Review Article

Temporomandibular disorders, neuropathic and idiopathic orofacial pain, and headaches: a literature review

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Background and Objective: Temporomandibular disorders (TMDs), headaches, and neuropathic, nociplastic, and idiopathic orofacial pain (OFP) overlap several specialties for diagnosis and management. A significant proportion of patients achieve inadequate pain relief. This article is intended to provide for practitioners an overview of the current diagnostic criteria and treatments.

Methods: PubMed and the Cochrane Database of Systematic Reviews were searched from 2000 to 2021 for human and English studies that involved comparison groups, and systematic reviews of such studies.

Key Content and Findings: Internationally-accepted diagnostic criteria now for exist all types of TMDs, headaches, and neuropathic, nociplastic, and idiopathic OFP. TMDs are managed by addressing the causative factors where known; and by using intraoral appliances (IA), medications and physical therapy (PT), amongst other modalities. Medications can be systemic, topical, or injected. Neuropathic, nociplastic, and idiopathic OFP treatments are mainly systemic medications, though supplements and topical agents are being used more frequently. Headaches are managed primarily with systemic medications. Botox, psychological treatment, and lifestyle changes are also used.

Conclusions: The diagnosis of these pain conditions has become increasingly standardized, with validated and internationally-accepted diagnostic criteria. The greatest need is for more analysis of existing treatments and development of new therapeutics for neuropathic, nociplastic, and idiopathic OFP and headache.

Keywords: Temporomandibular disorder (TMD); orofacial pain (OFP); neuropathic pain; headache

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Introduction

Temporomandibular disorders (TMDs), headaches, and neuropathic, nociplastic, and idiopathic orofacial pain (OFP) straddle several health disciplines, and are therefore diagnosed and managed by a number of specialists, including oral medicine specialists, physical therapists (TMDs), neurologists (neuropathic pain and headaches), primary care, and dentists. A frequent complaint among patients with these OFPs is the difficulty of finding a provider with adequate training in treating them, particularly TMDs and neuropathic, nociplastic, and idiopathic OFP. These patient complaints are reflected in those of providers as well, who often feel inadequately trained (1). The purpose of this

Table 1 The search strategy summary

Parameter	Details
Date of search	10/26/2020 – 2/15/2021
Databases and other sources searched	PubMed, Cochrane Database of Systematic Reviews
Search terms used	The search terms were used, either individually or in combination: temporomandibular disorder, TMD, myalgia, myofascial, pain, arthralgia, disc displacement, degenerative joint disease, neuropathic, orofacial, headache, trigeminal, neuralgia, neuropathic, neuropathy, nociplastic, burning, migraine, and tension-type Also the references of included manuscripts were searched
Timeframe	1/1/2000 – 2/15/2021
Inclusion and exclusion criteria	Inclusion: clinical trials with comparison groups Systematic reviews of clinical trials with comparison groups Exclusion: publications lacking comparison groups
Selection process	Andrew Young, Ladan Sahabi conducted the search independently. Consensus was obtained through discussion. Only articles that both authors agreed upon were included
Any additional considerations, if applicable	For treatments that did not have studies involving comparison groups, studies without comparison groups were included

review is to update the reader on the current evidence regarding diagnosis and management of these conditions, so optimal care can be provided for these patients.

We present this article in accordance with the Narrative Review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-86/rc).

Methods

PubMed and the Cochrane Database of Systematic Reviews were searched from 1/1/2000 until 2/15/2021 for studies and systematic reviews on temporomandibular disorders, neuropathic orofacial pain, nociplastic pain, and headaches written in English (*Table 1*). The references of retrieved articles were also searched. Sources were limited to studies that had comparison groups, or systematic reviews of studies with comparison groups, unless such articles could not be found for a given treatment. The following search terms were used either individually or in combination: temporomandibular disorder, TMD, myalgia, myofascial, pain, arthralgia, disc displacement, degenerative joint disease, neuropathic, orofacial, headache, trigeminal, neuralgia, neuropathic, neuropathy, nociplastic, burning, migraine, and tension-type.

A systematic review utilizes more selective and rigorous search criteria and methodology to answer more focused questions. Because our objective is to provide a broad overview to the reader on diagnostic criteria and treatments currently in use, a narrative review format was chosen.

Discussion

TMDs

Overview

TMDs are a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joint (TMJ), the masticatory muscles, and associated structures (2). Estimates of painful TMD in the general population range from 10–15%, making it the second most common musculoskeletal pain condition (3). The etiology of TMDs is multifactorial in any given individual, and the factors can be predisposing, initiating, or perpetuating, depending on the individual and the circumstances. Factors include direct trauma, indirect trauma, microtrauma, systemic conditions (such as hypermobility), local factors (such as cervical muscle activity), genetics, and psychosocial factors (2).

In 1992, the Research Diagnostic Criteria for TMD (RDC/TMD) (4) was published as an expert-based classification of TMDs, and became the standard diagnostic

criteria for TMD research. Its validation testing from 2001–2008 revealed a need for revision. The revised form, named the Diagnostic Criteria for TMD (DC/TMD), was published in 2014 (5), and is currently the most widely accepted diagnostic criteria and classification system for research in TMD, and is also intended to be used in clinical, non-research settings. The complete set of validated diagnostic tools, which include screening questionnaires, patient history forms, examinations forms, decision-making trees, physical examination manuals, and psychosocial assessment forms are available in multiple languages at https://www.iadr.org/INfORM/DC-TMD. Diagnosis is primarily made through patient history and physical examination; radiographic or magnetic resonance imaging is sometimes necessary.

The DC/TMD classification scheme includes masticatory muscle disorders, arthralgia, headache attributed to TMD, intra-articular disorders (various forms of disc displacement), subluxation, and degenerative joint disease. The Expanded Taxonomy of the DC/TMD (6) includes diagnostic criteria for additional, less common, TMD conditions, including arthritis.

More recently, the International Headache Society (IHS), which publishes the international standard for headache and neuropathic pain diagnoses (the International Classification of Headache Disorders, 3rd Edition, or ICHD-3), produced the International Classification of Orofacial Pain (ICOP) (7), which includes TMDs. However, the ICOP is expressly not an entirely new classification system. Rather, it uses the diagnostic criteria of the DC/TMD, but only lists the painful TMDs, and divides these conditions further according to whether they are acute or chronic, primary or secondary, have referral, and by frequency. Primary pains are those for which a cause has not been determined. Secondary pains have an identified causative disorder, such as disc displacement or a generalized pain condition; if pain is to be alleviated, it would need to address the underlying disorder. Acute pains are those that started within the last three months, and chronic pains are must be present for more than three months. Sensitization and maladaptive thinking or behavior can develop and worsen over time, resulting in new or additional pathophysiology compared to when the pain was originally acute. This is at least partly why chronic pain, compared to acute pain, generally has differences in the management approach, needs more treatment, and usually has a less favorable prognosis. These mechanisms also apply to neuropathic and nociplastic pain and headache.

Management

A myriad of treatments are used for TMD, and many patients undergo multiple treatments, often simultaneously.

A number of treatments aim to decrease the causative factors of TMD. Behavioral modification includes avoidance of activities that aggravate pain, frequent breaks during sustained oral function, and habit awareness. The DC/TMD has an Oral Behaviors Checklist to help patients identify such habits, which can be found on its website. Behavioral modification may also include ergonomics, which in combination with other active physical therapy (PT) treatments, may be effective, according to a systematic review (8). Psychological therapy has also shown potential, according to a systematic review. Cognitive behavioral therapy, alone or in combination with other physical or psychological treatments, is effective for TMD. Biofeedback, electromyogram training, proprioceptive re-education, and relaxation may be more effective than placebo, occlusal splints, or no treatment. Psychological treatment may be more effective in long-term pain reduction than stabilization splints, in patients with more severe TMD pain with psychosocial problems (9). While there appears to be a correlation between sleep quality and TMD (10), more prospective studies are needed to determine the causal relationship. PT in general has been shown to be effective, similar in efficacy to intraoral appliances (IA) for short-term pain reduction, according to a systematic review (11).

IA, which as a group are also known as splints, orthotics, and night guards, are very frequently used for TMD, but their mechanism of action remains undetermined. They have in general mixed evidence regarding their efficacy for symptom reduction, according to several systematic reviews (12-14). Several studies have concluded that there is insufficient evidence of superiority over other active interventions. Some studies have compared IA to no treatment, and found them superior for symptom reduction (12). Numerous designs of IAs exist, varying by arch, mandibular position, presence of a ramp, and hardness. In general, IA design does not appear to have a significant effect on IA efficacy (2). However, the partial-coverage IAs have been associated with more adverse events, primarily related to occlusion or individual teeth (13). The efficacy of IAs can be assessed according to the particular TMD condition or symptoms. They appear to be effective for myalgia and arthralgia without degenerative joint disease, but do not reduce clicking (14).

Pharmacologic treatment involves a large variety of

options, and is best used for patient comfort during the interim period when a home care regimen and behavioral modification are still taking effect. Among the non-steroidal anti-inflammatory drugs (NSAIDs), naproxen was superior to placebo for TMJ arthralgia, while celecoxib, diclofenac, and piroxicam were not, according to a Cochrane Review (15). For systemic corticosteroids, data is lacking. Palmitoylethanolamide (PEA) twice a day was significantly superior to 600 mg ibuprofen taken twice a day, in a small blinded study (16). Benzodiazepines are used for their anxiolytic and analgesic effect. However, randomized placebo-controlled trials on TMD have not demonstrated a significant effect on muscle pain, TMJ pain, or jaw pain in general (17). Most muscle relaxants require dose tapering, which can discourage prescribers, but cyclobenzaprine and metaxalone do not. Cyclobenzaprine has demonstrated promise (17), but may lose its efficacy over time. Amitriptyline can be used to replace cyclobenzaprine for long-term use, according to a systematic review (18). Gabapentin has been demonstrated to be superior to placebo for spontaneous TMJ pain, muscle pain, and global function in TMD patients in a randomized controlled trial (RCT) (19). Propranolol reduces pain intensity, but not pain duration, according to a randomized double-blinded crossover study (20).

Pharmacological agents can also be delivered topically. Mena *et al.* performed a systematic review of the current treatments (21). Capsaicin cream, as well as bee venom, was not more effective than the placebo for arthralgia. Diclofenac sodium solution reduced TMJ pain similarly to oral diclofenac 50 mg, but with markedly less gastric side effects. Cannabidiol (CBD) oil was also effective for arthralgia compared to placebo. Ping On ointment containing 18% peppermint oil and 20% menthol, and Theraflex-TMJ Cream containing methyl salicylate, were superior to placebo for TMJ or muscle pain.

Agents can also be delivered by injection into either the masticatory muscles or the TMJ. Intramuscular botulinum toxin A (Botox) has had mixed results against placebo (22,23). These RCTs have reported side effects such as asymmetric smile, temporary regional weakness at injection sites, pain at injection sites, and edema at injection sites (23), though one RCT reported no significant difference in side effects between Botox and placebo (24). A small uncontrolled trial of glucocorticoid injected into the TMJ showed improvement in symptoms (25). The evidence for hyaluronate injections into the TMJ are inconclusive, according to a systematic review; some report hyaluronate to perform significantly better than the comparison group, while others report no difference (26). Botox has also shown efficacy for neuropathic and nociplastic pain, and chronic migraine headaches, as will be discussed in subsequent sections.

Injections themselves, without medication, can also be effective. Trigger point injections aim to physically disrupt hyperactive muscle fibers (trigger points). The current literature lacks placebo-controlled studies. A blinded, randomized study comparing trigger point injections to massage and stretch found both to decrease pain intensity, but without significant difference between the two treatments (27). Acupuncture does not aim for trigger points, and its exact mechanism is disputed. However, systematic reviews have concluded it to be more effective than placebo (12,28). These studies reported no side effects (28).

Arthrocentesis was not superior to noninvasive treatment in RCTs, at the 26 or 52 week points (29,30). TMJ arthroscopy and surgery were well-compared in a Cochrane review in 2011 (31). TMJ arthroscopy is more effective than open joint surgery in reducing pain after 12 months, but not in improving function, opening range, or decreasing joint sounds. TMJ arthroscopy was also superior to arthrocentesis for improving opening, but not for improving pain. Yet overall, arthroscopy was not superior to nonsurgical treatment for reducing pain after 6 months.

Various treatment options are available for TMD. Overall, according to a systematic review, patients without major psychological symptoms do well with simple care. Those with major psychological symptoms benefit more from multimodal, interdisciplinary treatment (32).

Neuropathic, nociplastic, and idiopathic OFP

Overview

Neuropathic OFP is pain in the oral and facial region that is caused by an injury or disease affecting the peripheral or central nervous system (33). More recently, the term "nociplastic pain" has been used to describe pain, usually in the form of increased sensitivity, caused by altered function of pain-related sensory pathways (33). The mechanism of nociplastic pain involves amplification of pain signals and/or decreased activity of endogenous pain inhibition activity. Nociplastic pain is not a mutually-exclusive mechanism; patients may have co-existing inflammatory and nociplastic pain, for example.

Unlike the more common somatic pains, neuropathic and nociplastic pains are not merely a symptom of a

somatic lesion. They are less common than TMD and headache. However, they are typically more challenging to manage than TMD. The prevailing diagnostic criteria for neuropathic and nociplastic OFP has been the ICHD-3 (34), created by the IHS, for both clinical and research settings. Neuropathic OFPs are in category 13, titled "Painful lesions of the trigeminal nerves and other facial pain". Its subcategories include variants of trigeminal neuralgia, painful trigeminal neuropathy, and glossopharyngeal neuralgia. The criteria can be accessed at https://ichd-3.org.

More recently, the IHS published the ICOP in 2020 (7), which is more extensive in its categorization of neuropathic and nociplastic OFPs than the ICHD-3, and also has the category "Idiopathic orofacial pain". One of the newly-tabulated conditions is pain localized to a tooth or tooth site, called persistent idiopathic dentoalveolar pain (PIDAP, formerly called "atypical odontalgia"). PIDAP has been conventionally considered to be a form of neuropathic pain or assumed to arise due to mental and psychological factors, but as its new name implies, it is now considered idiopathic. Some have proposed it may be a nociplastic pain (35). Burning mouth syndrome and atypical facial pain likewise had been considered neuropathic in the past, but have been moved to the idiopathic pain category in the ICOP, and may be nociplastic (33).

Another set of conditions newly classified in the ICOP is pains in the orofacial region that resemble headaches, such as orofacial migraine, tension-type OFP, trigeminal autonomic OFP (including orofacial cluster attacks, paroxysmal hemifacial pain, and hemifacial continuous pain with autonomic symptoms). Diagnosis involves a thorough patient history, sensory nerve testing when the patient reports sensory changes, an intraoral examination and/or imaging when dental, periodontal, bony, or mucosal causes must be ruled out. The ICOP can be accessed at https://journals.sagepub.com/doi/10.1177/0333102419893823.

Management

The majority of management performed for neuropathic, nociplastic, and idiopathic OFP pain is pharmacological (36). Numerous practice guidelines exist for management of neuropathic pain in general (not neuropathic OFP specifically), which include those of the European Federation of Neurological Societies (EFNS), the Canadian Pain Society (CPS), the Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (NeuPSIG), the National Institute for Health and Clinical Excellence (NICE, United Kingdom), all of which are updated regularly, and those of South Africa (funded by Pfizer), Latin America, the Middle East (funded by Pfizer), the French, and the Danish.

There is much agreement among the various guidelines (36). In general, there is broad agreement that gabapentin, the TCAs (amitriptyline, nortriptyline, and desipramine), and topical lidocaine be used as first-line medications. The NeuPSIG, the French, and the South African guidelines recommend the serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine as first-line medications as well. Only the French recommend opioids as first-line treatments.

For second-line medications, the CPS, Middle East, and French guidelines include SNRIs (duloxetine and venlafaxine). Most societies place opioids (morphine, oxycodone, methadone, levorphanol, and tramadol) in the second-line group, except the CPS and South African guidelines, which place opioids in the third line group.

For third-line medications, the NeuPSIG places carbamazepine and oxcarbazepine, lamotrigine, serotonin-selective reuptake inhibitors (SSRIs) citalopram and paroxetine, sodium channel blockers (mexiletine), NMDA-receptor antagonists (dextromethorphan and memantine), and topical capsaicin. The Latin American guidelines place SNRIs (duloxetine and venlafaxine) in the third-line category.

For fourth-line medications, cannabinoids and antiepileptic drugs (AEDs; lamotrigine and clonidine) are placed by the CPS and Latin American guidelines. The CPS also puts SSRIs (citalopram and paroxetine), sodium channel blockers (mexiletine), and methadone into this category.

For specifically orofacial neuropathic, nociplastic, and idiopathic pains, the most commonly used medications are antidepressants and AEDs. The most commonly used antidepressants are amitriptyline, nortriptyline, desipramine (37), and duloxetine, which have demonstrated efficacy (38). Among the AEDs, carbamazepine is among the oldest that is still being used for TN. The RCTs that have been done on carbamazepine for TN are likewise old, but support its usage for decreasing pain intensity and frequency, according to a systematic review (39). However, it has among the most frequent and significant side effects of any medication used for these OFPs, including leucopenia and abnormal liver function. Oxcarbazepine has less significant side effects and performed similar to carbamazepine in one RCT (40). The same was found for gabapentin, according to a meta-analysis (41). Lamotrigine appeared to perform better than placebo in one RCT (42).

Baclofen, which is both an AED and a muscle relaxant, resulted in roughly half of trigeminal neuralgia subjects being pain-free, and roughly 20% had a pain reduction of more than 50% (39).

Patients often are prescribed more than one medication for neuropathic, nociplastic, or idiopathic OFP, because any given medication often gives only partial relief, and side effects can limit the achievable dose (and thus achievable relief). However, the actual studies on such polypharmacy are few. One double blind crossover RCT, with 20 subjects per group, found gabapentin alone (300 mg per day) improved pain by 50%, ALA alone (600 mg per day) by 55%, gabapentin and ALA together improved pain by 70%, and placebo improved pain by 15% (43).

Non-pharmacological agents are also used. Alpha lipoic acid (ALA) is a nutritional supplement that is used as an antioxidant, and increasingly for nerve-related pains. RCTs on its efficacy have been mixed (44). Capsaicin, the spicy agent in chili peppers, can be taken systemically or topically for neuropathic pain. RCTs have been positive for efficacy, but side effects can be significant (44). Catauma is an herbal drug that has been studied for nociplastic pain. One double-blind RCT reported significant improvement (45).

Neuropathic, nociplastic, and idiopathic OFP medications can also be taken topically. Usually, this is intraoral, but without swallowing. Capsaicin resulted in a significant reduction in pain at the one-week mark for BMS in a double-blind crossover RCT, with 15 subjects (46). This is often the preferred way to take capsaicin, as it reduces the risk for gastric upset. Clonazepam, which has the potential for significant side effects and addiction, can be taken topically to reduce the risk for those occurrences (44). Benzydamine (an NSAID) (47) in a double-blind RCT, and lycopene-enriched olive oil in a triple-blind RCT (48), were not found to be more effective than placebo.

A custom-compounded gel containing 4% carbamazepine, 1% lidocaine, 4% ketoprofen, 4% ketamine, and 4% gabapentin was evaluated in a retrospective study in which 12 subjects received only the topical gel, 10 received only systemic medications, and 17 received a combination of topical and systemic medications. All groups had a significant decrease in pain intensity on the VAS (40.9, 40.6, and 52.0 respectively), and pain relief was achieved significantly more quickly for the topical group (3 weeks) than for the systemic and combination groups (4 and 5.5 weeks, respectively) (49). Such topical formulations offer significant promise in treating neuropathic, nociplastic, or idiopathic OFP; many of the common systemic medications (TCAs and AEDs) have dose-limiting side effects, a delay in onset, and for patient safety require time-consuming tapering to start and stop the medication when trying to find an effective systemic medication. Also, as such conditions are typically chronic, a topical delivery decreases the risks of chronic drug intake. For individuals in which partial but inadequate pain relief is achieved with either systemic or topical medication, a combination of the two can increase the pain relief with less side effects than solely a higher dose of systemic medication.

Botox appears to reduce neuropathic pain when compared to placebo; a meta-analysis determined an odds ratio of 7.46 of achieving a 50% reduction in VAS for Botox. The side effect profile is similar for when Botox is used for myofascial pain; the side effect of facial asymmetry prevalence is 0.1 (39,50).

Non-pharmacological treatments are also done. Low-level laser has mixed evidence, with some studies finding significant improvement compared to sham laser in as long as 12 weeks follow up, but others finding minimal to no significant difference from placebo (51). Noninvasive brain stimulation can be delivered through different protocols. Systematic reviews (51,52) have concluded that overall, the evidence is low. But of those studies, for repetitive transcranial magnetic stimulation, there was a significant pain reduction compared to control, for TN, trigeminal neuropathic pain, trigeminal neuropathy, and persistent idiopathic facial pain (52).

The NeuPSIG (of the International Society for the Study of Pain) recommendations (53) state that of the neuropathic OFPs, surgery is mainly an option for TN. Peripheral nerve surgeries are either ineffective, or lack supporting evidence. Percutaneous rhizotomy directed at the trigeminal ganglion may be beneficial. Radiosurgery and microvascular decompression may be beneficial in medically-refractory TN, with microvascular decompression having the longest duration and most impactful pain relief (53). Motor cortex stimulation and deep brain stimulation data on peripheral neuropathic facial pain is inconclusive (53).

In general, neuropathic, nociplastic OFP is challenging to treat, and pain relief is slow and incomplete, with significant side effects.

Headache

Overview

Headaches are common conditions that affect the head or upper neck, often leading to poor quality of life and

productivity. Lifelong prevalence of headache is 96%, with a female predominance (54). Headaches can be classified as primary or secondary. Primary headaches are themselves conditions, rather than symptoms of another condition; examples are migraine, tension-type headache, and cluster headache. Secondary headaches are symptoms of another disorder, such as injury or infection; examples are headaches attributed to trauma or injury to head and neck, medication overuse headache, and headache attributed to infection. The large number of specific headaches are described, along with their diagnostic criteria, in the ICHD-3 (34), and are available at https://ichd-3.org/. There is growing evidence that some headaches, such as chronic migraine headaches, may have significant nociplastic elements (33). Diagnosis of headaches is made primarily through patient history. Imaging is used to rule out primary causes of headache symptoms, when such causes are suspected.

The two most common primary headaches are tension-type headache and migraine headache. Tension-type headaches have a lifetime prevalence between 30% and 78% (34), and are dull, bilateral, mild to moderate intensity pressure pain (54). Migraine is the third most prevalent disorder in the world, and the third highest cause of disability worldwide in both males and females under age of 50 (34), with a worldwide prevalence between 8–18% (55). Trigeminal autonomic cephalgias (TACs), which include cluster headaches (CH), paroxysmal hemicrania (PH), hemicranias continua (HC), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) are less common, but because some of their symptoms are similar to neuropathic and nociplastic OFPs (7), their management will also be briefly described in the following section.

Migraine, tension-type, and TAC symptoms can also present in solely the orofacial region. Their management tends to be the same for as their headache counterpart.

Migraine management

Migraine treatments can be abortive or prophylactic. Abortive migraine treatment provides symptom relief during the acute headache (56). Preventive migraine therapy reduces the frequency, severity and duration of migraine attacks over time.

Preventive migraine treatments

Numerous preventive medications are available. First line preventive migraine medications include AEDs, such as divalproex/sodium valproate and topiramate, which have moderate benefit in reducing headache burden. Anti-hypertensive (beta blockers) medications, such as metoprolol, propranolol, and timolol are also considered first line prophylactic treatments, with moderate benefit in reducing headache burden, according to a meta-analysis (55).

Second line preventive migraine medications include anti-depressants, such as amitriptyline and imipramine. Amitriptyline has been demonstrated to reduce episodic migraine headaches by one or two headaches per month, according to a systematic review (57) (migraineurs suffer an average of six headache per month), but has more side effects other preventive medications. Other examples of second line prophylactic migraine medications are venlafaxine (an SNRI) and anti-hypertensives such as atenolol and nadolol. Atenolol has moderate benefit in reducing headache burden (55).

Numerous third line preventive options are available. Pizotifen, a serotonin agonist, has moderate benefit in reducing headache burden (58), as does the calcium channel blocker Flunarizine (59). Fluoxetine, an SNRI, has a small effect in reducing headache burden, according to a Cochrane Review (60). Anti-hypertensives (candesartan, clonidine, guanfacine, lisinopril, nebivolol, and pindolol), AEDs (carbamazepine) and anti-histamines (cyproheptadine) are also used. Melatonin is generally safe, with the adverse events being relatively few or mild. It has been reported that even at very high doses, melatonin was outstandingly safe causing no serious adverse effects, based on a systematic review (61). Two emerging prophylactic classes of medications that have shown promise are angiotensin converting enzyme (ACE) inhibitors, such as benzapril, captopril, enalapril, and lisinopril, and angiotensin receptor blockers (ARB), such as losartan and Olmesartan, according to a systematic review (55).

Calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) are the latest preventive migraine therapy, with four being FDA-approved for the treatment of migraines. They act on the CGRP pathway: one targeting the CGRP receptor (erenumab) and three targeting the CGRP peptide (eptinezumab, fremanezumab, and galcanezumab) (62-64). All are administered subcutaneously monthly. The most common adverse effects are upper respiratory tract infection (55%) and injection site reactions (65). All four CGRP mAbs show promising results in episodic and chronic migraine in RCTs (66-69).

Supplements are also used for migraine prevention. Co-enzyme Q10 (CoQ10) is an endogenous enzyme cofactor. The American Academy of Neurology guidelines consider

it to be possibly effective in preventing migraine attacks with low incidence of adverse events. A meta-analysis found it to be more effective than placebo (70). Magnesium deficiency has been associated with migraine attacks. Oral magnesium is considered adjunctive therapy for prophylaxis of migraine, reducing the frequency and intensity of attacks, based on a meta-analysis (71).

Botox has been FDA-approved for chronic migraines since 2010. The mechanism of action is not very clear. It is thought to reduce pain by inhibiting the release of CGRP and substance P, with few side effects (72,73). It may reduce the number of migraine days by two days per month compared with placebo in people with chronic migraine.

Abortive migraine treatments

In general, acute treatment of migraine is based on two classes of medicines: nonspecific (analgesics and nonsteroidal anti-inflammatory drugs) and specific migraine drugs (triptans and ergot derivatives) (74). The first line therapy for the acute treatment of migraines includes the NSAIDs (such as ibuprofen), paracetamol, ergotamines, opioids, and triptans.

For mild migraine attacks, paracetamol and NSAIDs [including aspirin (ASA)] are recommended (59). Patients with a history of gastrointestinal bleeding and peptic ulcer disease should not use NSAIDs. Also, patients with cardiovascular disease (CVD) should be cautious. The powdered form of diclofenac and aspirin has a faster onset than tablets (59). There is not enough evidence in favor of paracetamol for the acute treatment of migraine in children or adolescents, according to a systematic review (75). Ibuprofen is inexpensive, and readily available, making it an excellent first choice, also according to systematic reviews (75,76).

Dihydroergotamine mesylate (DHE) is an ergot alkaloid that has been extensively used in acute and chronic migraine (77), but became less-commonly used with the advent of triptans, which have a better side-effect profile (78). There is not enough evidence for oral DHE in the treatment of migraine in children or adolescents. Nasal and injectable DHE may be more effective for more severe migraines (maximum pain with rapid onset, nausea and vomiting).

For many patients with moderate to severe migraine, triptans are considered the first-line therapy. Triptans are usually preferred over DHE because of their wider availability, tolerability, adverse effect profile, and better efficacy (79). The standard dose has better outcomes than ergotamines, NSAIDs (including ASA) and paracetamol, based on guidelines of the Canadian Headache Society (80,81), and will achieve pain relief within 2 hours in 43–76% of patients, based on a systematic review (82). Specific triptans include almotriptan, eletriptan (tablets have more favorable outcomes), naratriptan, rizatriptan (orally-dissolving tablets have the most favorable outcomes), sumatriptan (subcutaneous injection has the most favorable outcome), or zolmitriptan. For migraines with maximum pain with rapid onset, and migraines with nausea and vomiting, intranasal and subcutaneous sumatriptan and intranasal zolmitriptan are recommended (82). Triptans in combination with ASA or acetaminophen or an injectable triptan have better outcomes than standard dose triptans, according to the NICE guidelines (83).

Triptans are often effective at providing pain relief in children and adolescents. They may cause minor adverse effects such as fatigue, taste disturbance, nasal symptoms, dizziness, nausea, or vomiting. They are contraindicated for migraineurs with cardiovascular or cerebrovascular disease or uncontrolled hypertension because of their vasoconstrictive effects, according to a RCT (84). The combination of sumatriptan and naproxen is effective in adolescents. If patients have an inadequate response to triptans or suffer from frequent recurrent migraines, sumatriptan with an NSAID, such as naproxen, should be considered. There is some evidence that this may reduce headache recurrence and response (75).

Lasmiditan has a high-affinity for the 5-HT1F receptor, which acts on the trigeminal system without causing vasoconstriction, making it a new option particularly for migraineurs who have cardiovascular risk factors, those with stable CVD, or patients who respond poorly to their current treatment, according to a meta-analysis of RCTs. It does have a higher risk of developing central nervous system related adverse events (85)

CGRP receptor antagonists block CGRP and terminate migraine acutely, according to a meta-analysis (86,87); they are good options for patients who are unable to take triptans, and have lower toxicity than triptans (88). There are several small molecule CGRP receptor antagonists (called gepants), including olcegepant, telcagepant, (MK-3207), (BI-44370 TA), rimegepant, and ubrogepant (89,90). According to a meta-analysis, they all show more effective pain relief two hours after treatment compared to placebo. Olcegepant and BI-44370 have good efficacy against migraine, but come with relatively high toxicity (though lower than triptans). BI-44370 has the highest risk

of adverse events. Therefore, these two types of gepants have limited clinical usefulness. Ubrogepant has the lowest risk of adverse events (lower toxicity) (90-92). Rimegepant exhibits good efficacy and safety for the acute treatment of migraine, according to a RCT (93,94).

Several alternative options of headache treatment are available. Intravenous magnesium has been demonstrated to reduce acute attacks within 15 minutes, according to a meta-analysis of RCTs (95-99). Non-pharmacological self-management includes meditation, acupuncture, cognitive behavioral therapy (CBT), mindfulness, herbal and nutritional health products, and hypnosis. According to a meta-analysis, self-management interventions for migraine and tension-type headache are more effective than usual care in improving many outcomes, but do not affect headache frequency (100). They enable patients to handle headache symptoms more efficiently (101). A 2016 Cochrane analysis found acupuncture to be effective in reducing the frequency of attacks (54).

Tension type headache treatment

Preventive agents include tricyclic antidepressant medications (amitriptyline, nortriptyline, imipramine) and various muscle relaxants (baclofen, carisoprodol, cyclobenzaprine, tizanidine). SSRI and selective SNRI, recommended in the past for tension type headache, have been shown to be ineffective. Monoamine oxidase inhibitor drugs are effective but used infrequently due to potential adverse events. Memantine may have some benefit in chronic tension type headache and chronic migraine (54). A course of acupuncture for tension-type headache is the only non-pharmacological treatment recommended in National Institute and Health Care Excellence (NICE) guidelines. Some non-medication management therapy for TTH includes PT and dry needling. Current evidence for the benefit of dry needling in the treatment of tension or cervicogenic headache is inconclusive, according to a systematic review (102).

Cluster headache treatment

Cluster headache treatments, in general, aim to either interrupt a current attack (abortive), prevent future attacks (preventive), or interrupt attacks while preventive treatments are gaining efficacy (bridging, or transitional). For abortive treatments, a systematic review of double-blinded RCTs for the American Headache Society Evidence-Based Guidelines (103) concluded that subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen had established efficacy. Sumatriptan nasal spray, oral zolmitriptan, and sphenopalatine ganglion stimulation had probable efficacy. Preventive treatments are started at the beginning of a cluster, and may take weeks to achieve full effect. The same review found only suboccipital steroid injection to have sufficient evidence as an established effective treatment, and only civamide nasal spray to be probably effective. All other treatments considered, including lithium, verapamil, and prednisone, were deemed possibly effective or less. For transitional treatments, steroids are the main agents. Oral prednisone reduced cluster attacks from 9.5 per week to 7.1 when compared to placebo in a double-blind multi-center RCT (104). Suboccipital nerve block injections with steroids also effected pronounced reductions in attack frequency in placebo-controlled RCTs (105,106).

PH, HC, SUNCT, and SUNA treatment

Evidence for treatments of non-cluster TACs is very weak. Controlled trials are difficult to perform when the conditions are rare. PH and HC are managed primarily with indomethacin; non-blinded, non-controlled study reported efficacy against PH (107). Case reports and case series have reported SUNCT improvement with lamotrigine, carbamazepine, and gabapentin (108).

Summary

The diagnosis of these pain conditions has become increasingly standardized, with validated and internationally-accepted diagnostic criteria for TMD, neuropathic and nociplastic OFP, and headaches. The criteria, as well as diagnostic tools, are publicly available through the links and citations provided in this article. This has allowed more coordinated research and meta-analyses, and with increasing use among clinicians, should also continue to improve diagnostics, patient care, and appropriate referrals. The greatest need is for more analysis of existing treatments and development of new therapeutics for neuropathic and nociplastic OFP and headache, and communicating these findings to the practitioners.

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