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Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management

Flavia Penteado Kapos[a,b], **Fernando Gustavo Exposto**[c,d], **Juan Fernando Oyarzo**[e], **Justin Durham**[f]

[a]Department of Epidemiology, School of Public Health, University of Washington, Seattle, United States

[b]Department of Oral Health Sciences, School of Dentistry, University of Washington, Seattle, United States

[c]Section of Orofacial Pain and Jaw Function, Department of Dentistry, Health, Aarhus University, Aarhus, Denmark

[d]Scandinavian Center for Orofacial Neurosciences (SCON), Aarhus, Denmark

[e]Orofacial Pain and TMD Program, Faculty of Odontology, Universidad Andres Bello, Santiago, Chile

[f]Centre for Oral Health Research & Institute of Health and Society, Newcastle University, Newcastle, United Kingdom

Abstract

Temporomandibular disorders (TMD) is a collective term for a group of musculoskeletal conditions involving pain and/or dysfunction in the masticatory muscles, temporomandibular joints (TMJ) and associated structures. It is the most common type of non-odontogenic orofacial pain and patients can present with pain affecting the face/head, TMJ and or teeth, limitations in jaw movement, and sounds in the TMJ during jaw movements. Comorbid painful and non-painful conditions are also common among individuals with TMD.

The diagnosis of TMD have significantly improved over time with the recent Diagnostic Criteria for TMD (DC/TMD) being reliable and valid for most common diagnoses, and an efficient way to communicate in multidisciplinary settings. This classification covers 12 most common TMD, including painful (myalgia, arthralgia and headache attributed to TMD) as well as the non-painful (disc displacements, degenerative joint disease and subluxation) TMD diagnoses.

Recent studies have demonstrated that the pathophysiology of common painful TMD is biopsychosocial and multifactorial, where no one factor is responsible for its development. Importantly, research has suggested different predisposing, initiating and perpetuating factors, including both peripheral and central mechanisms. This is an active field of investigation and

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future studies will not only seek to clarify specific causal pathways but translate this knowledge into mechanism-directed diagnosis and treatment.

In accordance with this complex aetiology, current evidence supports primarily conservative multidisciplinary treatment including self-management strategies, behavioural therapy, physical therapy and pharmacotherapy.

The aim of this review is to present an overview of most recent developments in aetiology, pathophysiology, diagnosis and management of TMD.

Keywords

temporomandibular disorders; orofacial pain; aetiology; diagnosis; management

Background

Temporomandibular disorders (TMD) is a collective term for a group of musculoskeletal conditions involving pain and/or dysfunction in the masticatory muscles, temporomandibular joints (TMJ) and associated structures.[1,2] Although TMD is defined by pain and dysfunction in the orofacial region, common painful and non-painful comorbidities of common painful TMD include headaches, fibromyalgia, irritable bowel syndrome, tinnitus, chronic fatigue syndrome, depression and sleep disturbances.[3–6] As with many chronic pain conditions, recent research reinforces the biopsychosocial nature of common painful TMD (myalgia and/or arthralgia) and their interconnections with general health.[7]

In addition to being the most common type of non-odontogenic orofacial pain, TMD pain is a major driver of treatment seeking,[8,9] healthcare costs[10,11] and reduced quality of life[12] among individuals with TMD. Care pathways that support early diagnosis and management are likely to improve prognosis, quality of life and reduced healthcare costs for patients with TMD.[10,13,14] In this paper, we present a review of TMD epidemiology, aetiology and pathophysiology in light of recent developments of the field, as well as the current evidence on diagnosis and management, with a focus on common painful TMD. Lastly, we discuss how novel findings may fit in the future direction of TMD research and practice.

Incidence of painful TMD

A large multisite prospective cohort study in the US (OPPERA study) estimated that each year 4% of TMD-free adults aged 18–44 years develop clinically-confirmed first-onset painful TMD, and that annual incidence increases with age (18–25 years=2.5%; 25–34 years=3.7%; 35–44 years=4.5%).[7] A total of 19% of adults per year reported an initial painful ‘TMD symptom episode’ (i.e. orofacial pain for at least 5 consecutive days per month for one or more months). However, the majority of these episodes were considered preclinical symptoms, since participants did not meet Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) for myalgia and/or arthralgia upon clinical examination.[15]

In a large population-based study in adolescents aged 11–14 years, the estimated incidence of clinically-confirmed painful TMD was 2% annually, with an additional 10% developing facial pain symptoms not meeting RDC/TMD criteria for painful TMD diagnosis (myalgia and/or arthralgia).[16] Similarly, another study of adolescents aged 12–19 years reported a 3% annual incidence of painful TMD.[17] In contrast to adults, young adolescent females were at higher risk of new onset painful TMD (OR=2.0, 95%CI 1.2–2.3).[16] In adolescents aged 12–19 years, incidence was also higher in females, especially with increasing age.[17]

Prevalence of signs and symptoms of TMD

A large population-based study using the RDC/TMD estimated the prevalence of painful TMD (myalgia and/or arthralgia) is 36% in adults aged 20–49 years.[18] TMJ 'clicking' was reported by 30% of adults, while only 8% were diagnosed with a disc displacement (DD).[18] The estimated prevalence of TMD degenerative joint disease (DJD) diagnosis, also associated with TMJ noises, is 17%. Of note, TMJ DD, the presumed cause of TMJ 'clicking', has been argued to be a normal anatomical variant of TMJ disc position, given its high prevalence in asymptomatic populations.[19] A meta-analysis of non-patient studies estimated the need for TMD treatment in adults is 16%, with higher values for studies of older individuals (≥46 years) and those where need was clinically assessed (vs. perceived by participants).[20]

Estimates of signs and symptoms of TMD in children and adolescents are more variable, since there is not a validated diagnostic protocol for this population.[21] Studies using the RDC/TMD estimated the prevalence of painful TMD ranges from 4–13% in children and adolescents aged 6–25 years.[8,17,22–24] A meta-analysis of 11 studies including participants aged 3–18 years estimated the prevalence of clinically identified TMJ noises is 16%.[25]

Prognosis from acute to chronic and persistence of TMD

When adults with incident TMD were re-examined after an average of 8-months since initial diagnosis, 51% no longer met criteria for TMD.[7] Longer-term follow-up studies of clinical and community painful TMD cases reported remittance rates of 49% after 5 years[26] and 28% after 8 years.[27]

Somewhat surprisingly, the OPPERA cohort study found only a slightly elevated risk of new onset TMD in females (hazard ratio [HR]=1.34, 95%CI 1.03–1.75), which was nullified in the fully adjusted multivariable model.[6] Also in contrast to the baseline OPPERA case-control study of chronic TMD,[28] pain sensitivity (quantitative sensory testing, [QST]) and autonomic function measures did not predict TMD incidence.[29] Authors speculate that given their prominent associations with chronic painful TMD cases; sex and pain sensitivity may be important contributors to TMD prognosis. More details about risk factors for the onset and maintenance of painful TMD are described in the Aetiology and Pathophysiology section.

TMJ noises and intra-articular diagnoses (DD and/or DJD) are poorly correlated with patient-reported jaw pain intensity, jaw function and disability.[30] Furthermore, an 8-year follow-up study demonstrated that structural intra-articular diagnoses remained stable in 71 to 76% of joints, with similar percentage of progression (14–15%) and reversal (10–14%).[31]

Aetiology and Pathophysiology

Painful TMD have been shown to be biopsychosocial and multifactorial disorders, thus a singular cause is highly unlikely to be identified in any given patient.[7] Individuals' psychological profile and a state of pain amplification are two domains hypothesized to play a role in the aetiology of painful TMD.[32] Number of comorbid conditions (e.g. irritable bowel syndrome, insomnia) and nonspecific orofacial symptoms (e.g. stiffness, fatigue) were also strong independent predictors of painful TMD onset, which may represent another causal domain related to "general health and global symptoms".[7,33] Each of these three domains, composed of a variety of specific risk factors, are thought to be regulated by gene expression and influenced by social and environmental factors.[32] To date, there is evidence of a greater contribution of the psychological and global symptoms domains to the first onset of TMD, while pain amplification is associated with prognosis.[7,34]

Biological, psychological and social vulnerabilities interact with contextual and environmental stressors to produce painful TMD and comorbid symptoms, with or without identifiable initiating events (e.g. micro/macro trauma).[35] After initial onset, prognostic factors including pain interference,[36] general health, pain sensitivity,[34] psychological and social factors may contribute to perpetuation of symptoms or recovery. (Box 1)

Mechanisms

Although the exact pathophysiology remains unclear, several non-mutually exclusive mechanisms have been proposed to explain how biological, psychological and social factors can combine to predispose, perpetuate, or initiate painful TMD. Studies of chronic pain and TMD suggest putative neurologic, endocrine and inflammatory pathways outlined below, which can be further studied as potential diagnostic biomarkers or therapeutic targets. Some of these hypothesized mechanisms also highlight possible explanations for the occurrence of painful and non-painful comorbidities.

An evaluation of 3,295 single-nucleotide polymorphisms (SNPs) representing 358 genes previously linked to systems involved in pain perception revealed associations between five SNPs and phenotypes that were predictive of TMD incidence.[37] Genes in which these significant SNPs are contained and mechanisms hypothesized to explain their role in TMD pathophysiology are described in Table 1.[37]

Reduced Catecholamine-O-methyltransferase (COMT) activity has also been associated with pain and TMD.[38] This enzyme regulates extracellular concentration of epinephrine, norepinephrine, and dopamine, which are involved with many neurological functions, including pain perception (e.g. through activation of β-adrenergic receptors) and stress reactivity.[39] TMD-free women with 'low COMT activity' haplotypes were 2.3 times (95%CI 1.1–4.8) more likely to develop new onset painful TMD during a 3-year follow-up.[38] Likewise, adrenal dysregulation of the sympathetic nervous system has been associated with pain in individuals with chronic TMD and fibromyalgia, leading to investigations of the use of β-blockers in this population.[40,41] However, the importance of the environment should be highlighted: the association between COMT haplotypes and pain sensitivity was only detectable in males and females in low and no-stress scenarios.[39] The presence of any

stress presumably overwhelms the system with epinephrine, overriding differences between COMT haplotypes, especially in females.[39]

Additionally, several alterations in pro- and anti-inflammatory cytokines have also been found in individuals with chronic painful TMD relative to TMD-controls, including elevated circulating levels pro-inflammatory monocyte chemotactic protein (MCP-1),[42] reduced levels of anti-inflammatory (omentin-1)[43] and reduced transcription of anti-inflammatory transforming growth factor β1 (TGFβ1). Inflammation may play a more substantial role in TMJ arthralgia and DJD, based on associations with several altered markers in the joints or synovial fluid.[44] Specifically, CGRP is a neuropeptide released from trigeminal nerves that activates neurogenic inflammation and has been found to mediate peripheral and central sensitization to pain in an animal model of TMD.[45] Although its value in TMD treatment is unknown, CGRP is a promising therapeutic target in novel monoclonal antibody treatments for migraine and other headache disorders that are already commercially available.[46,47]

Presentation

Symptoms of painful TMD tend to present as recurrent (recurrent=65%; persistent episode=19%; single episode=12% of incident cases), and the vast majority of incident painful TMD cases have both TMJ arthralgia and myalgia diagnoses (myalgia only=23%; arthralgia only=4%; both=73%;).[48] Interestingly, 23% of incident cases described their TMD pain as ‘headache only’.[48] Approximately 14% of painful TMD cases report moderate to severe limitation in usual activities due to their symptoms (grades IIb-IV in the Graded Chronic Pain Scale [GCPS]).[18,48]

The presence of any RDC/TMD diagnosis in population-based studies of adults is associated with female gender (odds ratio [OR]=2.2, 95%CI 1.9–2.7).[49] Chronic painful TMD (myalgia and/or arthralgia) is associated with older age (e.g. OR=2.3, 95%CI 1.5–3.6, comparing individuals aged 35–44 years with 18–24 years).[50] Children and adolescents with TMD are also more likely to be females, especially with increasing age.[8,23] Additionally, female adolescents may present greater TMD pain impact (e.g. jaw functional limitation, school absences and analgesic consumption) compared to males with the same pain intensity.[17] Painful TMD cases in a population-based study of adults aged 20–49 years reported an average duration of symptoms of six years.[18]

Painful and non-painful comorbid conditions such as headaches, neck and back pain, irritable bowel syndrome, insomnia, depression, anxiety and tinnitus are relatively common among both acute and chronic painful TMD cases in children, adolescents and adults.[6,23,51] Somatic awareness and increased pain sensitivity (including in non-trigeminal areas) are strongly associated with chronic painful TMD (standardized OR>2.0).[28] Weaker associations have also been identified between chronic painful TMD and autonomic function,[28] inflammatory markers[43] and endogenous pain modulation.[28,52]

Diagnosis

In the past many different forms of TMD assessment have been proposed of which the most used were the Helkimo Index[53] and the Research Diagnostic Criteria for

Temporomandibular Disorders (RDC/TMD).[54] After many years of validating and revising the RDC/TMD, the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) has been proposed and is an evidence-based set of tools with which to diagnose TMD.[55] The DC/TMD offers a standardized and operationalized method to examine the masticatory structures physically (Axis I) and also to screen the presenting patient for psychosocial and comorbid factors (Axis II). The most important new part of the examination is confirmation that any pain elicited during examination is familiar, meaning that it reproduces or is similar to the pain that the patient experiences in their life and which was reported in the history section of the assessment.

Screening

For assessing the presence of painful TMD in a simple and reliable manner, the DC/TMD recommends the use of a screening questionnaire called the TMD Pain Screener.[55,56] Other validated TMD screeners such as the 3Q/TMD are also available.[57,58] Although these questionnaires do not allow for specific TMD diagnoses to be determined, a quick screening may be appropriate in busy clinical or research settings. Clinicians who are not trained in the DC/TMD examination protocol or do not have time to use it can use one of these brief assessments to inform their decision to refer patients to a colleague with orofacial pain training. (Box 2)

Axis I

For more specific TMD diagnoses, the DC/TMD requires a physical examination.[55] This has been described in detail with the commands and procedures being validated in several different languages.[59] The 12 most common TMD diagnoses, most of which have established sensitivity and specificity, are: myalgia (local myalgia, myofascial pain, myofascial pain with referral), arthralgia, four types of disc displacement disorders, degenerative joint disease, subluxation and headache attributed to TMD (Box 3).[55] It is important to note that an individual may present with multiple simultaneous painful and/or non-painful TMD diagnoses.[55] An expanded version of the DC/TMD including less common TMD is also available.[60] It should be stated that sensitivity and specificity for most of the less common conditions have not yet been established.

Axis II

Studies have shown that TMD patients present with a higher psychosocial burden[61–63] and frequency of comorbid conditions[61] than TMD-free individuals and that these conditions can lead to persistence and aggravation of TMD pain.[26,64] Consequently, it is important to assess these parameters when managing TMD patients, which can be done through validated instruments recommended in the Axis II of the DC/TMD. These instruments assess, among other things, pain behaviour, psychosocial status and functioning,[55] which can highlight contributing factors and guide tailored treatment decisions.[65] Table 2 shows the recommended instruments for screening and for a comprehensive assessment. The comprehensive assessment is intended to be used by clinical specialists or researchers in order to obtain more details about psychosocial status and its possible role in the TMD presentation. The screening instruments may aid in determining the need for a

comprehensive assessment or referral to colleagues with training in psychosocial aspects of health.

For example, Visscher et al. provide management recommendations for painful TMD patients based on 3 of the Axis II screening tools: Pain drawing (pain location), GCPS (pain intensity and disability) and PHQ-4 (psychological distress). Patients with localized pain, low GCPS (0-II) and low PHQ-4 (0–5) scores may be treated in primary care including pain education and self-management. Whereas, patients with widespread pain, a high GCPS score (III-IV), or a high PHQ-4 score (6–12), should be treated by an orofacial pain specialist in a multidisciplinary pain team.[65]

‘Red flags’ requiring special attention

Although common TMD are not life-threatening, there are more significant or sinister clinical entities that may mimic common TMD and the clinician should be aware of ‘red flags’ that may suggest their presence (Table 3). One such example is temporal arteritis (giant cell arteritis) that may cause soreness and fatigue in the temple and jaw when chewing, as well as permanent vision loss; the ‘red flags’ would be jaw claudication with onset in an individual over 50 years of age, with possible induration of the temporal artery upon palpation and vision changes. If a more ominous reason for the patient’s presenting symptoms is suspected, further diagnostic workup and/or referral to appropriate colleagues such as oral (and maxillofacial) surgeons, oral medicine specialists, ENT, neurologists or neurosurgeons is highly recommended.

Management

Given the complex biopsychosocial and multifactorial aetiology of TMD, treatment directed exclusively at local mechanical factors (e.g. jaw position) are not consistent with the current evidence. Instead, management should focus on addressing pain experience, jaw and psychosocial functioning. Given their poor correlation with pain, function, disability and prognosis,[30] the presence of TMJ noises and intra-articular diagnoses (DD and/or DJD) should only guide treatment decision-making in the presence of pain or clear functional impairment[66] (e.g. inability to open mouth wide due to intermittent or persistent locking).

Education about the benign non-progressive nature of TMD and providing a clear diagnosis to patients, even if provisional, is encouraged at the first point of contact to reduce unnecessary suffering from uncertainty surrounding their symptoms.[66] Reversible conservative therapies are recommended as first line of treatment by international consensus based on the evidence for risks and benefits,[67] and a large proportion of incident cases presenting as self-limiting and progress to remission within the first 6–15 months.[34] Multimodal strategies may be included in the treatment plan according to case complexity and contributing factors identified for each patient.

Reversible and conservative treatments

Self-care techniques—A TMD self-management program may include identification, monitoring and avoidance of oral parafunctions (e.g. daytime clenching, nail biting, gum chewing), advice about sleep hygiene, limited caffeine consumption, pain-free diet,

self-massage, therapeutic exercises, thermal therapy and relaxation techniques such as diaphragmatic breathing.[68,69] There are insufficient current data to suggest whether or not specific TMD diagnoses require modifications on self-management protocol.[69] In addition to initial management, these self-care strategies are also of utmost importance to provide patients with some autonomy to control their symptoms in recurrent TMD episodes or flare-ups.

Intraoral appliances—Several systematic reviews of the effects of occlusal appliances on TMD pain support that stabilisation splint (i.e. hard acrylic or soft polyethylene mouth-guard providing full coverage of occlusal surfaces) worn on upper or lower teeth at night leads to short-term improvement when compared with no treatment, but evidence is inconclusive when compared with placebo (non-occluding palatal splint).[70] Additionally, stabilisation splints produced a similar improvement in TMD pain compared to physical therapy, behavioural medicine, and acupuncture.[70] Partial coverage appliances such as the nociceptive trigeminal inhibition (NTI) and over the counter mouth-guards can be associated with adverse complications such as unwanted occlusal changes.[70–72]

Pharmacotherapy—A systematic review with network meta-analysis of chronic orofacial pain supports the short-term (3 weeks) effectiveness of the muscle relaxant cyclobenzaprine for reducing TMD muscle pain. The review also indicated possible effects of topical Ping-On ointment and melatonin, based on one study each.[73] In chronic TMD joint pain, there is evidence for non-steroidal anti-inflammatories (NSAIDs).[73]

Off-label use of neuromodulatory drugs such as tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, benzodiazepines, gabapentin and pregabalin as well as lidocaine patches have been reported,[74,75] especially for the management of more complex cases with persistent pain, comorbid conditions and/or with central sensitisation. However, the available evidence is mostly based on their use in other chronic pain conditions and potential mechanisms of action specific to TMD are not well understood.[73,76] Comorbid headaches, sleep disturbance and anxiety symptoms should also be considered in treatment selection.[75] Thorough evaluation of medical history should help prevent serious interactions with current medications or other known allergic reactions and complications.

Psychological and multimodal therapies—A systematic review and meta-analysis of the effect of cognitive behavioural therapy (CBT) suggest long-term (>3 months) improvements in TMD pain, depression and interference with activities compared to ‘usual care’ (education, counselling and an stabilization splint), for CBT alone or in combination with biofeedback.[77] Patients with TMD pain and major psychological symptoms may obtain more improvement with multimodal treatment than patients with TMD disc displacement and pain without major psychological symptoms.[70] Biofeedback was found to be superior to active control and similar to relaxation training for reducing TMD pain,[70] but did not add a significant benefit compared to CBT alone.[77]

Physical therapy—Although clinical protocols for interventions and control groups vary, randomized clinical trials (RCTs) of jaw mobilization or stretching exercises for TMD muscle pain suggest improvements in pain and jaw mobility compared to education and

trans cranial direct current stimulation, as well as improvements in pain compared to stabilization splint.[78] RCTs of postural exercises suggest improvements in TMD muscle pain and jaw mobility compared to education and CBT.[78]

For TMD joint pain, RCTs of jaw mobilization or stretching exercises suggest improvements in pain and jaw mobility compared to no treatment and stabilization splint.[78] Combinations of jaw strengthening and coordination exercises, and mobilization and postural exercises improved joint pain and jaw mobility compared to education and stabilization splint.[78]

Acupuncture, dry needling and substance injection for TMD myalgia—A systematic review including four small RCTs of acupuncture (traditional, trigger point and laser) provides evidence for short-term improvement in TMD muscle pain compared to placebo acupuncture, as well as similar results to stabilization splint.[79] Another systematic review and meta-analysis including 13 studies of TMD found improvements in TMD muscle pain for acupuncture compared to placebo (sham) acupuncture.[80]

Although a meta-analysis could not be performed due to heterogeneity of studies, a systematic review found support for short term improvements in TMD muscle pain for dry needling superior to false needling and to a combination of methocarbamol/paracetamol, but similar to local anaesthetic injections.[81]

A systematic review with network meta-analysis revealed equivocal evidence for the effects of intra-muscular botulinum toxin injections for TMD muscle pain compared to placebo injection.[73] Further studies are needed to determine its efficacy, safety and cost-benefit.

Irreversible and invasive treatments

In light of the biopsychosocial aetiology of TMD, its natural course, and the success rates of reversible and conservative therapy, only a small minority of cases of chronic TMD pain with severe functional impairment may benefit from minimally invasive and invasive procedures. There are insufficient predictive tools for TMD prognosis and treatment efficacy,[82] and failure of reversible and conservative treatments alone is not an indication to progress to irreversible and invasive approaches. Additionally, since chronic TMD generally requires long-term symptom management of recurrent episodes, appropriate expectation-setting is warranted.

Surgical treatments for TMJ intra-articular disorders (e.g. disc displacements and degenerative joint disease) and TMD arthralgia—One systematic review reported similar effects for arthrocentesis, arthroscopy, and physical therapy on pain intensity, jaw mobility and function in patients with DD without reduction, while another systematic review reported similar effects for arthrocentesis, arthroscopy, and discectomy.[70] Although some of these studies presented important methodological limitations, a more recent high-quality RCT corroborates these findings; Schiffman and colleagues found no additional effect of surgical interventions (arthroscopy and arthroplasty) on outcomes of DD without reduction with limited mouth opening compared to medical management or non-surgical rehabilitation.[83] There were no differences in TMJ pain intensity and frequency,

mandibular range of motion, TMJ sounds or impairment of chewing at 3, 6, 12, 18, 24, and 60-month follow-ups.[83]

One systematic review reported improvements in TMD joint pain for intra-articular injections of hyaluronic acid (HA) and corticosteroid compared to placebo injection,[73] but there was no comparison to conservative management. There was no evidence for differences between HA or plasma rich in growth factors (PRGF), between low or medium weight HA, between one or two-needle HA injection technique,[73] or between arthrocentesis with or without HA.[84]

Orthodontics and occlusal adjustments—There is no evidence for the efficacy of occlusal adjustment compared to placebo in TMD treatment or prevention, including therapeutic occlusal position or equilibration by orthopaedic, orthodontics or prosthodontics means.[85] Although occlusion is of evident functional importance to mastication and should be managed with care in dental practice,[85] current evidence does not support a causal role in the pathophysiology of TMD.[86]

Future Directions

Prior to the early 2010s, most of what was known about TMD was based on cross-sectional, case-control or follow-up studies of prevalent TMD cases (i.e. including participants with TMD at study enrolment, regardless of duration since first onset). However, studies of prevalent cases tend to over-sample individuals with longer TMD duration (i.e. chronic) resulting in length-biased sampling.[87] That is, the longer duration of chronic TMD cases makes them ‘more available’ for being observed at any one point in time, obscuring the early events of the disorder and potentially missing cases with more rapid resolution of symptoms. Accumulating evidence from studies of painful TMD incidence and follow-up of incident cases allow us to glean aetiological mechanisms and risk factors for the transition from acute to chronic painful TMD.

Future TMD aetiological research is bound to include more detailed evaluation of life stressors, rare genetic variants and genome-wide association studies (GWAS).[7] Despite substantial progress in the understanding of biological and psychological determinants of painful TMD, the investigation of multilevel social and contextual factors has been lacking.[6] Evidence from the broader pain literature indicates that neighbourhood disadvantage is associated with the onset of chronic musculoskeletal pain after motor vehicle collision[88] and onset of disabling pain in older adults.[89] Additionally, individual and neighbourhood social capital are associated with dental pain,[90] psychosomatic symptoms, musculoskeletal pain, and depression.[91]

A new classification system for all orofacial pain disorders, including TMD, is under development. The International Classification of Orofacial Pain (ICOP) has been recently released in its beta version.[92] Despite being a new classification, when it comes to TMD most of the criteria and the examination suggested in the ICOP are the same as for the validated DC/TMD.

Furthermore, since there has been some improvement in the understanding of the pathophysiology behind TMD and other pain disorders, future taxonomy will most likely begin to include a more mechanistic classification. This means that not only would the classification be divided into what type of pain disorder is present based on signs and symptoms, myalgia for example but it will also include: the type of mechanism responsible for the myalgia such as peripheral and/or central sensitization; the molecular target that is responsible for this specific mechanism, for example, CGRP or nerve growth factor.[93] Such improvements in diagnosis could clarify the substantial heterogeneity of prognosis and response to treatment within diagnostic categories observed in the current system. Upcoming research developments will likely support more precise risk prediction, treatment development and administration, allowing for different causal pathways to be addressed.[94]

Conclusions

A new generation of painful TMD research is helping to clarify its natural history and prognosis, with clear indications that it goes beyond a localized ‘jaw’ disorder. Moreover, a stronger grasp of the complex multifactorial aetiology of painful TMD may lead to better prevention, diagnosis and treatment strategies directed at causal contributing factors and mechanisms. Current evidence supports the need for a biopsychosocial assessment including validated DC/TMD diagnostic instruments and primarily conservative multidisciplinary management strategies.

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Box 1:

Summary of painful TMD aetiological and prognostic factors

Predisposing factors

The development of new onset painful TMD was most strongly predicted by baseline health status variables and social context, followed by the psychological and clinical orofacial domains. Specifically, four variables emerged as the most important predictors:[6]

- Greater number of comorbid conditions e.g. irritable bowel syndrome, fibromyalgia, insomnia and depression;
- Greater number of nonspecific orofacial symptoms e.g. stiffness, cramping, fatigue, pressure, soreness;
- Geographic location/study site - likely a proxy for unmeasured social and contextual factors;
- Higher overall pain interference with normal work

Additional important predictors included:[6]

- Greater number of oral parafunctions;
- Perceived limited mouth opening in the last month;
- Greater number of painful masticatory muscle sites on palpation during clinical exam;
- Greater somatic awareness;
- Older age

Initiating factors

Incident jaw injury (e.g. attributed to yawning, prolonged mouth opening, dental treatments, oral intubation, sports injury, motor vehicle accidents) is strongly associated with subsequent TMD incidence (HR=3.94, 95%CI 2.82–5.50), adjusting for study site, age, race, and sex.[95]

Additionally, baseline migraine (HR=1.67, 95%CI 1.06–2.62), higher baseline headache frequency (0–4 headaches/month) and worsening headache during the follow-up period predict TMD incidence.[96]

Perpetuating factors

Clinical measures of pain severity and comorbid conditions at diagnosis were associated with TMD persistence at an average of 8-months follow-up after initial diagnosis of new onset TMD, including:[34]

- Greater number of comorbid conditions;
- Higher pain intensity, frequency and duration in the previous month;

- Greater number of painful sites (masticatory muscles, TMJs, familiar headache and other body sites) on palpation or jaw movement during clinical exam;
- Pain modified by chewing hard or tough food

Box 2:

Examples of TMD screening instruments

TMD Pain Screener (short version)[56]

1. In the last 30 days, on average, how long did you have any pain in your jaw or temple area on either side last?
   - **a.** No Pain
   - **b.** From very brief to more than a week, but it does stop
   - **c.** Continuous
2. In the last 30 days, have you had pain or stiffness in your jaw on awakening?
   - **a.** No
   - **b.** Yes
3. In the last 30 days, did the following activities change any pain (that is, make it better or make it worse) in your jaw or temple area on either side?
   - **A.** Chewing hard or tough food
     - **a.** No
     - **b.** Yes

Scoring: ‘a’ responses = 0 points; ‘b’ responses=1 point; ‘c’ response=2 point.

Interpretation: A total sum of ≥2 points suggests need of further TMD evaluation.

3Q/TMD[57]

1. Do you have pain in your temple, face, jaw or jaw joint once a week or more?
   - **a.** No
   - **b.** Yes
2. Do you have pain once a week or more when you open your mouth or chew?
   - **a.** No
   - **b.** Yes
3. Does your jaw lock or become stuck once a week or more?
   - **a.** No
   - **b.** Yes

Scoring: Any affirmative answer yields a ‘3Q-positive’ result.

Interpretation: 3Q-positive score suggests need of further TMD evaluation.

Box 3:

Overview of the most common Temporomandibular Disorders (TMD) diagnoses.[55]

Painful TMD

Myalgia† is pain in the masticatory muscles. It can be divided into the following subtypes:

- Local myalgia when felt only at the site of palpation.
- Myofascial pain when felt at the site of palpation and that in addition spreads beyond the site of palpation but remaining within the boundaries of the muscle.
- Myofascial pain with referral when felt at the site of palpation and in addition is felt beyond the boundary of the palpated muscle.

Arthralgia† is pain in the temporomandibular joint(s) (TMJ).

Headache attributed to TMD† is headache located in the temple region as a consequence of TMD-related pain.

†In order to receive one of the painful TMD diagnoses above, the pain complaint has to be replicated (familiar pain) during clinical examination by provocation tests such as palpation, jaw movement or jaw function.

Non-painful TMD

Disc displacement‡ (DD) is a biomechanical disorder involving the condyle-disc complex. It can occur in the following forms:

- Disc displacement with reduction: the disc is positioned anterior to the condyle in the closed mouth position and reduces when the mouth opens and the condyle translates forward. Clicking or popping may occur with disc displacement and/or reduction.
- When the disc positioned anterior to the condyle in the closed mouth position does not reduce with mouth opening, preventing the forward translation movement of the condyle, it can lead to intermittent locking (Disc displacement with reduction with intermittent locking) or persistent locking with or without limited mouth opening (Disc displacement without reduction with or without limited opening).

Degenerative joint disease‡ (DJD) is characterized by deterioration of articular tissue with concomitant osseous changes in the condyle and/or articular eminence. Crepitus may be detected upon clinical examination by TMJ palpation during mandibular movements.

Subluxation is a hypermobility disorder in which when the mouth is open the condyle-disc complex is positioned anterior to the articular eminence.

Clinically, this prevents the patient from closing the mouth without a manipulative manoeuvre.

‡ TMJ imaging is required for gold standard diagnoses of DD (magnetic resonance imaging [MRI]) and DJD (cone beam computed tomography [CBCT]), while history and clinical examination provide provisional diagnoses. Importantly, we argue for judicious use of resources and minimizing exposure to radiation by weighing the need to rule out a 'red flag' and whether treatment would differ based on imaging findings.

Table 1:

Summary of OPPERA Prospective Cohort genetic findings and potential painful TMD aetiological mechanisms[37]

Gene	Encodes	Function	Phenotype	Implications
SCN1A	Alpha subunit of voltage-gated sodium channel Nav 1.1	Nav 1.1 is involved in the generation and propagation of action potentials in sensory nerves	Nonspecific orofacial symptoms†	SCN1A has also been associated with short-term memory performance in other studies and may alter somatic sensitivity
ACE2	Angiotensin I–converting enzyme 2	Angiotensin-related peptides have been suggested to function as neurotransmitters in the periaqueductal grey (PAG) and other brain regions involved in endogenous pain modulation. In addition to angiotensin I, pro and antinociceptive peptides (e.g. bradykinin, substance P, and opioids such as dynorphin and enkephalin) are substrates of ACE2	Nonspecific orofacial symptoms†	Pharmacologic inhibition of ACE has been associated with increase in nociceptive thresholds and tolerance, and risk of complex regional pain syndrome (CRPS)
PTGS1	Prostaglandin-endoperoxide synthase 1 (COX-1) enzyme	COX-1 catalyses the conversion of arachidonic acid into prostaglandins mediating inflammatory response and regulating neuronal sensitivity to pain	Global psychological symptoms‡	Could alter somatic sensitivity, awareness of autonomic activity and nociception
APP	Amyloid-β precursor protein	APP is expressed by neurons and is involved in synapse formation and neuronal plasticity. May modulate cognitive ability and cognitive aging	Stress and negative affect§	Increased expression of APP may underlie higher perception of stress
MPDZ	Multiple PDZ domain protein (MUPP1)	Scaffolding for G protein–coupled receptors involved in nociception and analgesia (e.g. serotonergic and GABAergic). May also regulate glutamate-related excitatory neurotransmission	Heat pain temporal summation¶	May be associated with temporal summation of pain through neurotransmitter regulation

†Global psychological symptoms is a composite measure built via principal component analysis, characterized by high loadings from SCL-90R Somatization Scale, Pennebaker Inventory of Limbic Languidness (PILL), and the Lifetime Stressor List/PTSD Checklist–Civilian Version PTSD symptom scale.

‡Stress and negative affect is a composite measure built via principal component analysis, characterized by high loadings from State and Trait Anxiety, Perceived Stress Scale (PSS), Profile of Mood States–Bipolar (POMS) Negative Affect scale, and Eysenck Personality Questionnaire–Revised (EPQ-R) Neuroticism scale; negative loadings from POMS Positive Affect scale and EPQ-R Extraversion scale.

§Nonspecific orofacial symptoms were measured as count of 6 aversive sensations of the face and jaw not described as pain: stiffness, cramping, fatigue, pressure, soreness, and ache.

¶Heat pain temporal summation is a quantitative sensory test measure of endogenous pain facilitation.

Table 2:

Summary of DC/TMD Axis II questionnaires for psychosocial assessment[55]

Assessment of	Instrument	Screening	Comprehensive
Pain intensity	Graded Chronic Pain Scale (GCPS)	X	X
Pain locations	Pain drawing	X	X
Physical function	Graded Chronic Pain Scale (GCPS)	X	X
Limitation	Jaw Functional Limitation Scale – short form (JFLS) Jaw Functional Limitation Scale – long form (JFLS)	X	X
Distress	Patient Health Questionnaire – 4 (PHQ-4)	X	
Depression	Patient Health Questionnaire – 9 (PHQ-9)		X
Anxiety	Generalized Anxiety Disorder – 7 (GAD-7)		X
Physical symptoms	Patient Health Questionnaire – 15 (PHQ-15)		X
Parafunction	Oral Behaviors Checklist (OBC)	X	X

Table 3:

‘Red flags’ that require special attention in the assessment of TMD/headache patients[†]

Red Flag	Differential diagnoses to consider
History of malignancy	Malignancy recurrence
Presence of lymphadenopathy or neck masses	Neoplastic, infective, or autoimmune cause
Sensory or motor function changes (specifically focusing on cranial nerves V, VII, and VIII)	Intracranial causes, or malignancy affecting the nerve’s peripheral branches
Recurrent epistaxis, purulent nasal drainage, or anosmia	Nasopharyngeal carcinoma or chronic sinusitis
Trismus	Oral malignancy
Unexplained fever, fatigue, weight loss	Malignant tumours, immunosuppression, and infective causes
Facial asymmetry or masses	Neoplastic, infective, or inflammatory causes
Occlusal changes	Growth disturbance of condyle, neoplasia, rheumatoid arthritis, and traumatic causes
Ipsilateral objective change in hearing	Acoustic neuroma, or other ear disease
Neurological symptoms (confusion, aphasia, dysarthria)	Artery dissection, intracranial haemorrhage
History of recent head and neck trauma	Arterial dissection, intracranial haemorrhage
Sudden onset headache	Subarachnoid haemorrhage
Postural or positional aggravation	Increased/decreased intracranial pressure (idiopathic intracranial hypertension, meningitis)
Onset >50 years of age + jaw claudication	Temporal arteritis
Persisting or worsening symptoms despite treatment	Misdiagnosis or more complex case

[†]Adapted from Durham et al. 2015[66] and Cady 2014[45]