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REVIEW ARTICLE

Distinguishing chronic pain from mechanical factors in chronic TMD: a narrative review

Blake Moore[a], Guangzhao Guan[a], Brian Whitley[b], Li Mei[c] and Ajith D. Polonowita[a]

[a]Department of Oral Diagnostic and Surgical Sciences, Faculty of Dentistry, University of Otago, Dunedin, New Zealand; [b]Consultant Oral & Maxillofacial Surgeon, Private Practice, Hamilton, New Zealand; [c]Department of Oral Sciences, Faculty of Dentistry, University of Otago, Dunedin, New Zealand

ABSTRACT

The International Classification of Diseases-11 (ICD-11) defines chronic pain conditions as those that lack identifiable underlying pathology at the site of pain. In parallel, the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) system was developed as a comprehensive framework for diagnosing and managing conditions previously classified under the broader category of temporomandibular disorders (TMD). While the DC/TMD system provides a structured and clinically useful approach, it does not fully distinguish between pain-related disorders and mechanical dysfunction associated with TMD. Specifically, mechanical temporomandibular joint (TMJ) conditions, as described in the DC/TMD, are distinct from chronic pain present in chronic TMD (cTMD). These mechanical issues may or may not involve chronic pain, and despite often coexisting with chronic facial pain, they represent separate diagnostic entities that necessitate individualised management strategies. This differentiation is essential for accurate diagnosis and effective treatment of chronic TMD patients. This review provides a comprehensive analysis of cTMD, synthesising evidence from genotyping studies, systemic inflammation, immune dysregulation, endocrine disturbances, advanced imaging, and the biopsychosocial model. By integrating these diverse perspectives, it explores the complex interplay between genetic predisposition, anatomical factors, systemic inflammation, immune and endocrine imbalances, and biopsychosocial influences in cTMD.

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Introduction

Chronic temporomandibular disorder (cTMD) refers to a chronic pain syndrome, as classified within the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD). It represents the progression of temporomandibular disorders (TMD) into a persistent pain condition (Polonowita et al. 2024a). cTMD is categorised under the International Classification of Diseases-11 (ICD-11) as either chronic primary or chronic secondary pain. Clinically, chronic pain is often non-specific usually without pathology

CONTACT Guangzhao Guan simon.guan@otago.ac.nz

or tissue damage. When pathology is present, the pain is often disproportionally severe (Nijs et al. 2021b).

The DC/TMD is a well-established classification system that provided valuable guidance at the time of its introduction. However, it combines mechanical disorders with chronic pain conditions. With advances in the understanding of chronic pain, the ICD-11 now distinguishes chronic pain as a separate entity from mechanical joint disorders or pathology. To align with current pain literature, it has been suggested that the chronic pain components be removed from the DC/TMD, leaving only the mechanical conditions of the TMJ. This perspective is supported by a key report from the National Academies of Sciences, Engineering, and Medicine, which criticised the dental community for its siloed approach to TMD, particularly in contrast to the broader chronic pain literature in medicine, ultimately to the detriment of patient outcomes (Yost et al. 2020).

Literature search and selection methods

This narrative review was to explore the distinctions between chronic pain and mechanical factors in TMD. Although the approach was not systematic, the selection process aimed to achieve a balance between breadth and scholarly rigour. Relevant literature was identified through searches of PubMed, Scopus, and Google Scholar, covering the period from 1999 to 2024. Search terms included combinations of keywords and Medical Subject Headings (MeSH), such as 'temporomandibular disorders', 'chronic pain', 'chronic TMD pain,' 'cTMD', 'myofascial pain', 'internal derangement', 'mechanical TMD factors', 'joint dysfunction', 'pain mechanisms', and 'biomechanics'. In addition, manual searches of reference lists from key articles were conducted to supplement the database results.

Studies were included if they focused on clinical research, reviews, or consensus guidelines addressing subtypes of TMD pain (e.g. myofascial versus articular), with particular emphasis on those differentiating between central sensitisation and local mechanical aetiologies. Case reports and non-English publications were excluded due to limitations in resources. The synthesis of the literature was organised thematically, focusing on (a) pathophysiological distinctions such as neuroplasticity versus disc displacement, (b) diagnostic challenges, and (c) implications for clinical management. Priority was given to studies published in high-impact journals and those frequently cited in the field.

Pain is described by the International Association for the Study of Pain (IASP) as '*an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*' (Raja et al. 2020). The conflicting messaging between cTMD and mechanical TMJ conditions is the fact that these are separate diagnostic entities. The former having established evidence for potential genetic susceptibility, and influenced by such factors as childhood trauma, biopsychosocial factors, chronic overlapping pain conditions, and development of central sensitisation, with similar pathophysiology to other chronic pain conditions (Treede et al. 2019; Polonowita et al. 2024a). In contrast, mechanical TMJ conditions encompasses abnormalities where there may be a direct physical source affecting function and may occur with or without pain. This might involve locking or restriction from internal derangement, ankylosis, post-traumatic deformity, condylar hyperplasia, or tumour obstruction (Olate et al.

2023). Mechanical TMJ disorders may or may not always require further management but some of these presentations may trigger chronic secondary pain as classified under the ICD-11.

The most recent classification, ICD-11 in 2019, defines chronic pain as persistent or recurrent pain of at least 3 months duration (Treede et al. 2019). The duration of acute pain is less than 3 months and not part of the scope of this discussion. The classification divides chronic pain into two subgroups: chronic primary pain and chronic secondary pain conditions. Chronic primary pain conditions arise from one or more regions of the body, where there is no pathology at the site of pain (Treede et al. 2019). Under the ICD-11, cTMD exists as a classification of orofacial pain, and the latter is a chronic primary pain condition subtype (Treede et al. 2019; Polonowita et al. 2024a). Chronic secondary pain conditions arise when there is a possible trigger from an underlying disease, but once three months have passed, then the pain (which is now chronic), not the trigger, becomes the entity to be focused on from a pain perspective. Residual pain may continue after the initial disease process (trigger) has been successfully managed (Treede et al. 2019). Many other secondary subtypes exist including post-cancer, post-surgical, and chronic neuropathic pain. Once chronic pain has developed, central and peripheral sensitisation of neural pathways has been established (Polonowita et al. 2024b). The authors use the term 'nociplasia' to indicate the pathophysiological process creating nociplastic changes in these pathways. Much like dysplasia, where there is variable severity of pathological changes, nociplasia more broadly reflects individual variation in neuroplastic changes due to the multifactorial nature of inputs contributing to nociplastic pain of chronic pain syndromes. The presence of nociplasia differentiates cTMD from mechanical TMJ disorders.

Chronic primary orofacial pain is split into primary and secondary pain conditions (Benoliel et al. 2019; Nicholas et al. 2019). The ICD-11 classification defines chronic orofacial pain as orofacial pain that '*occurs on at least 15 days per month for longer than 3 months. The duration of pain per day is at least 2 h (untreated), or several shorter attacks per day may occur*' (Nicholas et al. 2019). Chronic secondary orofacial pain is defined by ICD-11 as orofacial pain that

> occurs on at least 50% of the days during at least 3 months and lasting at least 2 h per day and is clearly associated with the effects of disease (regional or systemic), trauma (physical, chemical, radiation), infection, or a host of other factors. (Benoliel et al. 2019)

Currently, DC/TMD categorises TMD conditions into myogenous and arthrogenous origins under its axis I classification and focusses on pain-related disability and psychological status in its axis II classification (Schiffman et al. 2014). Local myalgia is characterised by muscle tenderness that is confined to the site of pain. Pain on movement, function, or parafunction replicated on muscle testing is defined as myalgia (Fernández-de-Las-Peñas et al. 2023). Myofascial pain, on the other hand, involves referred pain that extends beyond the muscle into surrounding structures. The authors believe that referencing anatomical boundaries or structures is unhelpful, particularly under the ICD-11 framework, where there may be no pathology at the site of pain. Headaches could be attributed to TMD when a headache in the temple area is replicated by provoking TMD pain (Schiffman et al. 2014). It should be noted that these terms are historical and refers to chronic pain whether primary or secondary.

DC/TMD describes four arthogenous origins: arthralgia, internal derangement, degenerative joint disease, and subluxation. Arthralgia is defined as joint origin pain on testing (Beecroft et al. 2024). Internal derangement refers to disc displacement and requires positive findings on MRI to satisfy the criteria for defining subtypes (Molinari et al. 2007). Disc displacement associated with reduction requires an anteriorly positioned disc in the closed mouth position that reduces with a click/pop upon opening. Reduction and intermittent locking occur when a patient has episodes without reduction. Disc displacement without reduction could occur with limited opening (assisted opening <40 cm) or normal opening (>40 cm assisted opening) (Schiffman et al. 2014). Degenerative joint disease (DJD) criteria are satisfied with a history of grinding, crepitus on exam and confirmatory changes on computed tomography imaging (Li et al. 2021). Subluxation refers to hypermobility of the jaw to the point of dislocation, where self-reduction is possible (Schiffman et al. 2014; Beecroft et al. 2024).

Axis II assessment is the second arm of the DC/TMD classification, designed to assess and screen for pain intensity, maladaptive pain behaviours (emotional functioning), psychological comorbidities (e.g. anxiety or depression), and physical functioning, both general and disease-specific (Schiffman et al. 2014; Beecroft et al. 2024). Prognostically, Axis II provides greater insight than the Axis I physical diagnosis, helping to explain why certain treatments are effective for some patients but not for others (Schiffman et al. 2014). Axis II assessment is divided into two levels: screening and comprehensive assessment (Schiffman et al. 2014; Busse et al. 2023). Screening involves the use of tools such as the graded chronic pain scale, jaw functional limitation scale (short form), patient health questionnaire (PHQ-4), oral behaviours checklist and pain drawing (Schiffman et al. 2014). Comprehensive assessment deviates from the screening by using the long form jaw functional limitation scale, patient health questionnaires PHQ-15 and PHQ-9, and generalised anxiety disorder (GAD-7) (Schiffman et al. 2014). Patients positive for screening should proceed to the comprehensive assessment arm (Schiffman et al. 2014; Beecroft et al. 2024). Specifically validated questionnaires can be utilised for pain syndromes such as the fibromyalgia survey questionnaire (FSQ) (Varallo et al. 2021; Savin et al. 2023).

Most patients referred to secondary centres do not require surgical intervention and often have experienced pain for over three months by the time they are seen (Rajapakse et al. 2017; Sidebottom 2024). Consequently, clinicians need to recognise and manage the pain as chronic. There are other important aspects of a patient's history that could be difficult to consider under the DC/TMD classification system. Current evidence highlights several factors that contribute to the complex nature of cTMD. These include underlying genetic susceptibility to chronic pain, correlations between imaging findings and reported symptoms, and the impact of mental health (Beecroft et al. 2024). Additionally, co-morbidities with other pain syndromes and the biopsychosocial model of chronic pain are significant contributors. These elements underscore the multifaceted nature of cTMD, demonstrating that it cannot be fully understood or managed by focusing solely on mechanical causes (Busse et al. 2023; Beecroft et al. 2024; Polonowita et al. 2024a). This review focuses on cTMD, offering a summary of the current evidence from genotyping studies, systemic inflammation, immune dysregulation, and endocrine disturbances, advanced imaging techniques, and the application of the biopsychosocial model (Table 1).

Table 1. Evidence from genotyping, imaging, systemic inflammation & immune dysregulation, endocrine and biopsychosocial model.

	Sample	Method	Clinical focus	Outcomes	Main findings	References
Genotyping	Blood (DNA)	PCR	TMJ Masseter	G1: C_T genotype for HTR3A. G2: T_T genotype for HTR3A. G3: A_C genotype for HTR3B. G4: C_C genotype for HTR3B.	Single nucleotide polymorphisms and genetic variations in key genes involved in central pain processing have been linked to chronic temporomandibular disorders (cTMD), as well as to altered pain perception, modulation, and individual pain experiences. These genetic factors may play a crucial role in the variability of how pain is processed and experienced, contributing to the pathophysiology of cTMD	Louca Jounger et al. (2016)
	Saliva (DNA)	PCR	TMJ, Temporalis muscle, Masseter, Archilles tendon	G1: G_A genotype. G2: A_A genotype. G3: G_A + A_A genotypes		Furquim et al. (2016)
	Blood (DNA)	PCR	Trapezius, Masseter, Arm	A118G SNP of the OPRM1 gene G1: AA genotype		Hastie et al. (2012)
	Blood (DNA)	PCR	TMJ, Temporalis muscle, Masseter, Arm, Hand, Foot	G1: LPS/LPS diplotype		Diatchenko et al. (2006)
	Blood (DNA)	PCR	Trapezius, Masseter, Arm	A118G SNP of the OPRM1 gene G1: A_A genotype.		Fillingim et al. (2005)
Imaging modalities		MRI	TMJ	Correlation of MRI TMJ findings to TMJ pain and symptoms	The severity of pain experienced in cTMD does not consistently correlate with the degree of abnormalities observed in imaging studies. This disconnect suggests that pain intensity in cTMD may be influenced by factors beyond structural changes, such as central pain sensitisation or individual variability in pain perception	Lamot et al. (2013)
		MRI	TMJ	Correlation of MRI TMJ findings to TMJ pain and symptoms		Higuchi et al. (2020)
		MRI	TMJ	Correlation of symptoms to disc position on MRI		Yoda et al. (2003)
		CBCT	TMJ	Correlation of degenerative imaging findings to TMD pain and symptoms		Palconet et al. (2012)
		CBCT	TMJ	Correlation of degenerative imaging findings to TMD pain and symptoms		Shahidi et al. (2018)
Systemic Inflammation & Immune Dysregulation	Blood	Immunoturbidimetric assay and cytokine assays	IL-1β, IL-6, TNF-α, IL10 CRP	Participants scored in Graded Chronic Pain Scale for TMD disability and Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) for sleep disturbance.	High TMD disability was associated with elevated inflammatory mediators and greater sleep disturbance.	Park and Chun, (2016)
	Saliva	ELISA	IL-1β	DC/TMD and Fibromyalgia Survey Diagnostic Criteria and Severity Scale.	Salivary IL-1β levels were significantly higher in TMD +/ – Fibromyalgia patients but not elevated in those with Fibromyalgia alone.	Cê et al. (2018)
		Mendelian randomisation study using genetic instrumental variables	Single nucleotide polymorphisms for	Comparison with genetic data from TMD patients from Finnish biobank donors	Those genetically predisposed to Rheumatoid arthritis and Multiple	X. Chen et al. (2024)

(*Continued*)

Table 1. Continued.

	Sample	Method	Clinical focus	Outcomes	Main findings	References
			many autoimmune diseases		Sclerosis are more likely to be associated with TMD.	
	Blood	Immunoassays	IL-1α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and multiple other chemokine/cytokine assays. RF, LAC, ds-DNA, CRP, ESR and multiple other autoantibody assays	Assessment of TMD comorbidity with a range of psychological scoring questionnaires.	Higher pain intensity and duration in TMD is associated with higher systemic inflammation across multiple inflammatory markers, consistent with health-related quality of life and disability assessment scoring.	Son et al. (2021)
Endocrine	Buccal mucosa samples (DNA)	PCR	ERα & ERβ	Gene polymorphisms G1: rs2234693 ESR1 G2: rs9340799 ESR1 G3: rs1256049 ESR2 G4: rs4986938 ESR2	The polymorphism rs1256049 ESR2 was associated with disc displacement and arthralgia in adults.	Küchler et al. (2020)
	Saliva samples	Liquid chromatography tandem mass spectrometry	Cortisol & Cortisone	Psychological stress scores using the Hospital Anxiety and Depression Scale and Coping Strategies Questionnaire	The TMD group had higher amounts of salivary glucocorticoid and had higher scores for pain catastrophising and anxiety/depression in psychological questionnaires.	Staniszewski et al. (2018)
	Saliva samples	Electrochemiluminescence immunoassay	Cortisol	Chronic Pain Grade questionnaire compared against assessment of individuals' HPA-axis function	Dysregulation of the HPA-axis is associated with chronic pain conditions and may be partly masked by the presence of depressive/anxiety disorders.	Generaal et al. (2014)
Biopsychosocial Model		Multimodal Internet based pain programme randomised pilot trial	cTMD	Internet based pain programme improved physical function	Adopting a biopsychosocial approach to the management of cTMD is crucial for effectively reducing pain severity and enhancing treatment outcomes. By addressing the complex interplay between biological, psychological, and social factors, this holistic approach can lead to more personalised and successful interventions, improving both pain management and overall quality of life for individuals with cTMD.	Lam et al. (2020)
		Randomised trial comparing different conservative therapies in cTMD	cTMD	Manual therapy, counselling, and occlusal splints were all equally effective in reducing pain, improving sleep quality and overall quality of life.		De Resende et al. (2021)
		Acceptance and commitment therapy (ACT) on cTMD symptoms systematic review	Chronic pain syndromes including cTMD	ACT appears to reduce symptoms of central sensitisation and improve quality of life.		Galvez-Sánchez et al. (2021)
		Catastrophising in cTMD systematic review	cTMD	Catastrophising increases symptom severity and is associated with a poorer response to treatment.		Häggman-Henrikson et al. (2020)

Central sensitisation in cTMD

Although the mechanisms involved in developing chronic pain are not fully understood, central sensitisation has significant involvement and is present in neuropathic and nociceptive pain (Ashmawi and Freire 2016; Nijs et al. 2021a, 2021b). The IASP uses three main phenotypes to describe painful conditions; nociceptive, neuropathic, and nociplastic pain (Kosek et al. 2016; Nijs et al. 2021a). Nociceptive pain is defined as the activation of receptors in terminals of primary afferent neurons in a proportional response to mechanical/thermal stimuli or noxious chemicals (Fernández-de-Las-Peñas et al. 2023). The IASP regards neuropathic pain to be present when there is direct disease of the peripheral or central nervous system causing pain, in a neuroanatomically plausible distribution, supported by clinical findings and investigations (i.e. imaging or laboratory tests) (Scholz et al. 2019). The pathophysiology of neuropathic pain and TMD is poorly understood (Minervini et al. 2023). Pain symptoms within cTMD patients are variable. cTMD can present with atypical pain symptoms, such as sharp rapid fluctuations in pain levels, more resembling neuropathic pain (Baggen et al. 2024). In a small qualitative study looking at this patient group (chronic orofacial pain with neuropathic symptom characteristics), authors found these patients had a delay in diagnosis of cTMD and had received invasive or non-invasive treatments for neuropathic pain, that were mostly unsuccessful (Baggen et al. 2024). cTMD is more commonly associated with nociceptive and/or nociplastic pain phenotypes in both adult and paediatric populations (Minervini et al. 2023; Baggen et al. 2024).

Central sensitisation is viewed as the primary driver of nociplastic pain. This occurs when there is an exaggerated response and/or lower activation threshold of peripheral afferents to nociceptive stimuli as well as a reduced downward inhibition (Nijs et al. 2021b). Pain can be deemed nociplastic if it has been present for longer than 3 months, has a diffuse regional distribution, is without neuropathic or nociceptive origin, and pain hypersensitivity (Nijs et al. 2021b). A fourth pain category 'mixed pain', where nociceptive, neuropathic, and nociplastic pain may coexist in different combinations and circumstances, may occasionally be present in cTMD patients (Baggen et al. 2024). In central sensitisation, modulatory neuroplastic changes occur in pain processing centres of the prefrontal cortex, anterior cingulate cortex and somatosensory cortex, affecting perception and emotional responses to chronic pain (Sessle 2021; Polonowita et al. 2024a). Repetitive and intense stimuli cause sensitisation of the peripheral nervous system. These inputs cause excitability and increased synaptic efficiency in the central network of nociceptive neurons (Ashmawi and Freire 2016; Fernández-de-Las-Peñas et al. 2023). Sensitisation of the peripheral afferent is mediated by neurotransmitters such as glutamate, bradykinin, substance P and calcitonin gene-related peptide (CGRP). Increased intracellular calcium is thought to be a major contributor to neuroplastic changes due to changes in plasma membrane excitability predominantly mediated via capsaicin-sensitive C-fibre nociceptors (Figure 1) (Ashmawi and Freire 2016; Treede et al. 2022; Polonowita et al. 2024a). Current literature supports the view that these mechanisms likely underpin development of chronic secondary pain in orofacial pain conditions (Fernández-de-Las-Peñas et al. 2023).

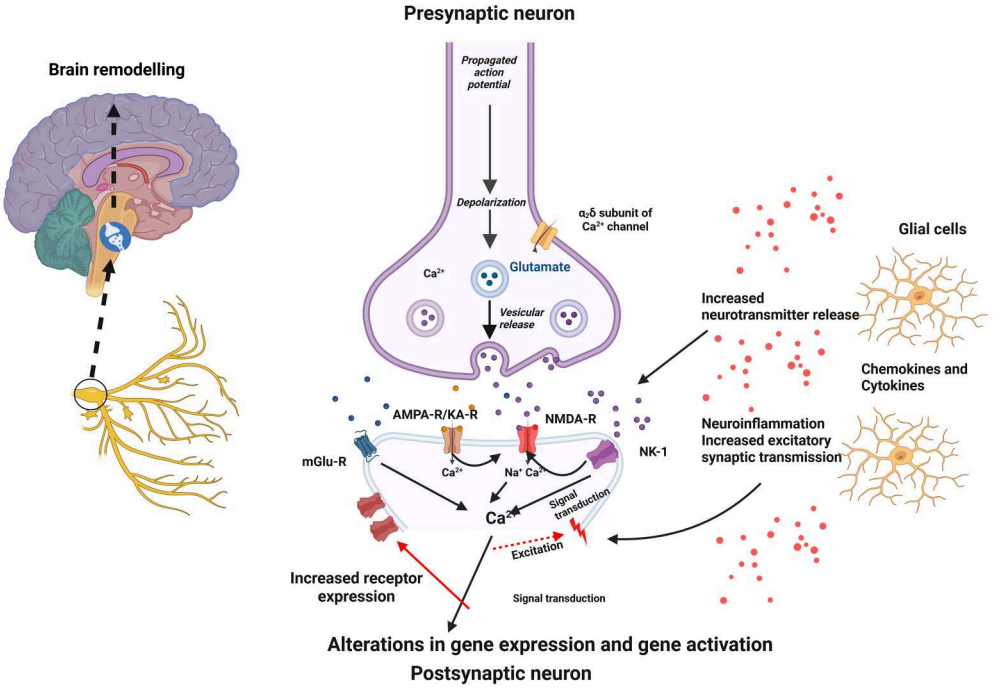

Figure 1. Brain remodelling and synaptic signal transmission. The figure illustrates key mechanisms underlying brain remodelling, emphasising synaptic transmission and pain signal amplification. In the presynaptic neuron, increased calcium influx through α-subunits of Ca^{2}? channels promotes the release of excitatory neurotransmitters, including glutamate and substance P (SP). Glutamate activates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate (KA), and N-methyl-D-aspartate (NMDA) receptors, facilitating calcium entry into the postsynaptic neuron. Simultaneously, SP binds to neurokinin-1 (NK-1) receptors, triggering intracellular calcium elevation via signal transduction pathways. The combined action of glutamate and SP, along with AMPA and NK-1 receptor activation, leads to a substantial rise in postsynaptic calcium levels, driving heightened excitation and long-term neuronal changes. This process enhances receptor expression on the postsynaptic membrane, reinforcing synaptic transmission. Additionally, chemokines and cytokines – many released by glial cells – modulate and amplify these pathways, contributing to neuroinflammation and the escalation of pain signals to higher brain centres. Together, these mechanisms highlight the dynamic interplay between synaptic activity, neuroimmune interactions, and brain remodelling. Created in BioRender. Guan, S. (2025) https://BioRender.com/g8wurps

Genes and cTMD

TMD is well known to be complex and multifactorial in nature, meaning its development and progression are influenced by a combination of various factors rather than a single cause. These factors include genetic predisposition, lifestyle choices, and environmental influences (Fillingim et al. 2005; Diatchenko et al. 2006; Hastie et al. 2012; Furquim et al. 2016; Louca Jounger et al. 2016). Despite extensive research, no specific single gene has been definitively identified as the sole contributor to TMD. This highlights the intricate nature of the disorder and the challenges in pinpointing its exact genetic underpinnings. However, emerging evidence suggests a significant association between catechol-O-methyltransferase (COMT), a gene involved in the regulation of neurotransmitters,

and cTMD (Yin et al. 2020; Brancher et al. 2021). This connection is supported by prior research that has established COMT's role in the biological processes related to pain perception. COMT is known to influence the breakdown of catecholamines, such as dopamine and norepinephrine, which play a role in pain modulation. Variations in COMT activity, therefore, could affect an individual's sensitivity to pain and their susceptibility to chronic pain conditions like TMD (Meloto et al. 2016). A recent meta-analysis has further strengthened this association by demonstrating that individuals with specific COMT polymorphisms (genetic variations) are at a significantly higher risk of developing painful TMD and myofascial pain. Myofascial pain, a common feature of TMD, involves discomfort and tenderness in the muscles controlling jaw movement. A growing body of evidence highlights the role of COMT polymorphisms in pain perception and modulation. A recent meta-analysis identified specific COMT variants that may be associated with an increased risk of chronic pain conditions (Tammimäki and Männistö 2012; Vetterlein et al. 2023). Notably, the Val158Met polymorphism has been significantly linked to fibromyalgia, greater pain intensity, depression, and sleep disturbances (Gerra et al. 2024). Several studies have shown that individuals with the Met/Met genotype of this polymorphism exhibit heightened pressure pain sensitivity and elevated levels of depression (Fernández-de-Las-Peñas et al. 2019). In patients with TMD, the Val158Met variant has been associated with increased pain sensitivity (Pinto Fiamengui et al. 2020). Supporting this, Lim et al. (2021) demonstrated that chronic TMD patients carrying the methionine (Met) allele showed significantly greater pain sensitivity and reduced μ-opioid receptor availability in the parahippocampal region during a sustained masseteric pain challenge compared to healthy controls. In addition to Val158Met, other COMT polymorphisms have also been implicated in TMD-related pain. For instance, the AA genotype of rs165774 may increase susceptibility to TMD and related pain, while the AA genotype of rs6269 has been associated with reduced postoperative chronic TMD pain and lower acute pain levels following dental extraction (Mladenovic et al. 2016). These findings align with the broader understanding of COMT's role in pain pathways, suggesting that genetic variations in COMT may contribute to the chronicity and severity of TMD-related pain (Brancher et al. 2021). Despite this, there has been conflicting data and non-reproducible outcomes within this literature.

A recent systematic review found sensitivity to thermal and mechanical pain stimuli was associated with afferent and efferent neuronal signalling (Soares et al. 2020). They specifically highlighted several genes, including COMT, which is involved in pain processing; opioid receptor mu 1, part of the opioid pathway; tumour necrosis factor α, associated with the inflammatory pathway; and dopamine receptor D2, linked to the dopaminergic pathway. Notably, no association was found with serotoninergic pathways involving the 5-hydroxytryptamine receptor 3A and 5-hydroxytryptamine receptor 3B in TMD. Current genetic literature emphasises the significant role of polymorphisms in these genes, contributing to the variability in pain perception and individual predisposition to chronic pain (Visscher and Lobbezoo 2015; Fillingim 2017). This highlights the importance of considering genetic factors when evaluating and treating chronic pain conditions like TMD.

However, genetic studies on TMD face several limitations. TMD is a multifactorial condition influenced by genetic, environmental, and biopsychosocial factors, making it

challenging to isolate the contribution of genetic variants. Many studies have limited sample sizes, reducing statistical power and the ability to detect significant associations. TMD include various subtypes, each with distinct symptoms and causes, making it challenging to identify consistent genetic markers across studies. Moreover, many genetic findings lack replication in independent cohorts, raising questions about their validity and broader applicability. Additionally, genetic associations with TMD often differ significantly among ethnic and population groups, further limiting the generalisability of these results to diverse populations. Many studies have overlooked the important roles of epigenetic modifications and gene-environment interactions, both of which may significantly contribute to TMD development. For instance, a genome-wide DNA methylation study involving identical twins and unrelated individuals identified differentially methylated regions (DMRs) linked to pain sensitivity. Notably, stable epigenetic signals, including one in the TRPA1 gene, point to potential molecular mechanisms underlying chronic pain that may also extend to other complex traits (Bell et al. 2014). Supporting this, a systematic review and meta-analysis found a potential association between TRPA1 hypermethylation and increased pain sensitivity, despite heterogeneity across studies (Celsi et al. 2023). Moreover, chronic pain has been shown to induce long-lasting epigenetic changes in key brain regions involved in pain and emotional processing, such as the periaqueductal gray, lateral hypothalamus, and nucleus accumbens. These changes, marked by reductions in activating histone modifications, suggest that nerve injury leads to sustained chromatin-mediated suppression of gene transcription, which may contribute to altered pain sensitivity and processing (Bryant et al. 2023). Focusing primarily on common genetic variants may result in the omission of rare variants that could have a substantial impact on TMD risk. Even when genetic associations are identified, translating these findings into clinical applications, such as personalised treatment or prevention strategies, remains a significant challenge.

Systemic inflammation, immune dysregulation, and endocrine disturbances

Recent research has increasingly highlighted the role of systemic inflammation, immune dysregulation, and endocrine disturbances in the development and persistence of TMD (Warren and Fried 2001; Hysa et al. 2023; Thomas et al. 2023; Zieliński and Pająk-Zielińska 2024). These factors may contribute to the complex pathophysiology of cTMD, particularly in cases where pain and dysfunction cannot be fully explained by local mechanical or structural abnormalities within the TMJ.

Systemic inflammation and immune dysregulation

cTMD has been associated with elevated levels of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α), which are markers of systemic inflammation (Park and Chung 2016). These cytokines are known to play a role in pain sensitisation and the maintenance of chronic pain states. For example, studies have shown that individuals with cTMD often exhibit higher levels of these inflammatory markers in their saliva, synovial fluid and blood compared to healthy controls (Alstergren et al. 1999; Cê et al. 2018; Sorenson et al. 2023). This suggests

that systemic inflammation may contribute to the persistence of pain and joint dysfunction in TMD patients. Additionally, immune dysregulation has been implicated in cTMD (Kopp 2001). Autoimmune processes, such as the production of autoantibodies targeting joint tissues, have been observed in some TMD patients, particularly those with comorbid autoimmune conditions like rheumatoid arthritis or systemic lupus erythematosus (Son et al. 2021; X. Chen et al. 2024). These autoimmune responses may lead to chronic inflammation and tissue damage within the TMJ, further exacerbating symptoms.

Endocrine disturbances

Endocrine disturbances, particularly those involving the hypothalamic–pituitary–adrenal (HPA) axis and stress-related hormones, have also been linked to TMD, and chronic pain in general (Generaal et al. 2014; Staniszewski et al. 2018). Dysregulation of the HPA axis, which controls the body's response to stress, may lead to abnormal cortisol levels and contribute to chronic pain conditions (Generaal et al. 2014). For instance, studies have found that individuals with TMD often exhibit altered cortisol profiles, including blunted diurnal cortisol rhythms, which are associated with heightened pain sensitivity and poor stress adaptation (Jones et al. 1997; AlSahman et al. 2024). Sex hormones, such as oestrogen, have also been implicated in the pathophysiology of TMD. Females are disproportionately affected by TMD, and fluctuations in oestrogen levels during the menstrual cycle, pregnancy, or menopause have been shown to influence pain perception and TMJ function (Küchler et al. 2020; Leucuța et al. 2024). Oestrogen may modulate inflammatory processes and pain signalling pathways, potentially explaining why women are more susceptible to TMD (Q. Chen et al. 2021).

Integration of evidence

The interplay between systemic inflammation, immune dysregulation, and endocrine disturbances provides a broader framework for understanding chronic pain and cTMD. These systemic factors may explain why some individuals develop chronic pain despite minimal structural abnormalities on imaging. For example, systemic inflammation and immune activation can sensitise the nervous system (Ji et al. 2018; Vergne-Salle and Bertin 2021). Similarly, endocrine disturbances may alter pain thresholds and contribute to the chronicity of symptoms (Tennant 2013). In summary, cTMD is increasingly understood as a condition influenced by systemic inflammation, immune dysregulation, and endocrine disturbances, which leads to changes including epigenetics that is important in the construction of the cTMD patient (Polonowita et al. 2024a). This broader perspective highlights the need for comprehensive, individualised treatment approaches that address both the local and systemic contributors to cTMD.

Imaging modalities for cTMD

cTMD, whether classified under ICD-11 as chronic primary pain or chronic secondary pain, is not primarily attributed to mechanical dysfunction within the TMJ (Polonowita et al. 2024b). This distinction is important because it highlights that the pain experienced

by individuals with cTMD is not solely or directly caused by structural issues within the joint itself. Instead, cTMD is increasingly understood as a complex pain condition that involves central and peripheral nervous system mechanisms, psychosocial factors, and other non-mechanical contributors. One of the key observations in cTMD is the frequent lack of correlation between the severity of imaging findings, such as disc displacement or degenerative joint disease (DJD), and the intensity of pain symptoms. For example, some individuals may exhibit significant structural abnormalities in the TMJ, such as disc displacement or joint degeneration, yet report minimal or no pain. Conversely, others may experience severe and debilitating pain despite having relatively normal or mild imaging findings. This discrepancy mirrors the well-documented phenomenon seen in other chronic pain conditions, such as chronic back pain, where the severity of pain often does not align with the degree of structural damage observed on spinal MRI imaging (Lamot et al. 2013; Delpachitra and Dimitroulis 2022). A randomised controlled trial investigated the effectiveness of jaw exercises for individuals with anterior disc displacement with reduction, comparing the outcomes to those of a control group. The study found that 62% of participants in the jaw exercise group reported a 'successful' improvement in their symptoms, suggesting that the exercises provided meaningful relief for a majority of participants. However, when post-intervention MRI results were analysed, only 23% of those who reported successful symptom improvement showed evidence of disc recapture. This discrepancy highlights that while jaw exercises may alleviate symptoms for many individuals, the underlying structural changes in the TMJ, such as disc repositioning, do not always align with the reported clinical improvements (Yoda et al. 2003). Recent cross-sectional studies have identified specific MRI findings that show a stronger correlation with TMJ pain. Notably, bone marrow oedema, joint effusion, and increased signal intensity of the posterior disc attachment have been significantly associated with the presence of pain. These findings suggest that certain inflammatory and structural changes visible on MRI may play a role in the pain experience of individuals with TMJ disorders (Higuchi et al. 2020). However, the relationship between imaging findings and pain is not always straightforward. For example, a prospective study involving 91 patients analysed MRI findings related to disc position and the articular surface of the condyle. Among symptomatic patients, 43.4% were found to have disc displacement, but the study noted a weak correlation between these radiological findings and the pain levels reported by patients (Wurm et al. 2018). While MRI findings could provide important diagnostic information about the structural integrity of the TMJ, they do not fully explain the pain experience or its chronicity. In addition, it does not reflect the efferent and afferent neural pathway dysfunction, or genetic and biopsychosocial aspects of chronic pain in cTMD (Polonowita et al. 2024a). As a result, clinicians must consider a broader, more holistic approach when diagnosing and managing TMJ pain, integrating imaging findings with clinical symptoms, patient history, and other contributing factors to develop effective treatment strategies (Vilanova et al. 2007; Wurm et al. 2018; Higuchi et al. 2020).

Clinically, most anterior disc displacements have a favourable expected natural outcome, with minimal difference between invasive and non-invasive treatments (Rajapakse et al. 2017; Beecroft et al. 2024; Sidebottom 2024). There is an unclear relationship between disc displacement on imaging and development of osteoarthritis. Significant controversy remains due to limited evidence concerning the aetiology of TMJ

osteoarthritis and lack of diagnostic standardisation in the spectrum of disease (Delpachitra and Dimitroulis 2022). The dissociation between imaging findings and pain severity underscores the importance of recognising cTMD as a condition that extends beyond purely mechanical or structural factors. It suggests that the pain experienced in cTMD is likely influenced by a combination of neurobiological, psychological, and environmental factors. For instance, central sensitisation may play a significant role in amplifying pain perception in chronic TMD, even in the absence of significant joint pathology. Additionally, psychosocial factors such as stress, anxiety, and depression can further modulate pain experiences and contribute to the chronicity of symptoms.

Biopsychosocial framework, management and cTMD

There is strong evidence that, as part of the assessment and management of patients, cTMD should be approached through a genetic and biopsychosocial framework (Driscoll et al. 2021; Busse et al. 2023; Beecroft et al. 2024). This framework asserts that there are numerous complex interactions between biological, psychological and social factors, explaining variability in individual pain experiences (Fillingim 2017; Polonowita et al. 2024a). The literature increasingly highlights the interconnectedness of genetic susceptibility, psychological factors and coping mechanisms, sleep, and social support systems in cTMD patients (de Resende et al. 2021; Polonowita et al. 2024a). This comprehensive model is further reinforced by high quality evidence of the effectiveness of cognitive behavioural therapy (CBT) for cTMD (Al-Moraissi et al. 2020; Häggman-Henrikson et al. 2020; Galvez-Sánchez et al. 2021; Busse et al. 2023; Beecroft et al. 2024). Maladaptive psychological behavioural responses, especially in pain catastrophising, affect patient symptom severity and response to treatment in cTMD (Häggman-Henrikson et al. 2020). In addition to CBT, emotional awareness and expression therapy (EAET) is a recent psychotherapeutic intervention that emphasises addressing connections between dysfunctional emotional behaviours and pain to reduce or eliminate centralised pain (Driscoll et al. 2021). Early studies have shown that EAET is superior to CBT in centralised musculoskeletal pain and fibromyalgia in older adults (Yarns et al. 2022). More research is needed to confirm its effect and possible role in cTMD. While a recent multimodal, internet-based pain programme led to improvements in symptoms and jaw function for cTMD patients, it proved no more effective than splint therapy alone (Lam et al. 2020). Currently, CBT with or without relaxation therapy, jaw-exercises, and manual trigger-point therapy has been shown to have the greatest reduction in chronic pain severity and is recommended in current UK clinical practice guidelines (Busse et al. 2023; Beecroft et al. 2024). Despite these advances in non-invasive treatments, concerns remain regarding the safety of more invasive procedures. An expert panel has expressed caution about the moderate risk of harm associated with treatments such as arthrocentesis, arthroscopy, and repeated intra-articular steroid injections for patients with cTMD (Busse et al. 2023). Additionally, procedures like discectomy, the use of irreversible splints, and the combination of long-term opioids with NSAIDs are considered to carry uncertain benefits and high clinical risks, and are not recommended (Busse et al. 2023).

Early intervention with self-management in patients with TMD may lead to successful outcomes in 75–90% of cases (Rajapakse et al. 2017; Tran et al. 2022; Beecroft et al. 2024;

Sidebottom 2024). Despite the variation in supported self-management programmes and the limited comparative evidence available, reported success rates remain consistently high across different approaches (Palmer et al. 2023). Key components of supported self-management include education, exercise therapy, thermal modalities, appropriate pain management therapeutics, self-massage, and addressing parafunctional behaviour. It is important to recognise that while some patients may experience a complete resolution of symptoms, others may see a reduction in the frequency and intensity of symptoms to a more manageable level (Beecroft et al. 2024). Several systematic reviews and practice guidelines have reinforced the growing consensus that supported self-management, along with physiotherapy, including both manual and exercise therapy, plays a crucial role in the effective management of cTMD (Rajapakse et al. 2017; Al-Moraissi et al. 2020; Tran et al. 2022; Busse et al. 2023; Beecroft et al. 2024). These comprehensive analyses have consistently demonstrated that these approaches not only alleviate symptoms but also empower patients to take an active role in their treatment. The emphasis on supported self-management underscores the importance of patient education, self-directed exercises, and behaviour modification as integral components of a successful treatment plan. Physiotherapy, particularly when tailored to the individual's specific needs, has been shown to improve jaw function, reduce pain, and enhance overall quality of life for those living with cTMD. The robust evidence supporting these interventions highlights their effectiveness and the vital role they play in a multidisciplinary approach to cTMD management (Tran et al. 2022; Busse et al. 2023; Beecroft et al. 2024). Conversely, these reviews found no compelling evidence of benefit for interventions such as low-level laser therapy, acupuncture therapy, and routine use of oral splints (Tran et al. 2022; Busse et al. 2023). It also emphasised that prosthodontic/occlusal treatments and orthodontic interventions have no established role in TMD management. The reviews supported intra-articular injection with hyaluronic acid in DJD and internal derangement, while cautioning that intra-articular corticosteroids should be administered on a case-by-case basis due to the potential risks and uncertain benefits (Tran et al. 2022). Although the existing evidence is of low quality, a recent systematic review of the efficacy for botulinum toxin in TMD found no benefit versus placebo (Saini et al. 2024).

Recommendation

The differentiation between mechanical TMJ problems and cTMD is crucial due to differences in their underlying pathophysiology, treatment response, and long-term prognosis. A summary of key points by the authors based on current research is found in Table 2 (Ohrbach and Dworkin 2016; Slade et al. 2016).

Mechanical TMJ problems typically involve structural issues such as disc displacement, osteoarthritis, or joint degeneration. Conservative treatments, including physical therapy, occlusal splints, and anti-inflammatory medications, often provide significant relief, particularly in cases of disc displacement without reduction or early osteoarthritis. In severe cases, such as advanced osteoarthritis or persistent disc displacement, surgical interventions like arthrocentesis, arthroscopy, or open joint surgery may be necessary, often yielding good short – to medium-term outcomes. Patients with mechanical TMJ problems generally have a favourable prognosis if treated appropriately; however,

Table 2. Key differences in management of mechanical TMJ issues and cTMD*.

	Mechanical TMJ issues	cTMD
Primary aetiology	Structural issues (e.g. internal derangement, degenerative joint disease, and subluxation)	Central (major) ± peripheral (minor) sensitisation, biopsychosocial factors
Response to Conservative Treatments	Good (e.g. occlusal splints, physical therapy)	Limited (requires multidisciplinary approach)
Response to Surgery	Often beneficial in severe cases	Not recommended, may worsen symptoms
Long-Term Prognosis	Favourable with appropriate treatment	Guarded, often chronic and persistent
Risk of Recurrence	Moderate (depends on biomechanical factors)	High due to central (major) ± peripheral (minor) sensitisation

*Given the wide variability in presentations of cTMD, there are no universally 'typical' clinical patterns. Structural or mechanical conditions are often supported by imaging findings, such as those seen on CT or MRI (e.g. internal derangement). Depending on individual clinical circumstances, these conditions may warrant surgical intervention.

degenerative conditions like osteoarthritis may progress over time, necessitating ongoing management. Recurrence of symptoms is possible, especially if underlying biomechanical factors, such as malocclusion or parafunctional habits, are not addressed.

cTMD involves persistent pain and dysfunction, often associated with psychosocial factors, and systemic comorbidities such as fibromyalgia and chronic fatigue syndrome. Conservative treatments like physical therapy and splints may provide some relief, but their efficacy is often limited due to the involvement of the central nervous system. A multidisciplinary approach, including CBT, stress management, and pharmacological treatments such as antidepressants and anticonvulsants, is typically more effective in managing cTMD. Surgical interventions are generally not recommended, as they do not address neuroplastic changes to the central nervous system and may exacerbate symptoms. The long-term prognosis for cTMD is more guarded due to its chronic nature and the complexity of contributing factors. Patients often experience persistent pain and functional limitations, with an increased risk of developing other chronic pain conditions. Early intervention focusing on psychosocial and behavioural factors can improve outcomes, but complete resolution of symptoms is less common compared to mechanical TMJ problems.

Conclusion

Mechanical TMJ conditions do not necessarily involve chronic pain and should be distinguished from chronic facial pain syndromes. Although some mechanical TMJ conditions may coexist with chronic facial pain, they remain separate entities that require tailored management approaches. This distinction is essential for ensuring accurate diagnoses and effective treatment plans for patients with cTMD.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

All data have been presented in the article.

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