trigeminal neuropathic pain. Biomolecules. 2022;12(12):1753.
86. Ossipov MH, Morimura K, Porreca F. Descending pain modulation and chronification of pain. Curr Opin Support Palliat Care. 2014;8(2):143–51.
87. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers. 2017;3(1):17002 (**2017/02/16**).
88. Penlington C, Araújo-Soares V, Durham J. Predicting persistent orofacial pain: the role of illness perceptions, anxiety, and depression. JDR Clin Transl Res. 2019;5(1):40–9 (**2017/02/16**).
89. Van der Cruyssen F, Peeters F, Gill T, De Laat A, Jacobs R, Politis C, et al. Signs and symptoms, quality of life and psychosocial data in 1331 post-traumatic trigeminal neuropathy patients seen in two tertiary referral centres in two countries. J Oral Rehabil. 2020;47(10):1212–21.
90. Ziegeler C, Brauns G, May A. Characteristics and natural disease history of persistent idiopathic facial pain, trigeminal neuralgia, and neuropathic facial pain. Headache. 2021;61(9):1441–2151.
91. Truelove E. Management is sues of neuropathic trigeminal pain from a dental perspective. J Orofac Pain. 2004;18(4):374–80.
92. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38(1):1–211.
93. McNicol ED, Midbari A, Eisenberg E. Opioids for neuropathic pain. Cochrane Database Syst Rev. 2013;2013(8): Cd006146.

94. Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpaa ML, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clinic Proc Mayo Clin. 2010;85(3 Suppl):S3-14.
95. Attal N. Pharmacological treatments of neuropathic pain: The latest recommendations. Rev Neurol (Paris). 2019;175(1–2):46–50.
96. Bendtsen L, Zakrzewska JM, Heinskou TB, Hodaie M, Leal PRL, Nurmikko T, et al. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. Lancet Neurol. 2020;19(9):784–96.
97. Koopman JS, Dieleman JP, Huygen FJ, de Mos M, Martin CG, Sturkenboom MC. Incidence of facial pain in the general population. Pain. 2009;147(1–3):122–7.
98. Araya EI, Claudino RF, Piovesan EJ, Chichorro JG. Trigeminal neuralgia: basic and clinical aspects. Curr Neuropharmacol. 2020;18(2):109–19.
99. VanderPluym J, Richer L. Tic versus TAC: differentiating the neuralgias (trigeminal neuralgia) from the cephalalgias (SUNCT and SUNA). Curr Pain Headache Rep. 2014;19(2):473 (**2014/12/11**).
100. Lambru G, Zakrzewska J, Matharu M. Trigeminal neuralgia: a practical guide. Pract Neurol. 2021;21(5):392–402.
101. Zakrzewska JM, Wu N, Lee JYK, Werneburg B, Hoffman D, Liu Y. Characterizing treatment utilization patterns for trigeminal neuralgia in the United States. Clin J Pain. 2018;34(8):691–9.
102. Zakrzewska JM. Medical management of trigeminal neuropathic pains. Expert Opin Pharmacother. 2010;11(8):1239–54.
103. Zhou M, Chen N, He L, Yang M, Zhu C, Wu F. Oxcarbazepine for neuropathic pain. Cochrane Database Syst Rev. 2017;12(12): Cd007963.
104. Wiffen PJ, Derry S, Moore RA, McQuay HJ. Carbamazepine for acute and chronic pain in adults. Cochrane Database Syst Rev. 2011;19(1): Cd005451.
105. Bendtsen L, Zakrzewska JM, Abbott J, Braschinsky M, Di Stefano G, Donnet A, et al. European Academy of Neurology guideline on trigeminal neuralgia. Eur J Neurol. 2019;26(6):831–49.
106. Moore D, Chong MS, Shetty A, Zakrzewska JM. A systematic review of rescue analgesic strategies in acute exacerbations of primary trigeminal neuralgia. Br J Anaesth. 2019;123(2):e385–96.
107. Wang QP, Bai M. Topiramate versus carbamazepine for the treatment of classical trigeminal neuralgia. CNS Drugs. 2011;25(10):847–57 (**2011/10/01**).
108. Anand KS, Dhikav V, Prasad A, Shewtengna. Efficacy, safety and tolerability of duloxetine in idiopathic trigeminal neuralgia. J Indian Med Assoc. 2011;109(4):264–6.
109. Obermann M. Update on the challenges of treating trigeminal neuralgia. Orphan Drug. 2015. https://doi.org/10.2147/ODRR.S53046.
110. Ferrell PB Jr, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008;9(10):1543–6.
111. Mushiroda T, Takahashi Y, Onuma T, Yamamoto Y, Kamei T, Hoshida T, et al. Association of HLA-A*31:01 screening with the incidence of carbamazepine-induced cutaneous adverse reactions in a Japanese population. JAMA Neurol. 2018;75(7):842–9.
112. Chen CB, Hsiao YH, Wu T, Hsih MS, Tassaneeyakul W, Jorns TP, et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. Neurology. 2017;88(1):78–86.
113. Xu R, Nair SK, Shah PP, Kannapadi N, Materi J, Alomari S, et al. A potential role for steroids in acute pain management in patients with trigeminal neuralgia. World Neurosurg. 2022;167:e1291–8.
114. Mauskop A. Trigeminal neuralgia (tic douloureux). J Pain Symptom Manage. 1993;8(3):148–54 (**1993/04/01/**).
115. DMKG study group. Misoprostol in the treatment of trigeminal neuralgia associated with multiple sclerosis. J Neurol. 2003;250(5):542–5. https://doi.org/10.1007/s00415-003-1032-1. PMID: 12736732.
116. Pfau G, Brinkers M, Treuheit T, Kretzschmar M, Sentürk M, Hachenberg T. Misoprostol as a therapeutic option for trigeminal neuralgia in patients with multiple sclerosis. Pain Med. 2012;13(10):1377–8.
117. Heinskou T, Maarbjerg S, Rochat P, Wolfram F, Jensen RH, Bendtsen L. Trigeminal neuralgia–a coherent cross-specialty management program. J Headache Pain. 2015;16:66.
118. Hadley GR, Gayle JA, Ripoll J, Jones MR, Argoff CE, Kaye RJ, et al. Post-herpetic neuralgia: a review. Curr Pain Headache Rep. 2016;20(3):17.
119. Truini A, Galeotti F, Haanpaa M, Zucchi R, Albanesi A, Biasiotta A, et al. Pathophysiology of pain in postherpetic neuralgia: a clinical and neurophysiological study. Pain. 2008;140(3):405–10.
120. Shrestha M, Chen A. Modalities in managing postherpetic neuralgia. Korean J Pain. 2018;31(4):235–43.
121. Gan EY, Tian EA, Tey HL. Management of herpes zoster and post-herpetic neuralgia. Am J Clin Dermatol. 2013;14(2):77–85.
122. Tay AB, Zuniga JR. Clinical characteristics of trigeminal nerve injury referrals to a university centre. Int J Oral Maxillofac Surg. 2007;36(10):922–7.
123. Neal TW, Zuniga JR. Post-traumatic trigeminal neuropathic pain: factors affecting surgical treatment outcomes. Front Oral Health. 2022;3: 904785.
124. Baad-Hansen L, Benoliel R. Neuropathic orofacial pain: facts and fiction. Cephalalgia. 2017;37(7):670–9.
125. Benoliel R, Kahn J, Eliav E. Peripheral painful traumatic trigeminal neuropathies. Oral Dis. 2012;18(4):317–32.
126. Lewis MAO, Sankar V, De Laat A, Benoliel R. Management of neuropathic orofacial pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endodontics. 2007;103:S32 (**e1-S.e24**).
127. Jia Z, Yu J, Zhao C, Ren H, Luo F. Outcomes and predictors of response of duloxetine for the treatment of persistent idiopathic dentoalveolar pain: a retrospective multicenter observational study. J Pain Res. 2022;15:3031–41.
128. Forssell H, Tasmuth T, Tenovuo O, Hampf G, Kalso E. Venlafaxine in the treatment of atypical facial pain: a randomized controlled trial. J Orofac Pain. 2004;18(2):131–7.
129. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;2015(7): Cd008242.
130. Clarkson E, Jung E. Atypical facial pain. Dental Clin North Am. 2020;64(1):249–53 (**2020/01/01/**).
131. Forssell H, Jääskeläinen S, List T, Svensson P, Baad-Hansen L. An update on pathophysiological mechanisms related to idiopathic oro-facial pain conditions with implications for management. J Oral Rehabil. 2015;42(4):300–22.
132. Koopman JSHA, Dieleman JP, Huygen FJ, de Mos M, Martin CGM, Sturkenboom MCJM. Incidence of facial pain in the general population. Pain. 2009;147(1-2–3):122–7.
133. Forssell H, Tenovuo O, Silvoniemi P, Jääskeläinen SK. Differences and similarities between atypical facial pain and trigeminal neuropathic pain. Neurology. 2007;69(14):1451–9.
134. Herrero Babiloni A, Nixdorf DR, Moana-Filho EJ. Persistent dentoalveolar pain disorder: a putative intraoral chronic overlapping pain condition. Oral Dis. 2020;26(8):1601–9.
135. Benoliel R, Gaul C. Persistent idiopathic facial pain. Cephalalgia. 2017;37(7):680–91 (**2017/06/01**).

136. Neuman DL, Chadwick AL. Utilization of low-dose naltrexone for burning mouth syndrome: a case report. A&A Practice. 2021;15(5): e01475.
137. Sangalli L, Miller CS. Low-dose naltrexone for treatment of burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol. 2023;135(4):e83–8 (**2023/04/01/**).
138. Padilla M, Clark GT, Merrill RL. Topical medications for orofacial neuropathic pain: a review. J Am Dent Assoc. 2000;131(2):184–95 (**2000 February 1**).
139. Heir GM, Katzmann G, Covalesky B, Cammarata J, Mangal J, Kalladka M, et al. Use of compounded topical medications for treatment of orofacial pain: a narrative review. J Oral Maxillofac Anesth. 2022;1. https://joma.amegroups.org/article/view/5773.
140. Casale R, Symeonidou Z, Bartolo M. Topical treatments for localized neuropathic pain. Curr Pain Headache Rep. 2017;21(3):15.
141. Rossella I, Alessandro V, Naman R, Gary K, Hervé SY. Topical clonazepam for burning mouth syndrome: Is it efficacious in patients with anxiety or depression? J Oral Rehabil. 2022;49(1):54–61.
142. Kuten-Shorrer M, Treister NS, Stock S, Kelley JM, Ji YD, Woo SB, et al. Topical clonazepam solution for the management of burning mouth syndrome: a retrospective study. J Oral Facial Pain Headache. 2017;31(3):257–63.
143. Dinan JE, Smith A, Hawkins JM. Trigeminal neuralgia with extraoral trigger zone successfully treated with intraoral injections of botulinum toxin: a case report. Clin Neuropharmacol. 2020;43(5):162–3.
144. Burmeister J, Holle D, Bock E, Ose C, Diener HC, Obermann M. Botulinum neurotoxin type A in the treatment of classical Trigeminal Neuralgia (BoTN): study protocol for a randomized controlled trial. Trials. 2015;3(16):550.
145. Wei J, Zhu X, Yang G, Shen J, Xie P, Zuo X, et al. The efficacy and safety of botulinum toxin type A in treatment of trigeminal neuralgia and peripheral neuropathic pain: a meta-analysis of randomized controlled trials. Brain and behavior. 2019;9(10): e01409.
146. Herrero Babiloni A, Kapos FP, Nixdorf DR. Intraoral administration of botulinum toxin for trigeminal neuropathic pain. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(6):e148–53.
147. Blumenfeld A, Ashkenazi A, Napchan U, Bender SD, Klein BC, Berliner R, et al. Expert consensus recommendations for the performance of peripheral nerve blocks for headaches–a narrative review. Headache. 2013;53(3):437–46.
148. Renton T, Beke A. A narrative review of therapeutic peripheral nerve blocks for chronic orofacial pain conditions. J Oral Facial Pain Headache. 2022;36(1):49–58.
149. Nardi NM, Alvarado AC, Schaefer TJ. Infraorbital Nerve Block. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2023, StatPearls Publishing LLC.; 2023.
150. Jurgens TP, Muller P, Seedorf H, Regelsberger J, May A. Occipital nerve block is effective in craniofacial neuralgias but not in idiopathic persistent facial pain. J Headache Pain. 2012;13(3):199–213.
151. Jan H, Jan M, Elena MK, Arne M. Greater occipital nerve block modulates nociceptive signals within the trigeminocervical complex. J Neurol Neurosurg Psychiatry. 2021;92(12):1335.
152. Robbins MS, Robertson CE, Kaplan E, Ailani J, Charleston L IV, Kuruvilla D, et al. The sphenopalatine ganglion: anatomy, pathophysiology, and therapeutic targeting in headache. Headache. 2016;56(2):240–58.
153. Mohamed B, Eman A-G, Eslam S, Ali A-H, Moiz B. Successful Treatment of Refractory Trigeminal Neuralgia with Sphenopalatine Ganglion Block (P2107). Neurology. 2018;90(15 Supplement):P2.107.
154. Kanai A, Suzuki A, Kobayashi M, Hoka S. Intranasal lidocaine 8% spray for second-division trigeminal neuralgia. Br J Anaesth. 2006;97(4):559–63.
155. Maizels M, Scott B, Cohen W, Chen W. Intranasal lidocaine for treatment of migraine: a randomized, double-blind, controlled trial. JAMA. 1996;276(4):319–21.
156. Gonçalves DA, Speciali JG, Jales LC, Camparis CM, Bigal ME. Temporomandibular symptoms, migraine, and chronic daily headaches in the population. Neurology. 2009;73(8):645–6.
157. Goncalves DA, Bigal ME, Jales LC, Camparis CM, Speciali JG. Headache and symptoms of temporomandibular disorder: an epidemiological study. Headache. 2010;50(2):231–41.
158. Romero-Reyes M, Pardi V, Akerman S. A potent and selective calcitonin gene-related peptide (CGRP) receptor antagonist, MK-8825, inhibits responses to nociceptive trigeminal activation: role of CGRP in orofacial pain. Exp Neurol. 2015;271:95–103.
159. Akerman S, Romero-Reyes M. Preclinical studies investigating the neural mechanisms involved in the co-morbidity of migraine and temporomandibular disorders: the role of CGRP. Br J Pharmacol. 2020;177(24):5555–68. https://doi.org/10.1111/bph.15263. Epub 2020 Oct 21. PMID: 32929719; PMCID: PMC7707098.
160. Cady RJ, Glenn JR, Smith KM, Durham PL. Calcitonin gene-related peptide promotes cellular changes in trigeminal neurons and glia implicated in peripheral and central sensitization. Mol Pain. 2011;7:94.
161. Bevilaqua Grossi D, Lipton RB, Bigal ME. Temporomandibular disorders and migraine chronification. Curr Pain Headache Rep. 2009;13(4):314–8.
162. Fernandes G, Franco AL, Goncalves DA, Speciali JG, Bigal ME, Camparis CM. Temporomandibular disorders, sleep bruxism, and primary headaches are mutually associated. J Orofac Pain. 2013;27(1):14–20.
163. Franco AL, Goncalves DA, Castanharo SM, Speciali JG, Bigal ME, Camparis CM. Migraine is the most prevalent primary headache in individuals with temporomandibular disorders. J Orofac Pain. 2010;24(3):287–92.
164. Tchivileva IE, Ohrbach R, Fillingim RB, Greenspan JD, Maixner W, Slade GD. Temporal change in headache and its contribution to the risk of developing first-onset temporomandibular disorder in the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study. Pain. 2017;158(1):120–9.
165. Goncalves DA, Camparis CM, Speciali JG, Castanharo SM, Ujikawa LT, Lipton RB, et al. Treatment of comorbid migraine and temporomandibular disorders: a factorial, double-blind, randomized, placebo-controlled study. J Orofac Pain. 2013;27(4):325–35.
166. Kang JH. Effects on migraine, neck pain, and head and neck posture, of temporomandibular disorder treatment: Study of a retrospective cohort. Arch Oral Biol. 2020;114: 104718.
167. Gonçalves DG, Camparis C, Franco A, Fernandes G, Speciali J, Bigal M. How to investigate and treat: migraine in patients with temporomandibular disorders. Curr Pain Headache Rep. 2012;16(4):359–64 (**2012/08/01**).
168. Penfield W, McNaughton F. Dural headache and innervation of the dura mater. Arch Neurol Psychiatry. 1940;44:43–75.
169. Ray BS, Wolff HG. Experimental studies on headache. Pain sensitive structures of the head and their significance in headache. Arch Surg. 1940;41:813–56.
170. Daudia AT, Jones NS. Facial migraine in a rhinological setting. Clin Otolaryngol Allied Sci. 2002;27(6):521–5.

171. Debruyne F, Herroelen L. Migraine presenting as chronic facial pain. Acta Neurol Belg. 2009;109(3):235–7.
172. Bartsch T, Goadsby PJ. Anatomy and physiology of pain referral in primary and cervicogenic headache disorders. Headache Currents. 2005;2:42–8.
173. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev. 2017;97(2):553–622 (**02/0804/01/pmc-release**).
174. Ailani J, Burch RC, Robbins MS. The American Headache Society Consensus Statement: update on integrating new migraine treatments into clinical practice. Headache. 2021;61(7):1021–39.
175. Buse DC, Andrasik F. Behavioral medicine for migraine. Neurol Clin. 2009;27(2):445–65 (**2009/05/01/**).
176. Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache. 2011;51(9):1358–73.
177. Puledda F, Younis S, Huessler EM, Haghdoost F, Lisicki M, Goadsby PJ, et al. Efficacy, safety and indirect comparisons of lasmiditan, rimegepant, and ubrogepant for the acute treatment of migraine: a systematic review and network meta-analysis of the literature. Cephalalgia. 2023;43(3):3331024231151419.
178. Lipton RB, Croop R, Stock DA, Madonia J, Forshaw M, Lovegren M, et al. Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial. Lancet Neurol. 2023;22(3):209–17.
179. Zhao YJ, Ong JJY, Goadsby PJ. Emerging treatment options for migraine. Ann Acad Med Singapore. 2020;49(4):226–35.
180. Haghdoost F, Puledda F, Garcia-Azorin D, Huessler EM, Messina R, Pozo-Rosich P. Evaluating the efficacy of CGRP mAbs and gepants for the preventive treatment of migraine: a systematic review and network meta-analysis of phase 3 randomised controlled trials. Cephalalgia. 2023;43(4):3331024231159366.
181. Ashina S, Mitsikostas DD, Lee MJ, Yamani N, Wang SJ, Messina R, et al. Tension-type headache. Nat Rev Dis Primers. 2021;7(1):24.
182. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. Lancet Neurol. 2018;17(1):75–83.
183. Buhimschi CS, Weiner CP. Medications in pregnancy and lactation: part 1. Teratology. Obst Gynecol. 2009;113(1):166–88.
184. Haanpää ML, Gourlay GK, Kent JL, Miaskowski C, Raja SN, Schmader KE, et al. Treatment considerations for patients with neuropathic pain and other medical comorbidities. Mayo Clin Proc Mayo Clinic. 2010;85(3 Suppl):S15–25.
185. Soldin OP, Dahlin J, O'Mara DM. Triptans in pregnancy. Ther Drug Monit. 2008;30(1):5–9.
186. Parikh SK, Delbono MV, Silberstein SD. Managing migraine in pregnancy and breastfeeding. Prog Brain Res. 2020;255:275–309.
187. Fillingim RB, Ohrbach R, Greenspan JD, Knott C, Dubner R, Bair E, et al. Potential psychosocial risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. J Pain. 2011;12(11 Suppl):T46–60.
188. Fillingim RB, Ohrbach R, Greenspan JD, Sanders AE, Rathnayaka N, Maixner W, et al. Associations of psychologic factors with multiple chronic overlapping pain conditions. J Oral Facial Pain Headache. 2020;34:s85–100.
189. Slade GD, Greenspan JD, Fillingim RB, Maixner W, Sharma S, Ohrbach R. Overlap of five chronic pain conditions: temporomandibular disorders, headache, back pain, irritable bowel syndrome, and fibromyalgia. J Oral Facial Pain Headache. 2020;34:s15–28.
190. Crandall JA. An introduction to orofacial pain. Dent Clin North Am. 2018;62(4):511–23.
191. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129–36.
192. Lipton RB, Stewart WF, Stone AM, Lainez MJ, Sawyer JP, Disability in Strategies of Care Study g. Stratified care vs step care strategies for migraine: the Disability in Strategies of Care (DISC) study: a randomized trial. JAMA. 2000;284(20):2599–605.
193. Aggarwal VR, Fu Y, Main CJ, Wu J. The effectiveness of self-management interventions in adults with chronic orofacial pain: a systematic review, meta-analysis and meta-regression. Eur J Pain. 2019;23(5):849–65.
194. Carlson CR. Psychological considerations for chronic orofacial pain. Oral Maxillofac Surg Clin North Am. 2008;20(2):185–95 (**vi**).
195. Schmidt JE, Carlson CR, Usery AR, Quevedo AS. Effects of tongue position on mandibular muscle activity and heart rate function. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;108(6):881–8.
196. Agha-Hosseini F, Sheykhbahaei N, Mirzaii-Dizgah I, Fatehi F. The efficacy of oral habit modification on headache. J Korean Assoc Oral Maxillofac Surg. 2017;43(6):401–6.
197. Menchel HF, Greene CS, Huff KD. Intraoral appliances for temporomandibular disorders: what we know and what we need to know. Front Oral Maxillofac Med. 2021. https://doi.org/10.21037/fomm-20-49.
198. Noma N, Watanabe Y, Shimada A, Usuda S, Iida T, Shimada A, et al. Effects of cognitive behavioral therapy on orofacial pain conditions. J Oral Sci. 2020;63(1):4–7.
199. Vickers AJ, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, et al. Acupuncture for chronic pain: update of an individual patient data meta-analysis. J Pain. 2018;19(5):455–74.
200. de Salles-Neto FT, de Paula JS, Romero J, Almeida-Leite CM. Acupuncture for pain, mandibular function and oral health-related quality of life in patients with masticatory myofascial pain: a randomised controlled trial. J Oral Rehabil. 2020;47(10):1193–201.
201. Zhao L, Chen J, Li Y, Sun X, Chang X, Zheng H, et al. The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial. JAMA Intern Med. 2017;177(4):508–15.
202. Zheng H, Gao T, Zheng QH, Lu LY, Hou TH, Zhang SS, et al. Acupuncture for patients with chronic tension-type headache: a randomized controlled trial. Neurology. 2022. https://doi.org/10.1212/WNL.0000000000200670.
203. Edvinsson L. CGRP and migraine: from bench to bedside. Rev Neurol (Paris). 2021;177(7):785–90.
204. Michot B, Kayser V, Hamon M, Bourgoin S. CGRP receptor blockade by MK-8825 alleviates allodynia in infraorbital nerve-ligated rats. Eur J Pain. 2015;19(2):281–90.
205. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014;33(4):451–9 (**2014/04/01**).
206. Hatfield E, Phillips K, Swidan S, Ashman L. Use of low-dose naltrexone in the management of chronic pain conditions: a systematic review. J Am Dent Assoc. 2020;151(12):891-902.e1.
207. Griffin CE 3rd, Kaye AM, Bueno FR, Kaye AD. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J. 2013;13(2):214–23.
208. Ashina M. Migraine. N Engl J Med. 2020;383(19):1866–76.
209. Robbins MS. Diagnosis and management of headache: a review. JAMA. 2021;325(18):1874–85.

210. Goadsby PJ. Therapeutic prospects for migraine: can paradise be regained? Ann Neurol. 2013;74(3):423–34.
211. Ailani J, Burch RC, Robbins MS, Board of Directors of the American Headache S. The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. Headache. 2021;61(7):1021–39.
212. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. Eur J Neurol. 2009;16(9):968–81.