INVITED REVIEW

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

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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 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.

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 structures1,2. 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 disturbances3–6. 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.

In addition to being the most common type of non-odontogenic orofacial pain, TMD pain is a major driver of treatment seeking, healthcare costs and reduced quality of life 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. In this study, 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 USA (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% and 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 1 or more months). However, the majority of these episodes were considered preclinical symptoms, as participants did not meet Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) for myalgia and/or arthralgia upon clinical examination.

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 TMD17. 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.

**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. TMJ ‘clicking’ was reported by 30% of adults, whereas only 8% were diagnosed with a disc displacement (DD). 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. 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).

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

**Prognosis from acute to chronic and persistence of TMD**

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

Somewhat surprisingly, the OPPERA cohort study found only a slightly elevated risk of new-onset TMD in women [hazard ratio (HR) = 1.34, 95% CI 1.03–1.75], which was nullified in the fully adjusted multivariable model. Also in contrast to the baseline OPPERA case–control study of chronic TMD, pain sensitivity and autonomic function measures did not predict TMD incidence. Authors speculate that given their prominent associations with chronic painful TMD cases; gender 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. Furthermore, an 8-year follow-up study demonstrated that structural intra-articular diagnoses remained...
stable in 71–76% of joints, with similar percentage of progression (14–15%) and reversal (10–14%)\textsuperscript{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\textsuperscript{7}. Individuals’ psychological profile and a state of pain amplification are two domains hypothesised to play a role in the aetiology of painful TMD\textsuperscript{32}. Number of comorbid conditions (e.g. irritable bowel syndrome, insomnia) and non-specific 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”\textsuperscript{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\textsuperscript{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 progression\textsuperscript{7,34}.

Biological, psychological and social vulnerabilities interact with contextual and environmental stressors to produce painful TMD and comorbidity symptoms, with or without identifiable initiating events (e.g. micro-/macro-trauma)\textsuperscript{35}. After initial onset, prognostic factors, including pain interference\textsuperscript{27}, general health, pain sensitivity\textsuperscript{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 hypothesised mechanisms also highlight possible explanations for the occurrence of painful and non-painful comorbidities.

An evaluation of 3295 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\textsuperscript{36}.

**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\textsuperscript{6}:

- Greater number of comorbid conditions, for example, irritable bowel syndrome, fibromyalgia, insomnia and depression;
- Greater number of non-specific orofacial symptoms, for example, stiffness, cramping, fatigue, pressure and 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\textsuperscript{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, sports injury and 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 gender\textsuperscript{24}.

In addition, 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\textsuperscript{25}.

**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\textsuperscript{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

Genes in which these significant SNPs are contained and mechanisms hypothesised to explain their role in TMD pathophysiology are described in Table 1\textsuperscript{36}.

Reduced Catecholamine-O-methyltransferase (COMT) activity has also been associated with pain and TMD\textsuperscript{37}. 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. 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. 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. However, the importance of the environment should be highlighted: the association between COMT haplotypes and pain sensitivity was only detectable in men and women in low and no-stress scenarios. The presence of any stress presumably overwhelms the system with epinephrine, overriding differences between COMT haplotypes, especially in women.

In addition, 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), reduced levels of anti-inflammatory (omentin-1) 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. Specifically, CGRP is a neuropeptide released from trigeminal nerves that activates neurogenic inflammation and has been found to mediate peripheral

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**Table 1** Summary of OPPERA Prospective Cohort genetic findings and potential painful TMD aetiiological mechanisms

<table>
<thead>
<tr>
<th>Gene</th>
<th>Encodes</th>
<th>Function</th>
<th>Phenotype</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCN1A</td>
<td>Alpha subunit of voltage-gated sodium channel Nav 1.1</td>
<td>Nav 1.1 is involved in the generation and propagation of action potentials in sensory nerves</td>
<td>Non-specific orofacial symptoms</td>
<td>SCN1A has also been associated with short-term memory performance in other studies and may alter somatic sensitivity</td>
</tr>
<tr>
<td>ACE2</td>
<td>Angiotensin I-converting enzyme 2</td>
<td>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</td>
<td>Non-specific orofacial symptoms</td>
<td>Pharmacologic inhibition of ACE has been associated with increase in nociceptive thresholds and tolerance, and risk of complex regional pain syndrome (CRPS)</td>
</tr>
<tr>
<td>PTGS1</td>
<td>Prostaglandin-endoperoxide synthase 1 (COX-1) enzyme</td>
<td>COX-1 catalyses the conversion of arachidonic acid into prostaglandins mediating inflammatory response and regulating neuronal sensitivity to pain</td>
<td>Global psychological symptoms</td>
<td>Could alter somatic sensitivity, awareness of autonomic activity and nociception</td>
</tr>
<tr>
<td>APP</td>
<td>Amyloid-β precursor protein</td>
<td>APP is expressed by neurons and is involved in synapse formation and neuronal plasticity. May modulate cognitive ability and cognitive aging</td>
<td>Stress and negative affect</td>
<td>Increased expression of APP may underlie higher perception of stress</td>
</tr>
<tr>
<td>MPDZ</td>
<td>Multiple PDZ domain protein (MUPP1)</td>
<td>Scaffolding for G protein–coupled receptors involved in nociception and analgesia (e.g. serotonergic and GABAergic). May also regulate glutamate-related excitatory neurotransmission</td>
<td>Heat pain temporal summation</td>
<td>May be associated with temporal summation of pain through neurotransmitter regulation</td>
</tr>
</tbody>
</table>

1 Global psychological symptoms is a composite measure built via principal component analysis, characterised 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.

2 Stress and negative affect is a composite measure built via principal component analysis, characterised 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.

3 Non-specific orofacial symptoms were measured as count of six aversive sensations of the face and jaw not described as pain: stiffness, cramping, fatigue, pressure, soreness and ache.

4 Heat pain temporal summation is a quantitative sensory test measure of endogenous pain facilitation.
and central sensitisation to pain in an animal model of TMD\textsuperscript{44}. Although its value in TMD treatment remains unknown, CGRP is a promising therapeutic target in novel monoclonal antibody treatments for migraine and other headache disorders that are already commercially available\textsuperscript{45,46}.

**Presentation**

Symptoms of painful TMD tend to present as recurrent (recurrent = 65%; persistent episode = 19% and 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% and both = 73%)\textsuperscript{47}. Interestingly, 23% of incident cases described their TMD pain as ‘headache only’\textsuperscript{47}. 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)\textsuperscript{18,47}].

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]\textsuperscript{8}. 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)\textsuperscript{49}. Children and adolescents with TMD are also more likely to be females, especially with increasing age\textsuperscript{8,23}. In addition, female adolescents may present greater TMD pain impact (e.g. jaw functional limitation, school absences and analgesic consumption) compared with males with the same pain intensity\textsuperscript{17}. Painful TMD cases in a population-based study of adults aged 20–49 years reported an average duration of symptoms of 6 years\textsuperscript{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\textsuperscript{6,23,50}. Somatic awareness and increased pain sensitivity (including in non-trigeminal areas) are strongly associated with chronic painful TMD (standardised OR> 2.0)\textsuperscript{28}. Weaker associations have also been identified between chronic painful TMD and autonomic function,\textsuperscript{28} inflammatory markers\textsuperscript{52} and endogenous pain modulation\textsuperscript{28,51}.

**Diagnosis**

In the past many different forms of TMD assessment have been proposed of which the most used were the Helkimo Index\textsuperscript{52} and the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD)\textsuperscript{53}. 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\textsuperscript{54}. The DC/TMD offers a standardised and operationalised 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\textsuperscript{54,55}. Other validated TMD screeners such as the 3Q/TMD are also available\textsuperscript{56,57}. 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\textsuperscript{54}. This has been described in detail with the commands and procedures being validated in several different languages\textsuperscript{58}. The 12 most common TMD diagnoses, most of which have established sensitivity and specificity, are as follows: myalgia (local myalgia, myofascial pain and myofascial pain with referral), arthralgia, four types of disc displacement disorders, degenerative joint disease, subluxation and headache attributed to TMD (Box 3)\textsuperscript{54}. It is important to note that an individual may present with multiple simultaneous painful and/or non-painful TMD diagnoses\textsuperscript{54}. An expanded version of the DC/TMD including less common TMD is also available\textsuperscript{59}. 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 and frequency of comorbid conditions than TMD-free individuals and that these conditions can lead to persistence and aggravation of TMD pain. 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, which can highlight contributing factors and guide tailored treatment decisions.

Box 2. Examples of TMD screening instruments

**TMD Pain Screener (short version)**

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
   b. No
   c. 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**

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.

Management

Given the complex biopsychosocial and multifactorial aetiology of TMD, treatment directed exclusively at local mechanical factors (e.g. jaw position) is 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, 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 (e.g. inability to open
milk 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. Reversible conservative therapies are recommended as first line of treatment by international consensus based on the evidence for risks and benefits, and a large proportion of incident cases presenting as self-limiting and progress to remission within the first 6–15 months. 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 programme may include identification, monitoring and avoidance of oral parafunctions (e.g. daytime clenching, nail biting and 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. There are insufficient current data to suggest whether or not specific TMD diagnoses require modifications on self-management protocol. 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 mouthguard 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). In addition, stabilisation splints produced a similar improvement in TMD pain compared with physical therapy, behavioural medicine and acupuncture. Partial coverage appliances such as the nociceptive trigeminal inhibition (NTI) and over the counter

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**Box 3. Overview of the most common Temporomandibular Disorders (TMD) diagnoses**

**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.

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 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 intermittent locking) or persistent locking with or without limited mouth opening (Disc displacement without reduction with or without limited opening).

Degenerative joint disease is characterised 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 minimising exposure to radiation by weighing the need to rule out a ‘red flag’ and whether treatment would differ based on imaging findings.
mouth-guards can be associated with adverse complications such as unwanted occlusal changes.\textsuperscript{69–71}

**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 Pingo-\textsuperscript{O}n ointment and melatonin based on one study each.\textsuperscript{72} In chronic TMD joint pain, there is evidence for non-steroidal anti-inflammatories (NSAIDs).\textsuperscript{72}

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,\textsuperscript{73,74} 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.\textsuperscript{72,75} Comorbid headaches, sleep disturbance and anxiety symptoms should also be considered in treatment selection.\textsuperscript{74} 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 with ‘usual care’ (education, counselling and an stabilisation splint), for CBT alone or in combination with biofeedback.\textsuperscript{76} Patients with TMD pain and major psychological symptoms may obtain more improvement with multimodal treatment than patients with TMD disc displacement and pain.

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**Table 2** Summary of DC/TMD Axis II questionnaires for psychosocial assessment\textsuperscript{54}

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

**Table 3** ‘Red flags’ that require special attention in the assessment of TMD/headache patients\textsuperscript{†}

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

\textsuperscript{†}Adapted from Durham et al. 2015\textsuperscript{65} and Cady 2014\textsuperscript{44}.
without major psychological symptoms\textsuperscript{69}. Biofeedback was found to be superior to active control and similar to relaxation training for reducing TMD pain\textsuperscript{69}, but did not add a significant benefit compared with CBT alone\textsuperscript{76}.

Physical therapy
Although clinical protocols for interventions and control groups vary, randomised clinical trials (RCTs) of jaw mobilisation or stretching exercises for TMD muscle pain suggest improvements in pain and jaw mobility compared with education and trans-cranial direct current stimulation, as well as improvements in pain compared with stabilisation splint\textsuperscript{77}. RCTs of postural exercises suggest improvements in TMD muscle pain and jaw mobility compared with education and CBT\textsuperscript{77}.

For TMD joint pain, RCTs of jaw mobilisation or stretching exercises suggest improvements in pain and jaw mobility compared with no treatment and stabilisation splint\textsuperscript{77}. Combinations of jaw strengthening and coordination exercises, and mobilisation and postural exercises improved joint pain and jaw mobility compared with education and stabilisation splint\textsuperscript{77}.

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 with placebo acupuncture, as well as similar results to stabilisation splint\textsuperscript{77}. Another systematic review and meta-analysis including 13 studies of TMD found improvements in TMD muscle pain for acupuncture compared with placebo (sham) acupuncture\textsuperscript{79}.

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\textsuperscript{80}.

A systematic review with network meta-analysis revealed equivocal evidence for the effects of intramuscular botulinum toxin injections for TMD muscle pain compared with placebo injection\textsuperscript{72}. 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\textsuperscript{81}, and failure of reversible and conservative treatments alone is not an indication to progress to irreversible and invasive approaches. In addition, as 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\textsuperscript{69}. 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 with medical management or non-surgical rehabilitation\textsuperscript{82}. 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\textsuperscript{82}.

One systematic review reported improvements in TMD joint pain for intra-articular injections of hyaluronic acid (HA) and corticosteroid compared with placebo injection\textsuperscript{72}, 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\textsuperscript{72} or between arthrocentesis with or without HA\textsuperscript{83}.

Orthodontics and occlusal adjustments
There is no evidence for the efficacy of occlusal adjustment compared with placebo in TMD treatment or prevention, including therapeutic occlusal position or equilibration by orthopaedic, orthodontics or prosthodontics means\textsuperscript{84}. Although occlusion is of evident functional importance to mastication and should be managed with care in dental practice\textsuperscript{84}, current evidence does not support a causal role in the pathophysiology of TMD\textsuperscript{85}.
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 as first onset). However, studies of prevalent cases tend to oversample individuals with longer TMD duration (i.e. chronic) resulting in length-biased sampling. 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). Despite substantial progress in the understanding of biological and psychological determinants of painful TMD, the investigation of multi-level social and contextual factors has been lacking. Evidence from the broader pain literature indicates that neighbourhood disadvantage is associated with the onset of chronic musculoskeletal pain after motor vehicle collision and onset of disabling pain in older adults. In addition, individual and neighbourhood social capital are associated with dental pain, psychosomatic symptoms, musculoskeletal pain and depression.

The International Classification of Orofacial Pain (ICOP), the first classification system for all orofacial pain disorders, including TMD, has been recently published. 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, as 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 sensitisation; the molecular target that is responsible for this specific mechanism, for example, CGRP or nerve growth factor. 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.

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 localised ’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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Author contributions

JD contributed with overall study conceptualisation and design; FPK, FGE and JFOS reviewed the substantive literature and contributed to manuscript drafting; In addition, all authors provided critical review for intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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