Review Article

Musculoskeletal disorders and orofacial pain: a narrative review

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Background and Objective: Musculoskeletal disorders comprise the largest subset of chronic pain conditions, contributing to great disability, lost productivity and increased utilization of healthcare services. Temporomandibular disorders (TMDs) are one of the most common chronic musculoskeletal disorders in the orofacial region. The term is inclusive of temporomandibular joint disorders (TMJDs) and disorders of the masticatory musculature (MMDs). The condition may occur in isolation affecting the components of the masticatory system locally, or it may be a component of multi-system condition. The objective of the article is to provide an overview of etiopathogenesis, risk factors, diagnosis and management of MMD and the global pain condition fibromyalgia.

Methods: A search was conducted on indexed databases (PubMed, Embase, Ovid Medline, Cochrane, Web of Science, Scopus) using keywords temporomandibular disorder, myofascial pain, fibromyalgia from 1st January 1959–31st May 2021 and 476 relevant full text articles in English were analysed and included in the narrative review.

Key Content and Findings: MMD and fibromyalgia are complex conditions with multiple risk factors and a the etiopathogenesis are yet to be completely elucidated. MMDs may involve multiple risk factors and currently it is suggested that multiple biopsychosocial factors interacting with genetic factors may act in cohort with environmental factors and enhance individual susceptibility to developing incident TMDs. Varying degrees of peripheral and central sensitization, upregulation of ascending pain pathways coupled with downregulation of descending modulatory pathways may be also be involved in their genesis. Various classification systems including International Classification of Orofacial Pain (ICOP), Diagnostic Criteria for TMD (DC-TMD), International Classification of Disease-11 (ICD-11) are currently in use.

Conclusions: MMDs and fibromyalgia are complex conditions. First line management for MMD may include patient education, counselling, home care, risk factor and behavioral modification, pharmacotherapy, short term intra oral appliances, nerve blocks, trigger point injections, physiotherapy, and psychotherapy. Distinction of acute and chronic MMDs, localized *vs.* systemic forms degree of peripheral and central sensitization and preventing transition of acute to chronic MMD is crucial to management. Fibromyalgia is a global systemic disorder and management of MMDs in fibromyalgia is primarily palliative and multidisciplinary or interdisciplinary management may have enhanced success rates. Precision medicine may enhance success rates.

Keywords: Temporomandibular disorders (TMDs); masticatory muscle disorders; temporomandibular joint disorders (TMJDs)

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Introduction

An estimated 50 million adults in the U.S. suffer from chronic pain (1). Musculoskeletal disorders comprise the largest subset of chronic pain conditions, contributing to great disability, lost productivity, and increased utilization of healthcare services. Temporomandibular disorders (TMDs) are one of the most common chronic musculoskeletal disorders in the orofacial region. The term is inclusive of temporomandibular joint disorders (TMJDs) and disorders of the masticatory musculature (MMDs) (2). The condition may occur in isolation, affecting the components of the masticatory system locally, or it may be a component of multi-system condition.

Epidemiologic studies on TMDs have reported wide variations in the incidence and prevalence of TMDs. This may be attributed to incidence-prevalence bias, sampling strategies, population studied, study design and diagnostic criteria used. The annual incidence of clinically verified TMDs in a community sample in the U.S. was estimated to be 4% (3). Among patients with new onset TMDs, 65% had recurrent pain episodes and 19.2% had persistent pain episodes. A combination of arthralgia and myalgia accounted for the vast majority of the incident cases (73%), while myalgia alone as a single diagnosis accounted for 23% of the incident cases (4). However, it is unclear in the cases designated as myalgia alone, how many are unilateral *vs.* bilateral. The incidence did not vary significantly with gender and was reported highest among African Americans. A systematic review on the prevalence of TMDs concluded that the prevalence of MMDs in the general population was 9.7%; it was the most common diagnosis in a patient population with TMDs (45.3%) (5). The prevalence was also reported to be higher in females and Caucasians.

The theories on the risk factors and their role in the genesis of TMDs has been controversial and debated for decades. The perspective has now shifted from mechanistic, anatomical, gnathological based approaches to the biopsychosocial model. The biopsychosocial model ascribes pain and disability in chronic pain conditions to a dynamic complex interplay between biological, social, and psychological factors. The shift toward the biopsychosocial model has also been accompanied by a focus on contributions of systemic conditions to chronic pain states in several conditions including TMDs. The landmark Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study was the most comprehensive study conducted to date to analyse phenotypic and genetic parameters, risk factors, health comorbidities, and key factors underlying the transition of acute states to chronic painful TMDs (6). The community-based study was conducted across four centres in the U.S., recruiting 4,346 subjects with three study designs; a prospective cohort study, a case control study, and a nested case control study (3). A total of 202 phenotypic risk factors were assessed across 6 domains (clinical orofacial characteristics, pain sensitivity, sociodemographic, health status, cardiac autonomic function, and psychosocial characteristics) (6). A panel of 2,924 single nucleotide polymorphisms (SNPs) (representative of 358 genes) identified as having a role in pain perception were also analysed. The study concluded that the following were the strongest predictors: comorbid systemic conditions, nonpainful symptoms in the orofacial region, jaw parafunction, psychosocial factors (frequency of somatic symptoms), deteriorating sleep quality, and six SNPs (3). The most important SNPs influencing biological mechanisms involved in pain perception affecting chronic TMDs included *voltage-gated sodium channel Nav1.1 alpha subunit* (sensory nerve action potential related mechanism possibly contributing to non-specific orofacial symptoms, jaw fatigue and stiffness), *prostaglandin-endoperoxide synthase 1 gene/COX-1* (contributing to psychological and global symptoms through inflammatory and nociceptive related mechanisms), *gene encoding amyloid beta (A4) precursor protein* (affecting neuronal plasticity and synapse formation and thus contributing to the negative affectivity and psychological stress components of chronic TMDs), *multiple PDZ domain protein gene SNP* (influencing temporal heat pain summation through G protein-coupled receptors mediating pain and analgesia), *glucocorticoid receptor gene* (through mechanisms contributing to the hypothalamic-pituitary-adrenal system), and *serotonin receptor gene* (affective and nociceptive pathway related mechanisms). Catechol O-methyltransferase (*COMT*) genotype may modify effects of psychological stress on environment-gene related

interaction, thus influencing sensitivity to noxious stimuli and contributing to incident TMDs (3). Genetic factors may function as upstream determinants and influence intermediate biological parameters which in turn may act in cohort with environmental factors and produce downstream phenotypic effects affecting modulating inflammatory responses, nociceptive sensitivity, psychological and autonomic responses. The complexity of the spectrum of TMDs may however involve multiple SNPs acting through different biological mechanisms and further research is warranted (7). Other factors associated with incidence of first onset painful TMDs include use of hormonal contraceptives (8), intrinsic/extrinsic trauma (9), negative affect, previous life events, and perceived stress (10). TMDs are also associated with a variety of painful and non-painful comorbidities and some of these conditions may serve as predictors for future development of TMDs (11).

Varying degrees of peripheral sensitization, segmental sensitization and central sensitization may be involved in chronic pain conditions. Enhanced synaptic activity of nociceptive neurons, upregulation of afferent nociceptive pathways, alterations in neuroimmune pathways, reactive oxygen species, increase in proinflammatory cytokines, reduced anti-inflammatory cytokines, cortical reorganization and impaired descending pain modulatory systems may play a role in chronic MMDs. Peripheral mechanisms may have a predominant role in initiation and acute and localized forms of TMDs whereas central and segmental mechanisms may play a critical role in sustenance, chronic TMDs with generalized symptoms and may also facilitate transition of acute to chronic TMDs (12-15).

Based on the biopsychosocial profiles (clinical features, psychological distress, and experimental pain sensitivity) TMD patients have been subclassified into 3 categories; adaptive cluster (relatively free of psychological distress and experimental hypersensitivity), pain sensitive (experimental pressure induced enhanced sensitivity to muscle pain), and global symptom cluster (increased psychological distress and muscle pain sensitivity) (16). A case control study of TMD patients and controls utilizing the cluster analysis of participants revealed that the majority of the chronic TMD patients (91.5%) belonged to the global symptom and pain sensitive clusters while most controls were in the adaptive cluster (41.2%) (16).

Over the years, several classification systems for research and clinical use have been proposed. Recently, the International Classification of Orofacial Pain (ICOP) and International Classification of Disease-11 (ICD-11) have also been proposed. ICD-11 classifies into chronic primary and chronic secondary pain conditions and this may also prove useful in discerning surgical *vs.* non-surgical diagnoses (17,18). The Research Diagnostic Criteria for TMD (RDC-TMD) were proposed in 1992. Subsequently, it was modified to the Diagnostic Criteria for TMD (DC-TMD), proposed for use in clinical and research setting, and is currently the most widely accepted and validated classification of TMDs to date. The DC-TMD has classified TMDs into TMJDs and MMDs. MMDs are further divided into muscle pain, contracture, hypertrophy, neoplasm, movement disorders, and masticatory muscle pain attributed to systemic/central pain disorders. Muscle pain is further classified as myalgia, tendonitis, myositis and spasm. Myalgia includes local myalgia, myofascial pain and myofascial pain with referral (2). In this paper we will be discussing the clinical features, diagnostic criteria as per DC-TMD.

Several dentists report a lack of requisite knowledge and skills for diagnosis and management of TMDs. The aim of the article is to provide an overview of etiopathogenesis, risk factors, diagnosis and management of MMD and the global pain condition fibromyalgia. We present the following article in accordance with the narrative review reporting checklist (available at https://fomm.amegroups.com/article/view/10.21037/fomm-21-103/rc).

Methods

The details of the search strategy have been mentioned in *Table 1*.

Discussion

Theories of MMD

The etiopathogenesis of orofacial MMD is still enigmatic. However, it shares similarities with myofascial pain syndrome. Trigger points are considered the hallmark of myofascial pain. Several hypotheses have been proposed and prominent among them is the integrated theory (19), to which several modifications have been added over the decades (20). It hypothesises that dysfunctional endplates at neuromuscular junction may occur due to excess acetyl choline (ACh) at the motor end plates, and this leads to prolonged contraction of sarcomeres, leading to formation of taut bands. The prolonged contraction leads to local hypoxia, and subsequent energy crisis occurs (20). Varying

Table 1 The search strategy summary

Items	Specification
Date of search	1st June 2021
Databases and other sources searched	PubMed, Embase, Ovid Medline, Cochrane, Web of science, Scopus
Search terms used	("temporomandibular joint disorders"[MeSH Terms] OR ("temporomandibular"[All Fields] AND "joint"[All Fields] AND "disorders"[All Fields]) OR "temporomandibular joint disorders"[All Fields] OR ("temporomandibular"[All Fields] AND "disorder"[All Fields]) OR "temporomandibular disorder"[All Fields]) OR "TMD"[All Fields] AND "myofascial"[All Fields] AND ("pain"[MeSH Terms] OR "pain"[All Fields]), "fibromyalgia"[MeSH Terms] OR "fibromyalgia"[All Fields] OR "fibromyalgias"[All Fields]) AND "TMD"[All Fields] AND "myofascial"[All Fields] AND ("pain"[MeSH Terms] OR "pain"[All Fields])
Timeframe	1st January 1959–31st May 2021
Inclusion and exclusion criteria	Clinical trials, systematic reviews, research studies, case reports were included
	Studies that were not relevant to the current topic, duplicates, or did not have the focused question were excluded
Selection process	Two authors MK, SA independently searched indexed databases using MeSH terms and screened the titles and abstracts of the identified studies. Disagreements were solved through mutual discussion between authors and in case of a lack of consensus through discussion involving a third author (JK)

degrees of peripheral and central sensitization may contribute to the condition as well. Two different theories have also been proposed to explain the onset of energy crisis in tonic and phasic muscles. The Cinderella theory proposes that during contraction the muscles are recruited in a hierarchical manner from smallest to largest, and the reverse happens during relaxation (21). Thus, small muscle fibers are subject to more prolonged duration of contraction. However, in slow twitch fibers, the muscle fibers are recruited in a shift manner and the prolonged duration of contraction with insufficient relaxation results in energy crisis as per the shift theory (22). Further research exploring these areas may help elucidate the exact mechanisms and their contribution to chronic pain states in MMDs.

Clinical features

Pain and limitation of opening are cardinal signs and symptoms of MMDs.

Pain associated with MMDs may vary in presentation; from dull aching to sharp, mild to severe, and intermittent or constant. It may be accompanied by autonomic symptoms, allodynia or hyperalgesia as well. Myalgia may be associated with hyperirritable spots in taut bands of muscle fibres referred to as trigger points, which have the ability to refer and radiate pain, and may be associated with headaches. Changes in occlusion may also be reported (11,19).

Myalgia

The DC-TMD, describes the primary clinical symptoms of myalgia as pain in the jaw, ear, temples, or preauricular area. On clinical examination, with either palpation of the masticatory muscles (temporalis, masseter, or other masticatory muscles) or with maximum assisted and unassisted opening movements of the jaw there is replication of the patient's complaints (2).

Myalgia is further subclassified into local myalgia, myofascial pain, and myofascial pain with referral.

Local myalgia

This condition presents with the characteristics of myalgia. However, pain on palpation is localized to the site of palpation (2).

Myofascial pain

The DC-TMD criteria for myofascial pain includes symptoms and signs of myalgia. In addition, there is referral

of pain beyond the site of palpation but within the boundary of the muscle being palpated (2).

Myofascial pain with referral

The characteristic symptoms and signs include those specified for myalgia with the additional symptom of referral of pain beyond the muscle being palpated (2).

Tendonitis: the origin of pain primarily involves the tendon and it is affected by functional, and/or parafunctional movements. Pain is replicated by provocation of the affected tendon (23).

Myositis: muscular pain is due to inflammation, infection or in chronic cases due to autoimmune conditions and may present with limitation of opening (23).

Spasm: generally an involuntary reversible sudden tonic contraction that can affect any masticatory muscle (23).

Contracture: generally, a non-painful shortening of a muscle due to fibrosis of muscle, tendon, or ligament and mostly secondary to radiation, infection of trauma (23).

Diagnosis of MMDs

Diagnosis of MMDs relies primarily on clinical examination and history. Comprehensive history and clinical exam are a prerequisite to identify comorbidities or additional chronic overlapping pain conditions (COPCs).

The guidelines for clinical exam have been detailed in the DC-TMD criteria (2,24). In brief muscles may be palpated by pincer or flat palpation at the origin, body and insertion of muscles using sustained pressure of 1 kg for 3–5 s to elicit pain referral patterns (2,24). Range of motion testing is also necessary. Serological testing is generally used to identify systemic comorbidities such as rheumatic diseases, musculoskeletal disorders, hypothyroidism, vitamin deficiencies, or iron deficiency anemia (25).

Ultrasound sonoelastography has been suggested to have promising use. High-definition ultrasound may be used to guide trigger point injections in difficult sites (25). Single needle electromyogram (EMG) and quantitative sensory testing (QST) may be used as adjunctive modalities for diagnosis (26). Future studies may dwell into validation of these diagnostic tools in diagnosis of MMDs.

Management

TMDs are multifactorial with a range of symptoms that may vary from mild, transient, and self-limiting to severe pain and disability that affects overall quality of life. Barriers to successful management include lack of coordinated care among different healthcare professionals, institution of overly aggressive treatment, lack of identification of qualified healthcare professionals, treatment expenses and presence of multiple co-morbidities (11). It is estimated that approximately 40% of patients with TMDs may recover spontaneously with no intervention (27). A study on TMD patients reported that in new onset TMD patients, symptoms, and pain sensitivity increased, and psychological function worsened. However, among participants with chronic TMD at baseline, several biopsychosocial parameters improved despite pain persisting for years, suggesting considerable potential for ongoing coping and adaptation in response to persistent pain (28).

TMDs should not be solely considered as a single entity; often it is inclusive of a variety of conditions with varying degrees of local and systemic contributions (27). Hence treatment needs to be based on an accurate diagnosis, holistic, interdisciplinary, and individually tailored. Conservative reversible procedures should be utilized primarily (29). Patient education on the diagnosis and comprehensive treatment plan are necessary. Identification and addressing of initiating and perpetuating behavioural factors are critical, in addition to home care and self-management strategies. Distinction between acute MMD and chronic MMD is also important. Early identification and treatment of acute pain conditions may prevent transition to chronic pain states.

Acute MMD

The condition is generally secondary to infection, overuse or trauma and treatment should be targeted for management of the causative factors. Most professional organizations concur on initial management which is conservative, non-invasive and reversible including palliative home care measures, pharmacotherapy [antibiotics if there is infection and non-steroidal anti-inflammatory drugs (NSAIDs) if there is inflammation], short term intra oral appliance (30). Prompt and immediate treatment of the underlying cause is essential to prevent chronicity.

Chronic MMD

The American Academy of Orofacial Pain recommends initial management of chronic MMD with conservative

Table 2 Differences between masticatory muscle disorders and fibromyalgia

Differentiating characteristics	Masticatory muscle disorder	Fibromyalgia
Diagnostic criteria	Positive for both of the following (I) pain in the jaw, temple, in the ear, or in front of ear (II) pain modified with jaw movement, function, or parafunction Positive for both of the following (I) Confirmation of pain location(s) in the temporalis or masseter muscle(s) (II) Report of familiar pain in the temporalis or masseter muscle(s) with at least one of the following provocation tests (i) Palpation of the temporalis or masseter muscle(s) (ii) Maximum unassisted or assisted opening movement(s)	(I) Multisite pain (defined as 6 or more pain sites from a total of 9 possible sites) (II) Moderate to severe sleep problems or fatigue (III) Multisite pain plus fatigue or sleep problems must have been present for at least 3 months
Anatomical extent	Single or multiple masticatory muscles Spreading or referral patterns may be present	Six or more (out of nine possible) pain sites throughout body
Clinical examination	Required: palpation and range of motion	Not required, but recommended to rule out other conditions and/or aggravators
Associated signs/symptoms	Limitation in range of motion common	Diagnostic criteria: moderate to severe sleep problems or fatigue Also common: dyscognition, environmental hypersensitivity or hypervigilance
Duration	No requirement	Must have been present for at least 3 months
Natural history	Often self-limiting	Sometimes self-limiting

modalities including patient education, home care, physical therapy, pharmacotherapy, intraoral appliance therapy, and behavioral/relaxation techniques (29,30). Majority of the chronic MMD patients have shown recovery with conservative modalities. Determination of degree of underlying peripheral and central mechanisms and their management is also essential. For instance, central mechanisms are predominant in fibromyalgia whereas local myalgia has peripheral mechanisms. *Table 2* depicts the differences in myofascial pain *vs.* fibromyalgia.

Home care regimen and exercises are one of the modalities recommended by most professional organizations such as the American Academy of Orofacial Pain, International Association for Study of Pain. These are especially beneficial in mild cases by providing rest and promoting recovery. They also enhance patient participation through awareness and conscious avoidance of parafunctional habits (29). Counselling may be beneficial and help in improvement of mouth opening, reduction of tenderness on palpation of masticatory musculature and help in eliminating or controlling deleterious habits.

Pharmacotherapy

A variety of medications have been prescribed for the treatment of MMDs and include NSAIDs, tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), muscle relaxants and steroids (30). Among the RCTs, no single medication has emerged superior to the others. The choice of medications is dictated by patient related factors, side effect profile, presence of comorbidities, and chronicity of condition. In acute MMDs, NSAIDs and occasionally steroids (especially if there is a comorbid autoimmune condition) are used short-term. TCAs, SSRIs, SNRIs, medications such as cyclobenzaprine are used in chronic MMDs, especially if there are comorbidities such as insomnia, or depression. Systematic reviews have suggested TCAs for TMDs,

cyclobenzaprine for MMDs (31).

Intra oral appliance therapy

Several designs of appliances are available and are classified based on their coverage, repositioning ability etc. However, considerable variations in the study design and criteria for selection of patients have resulted in varying conclusions with some studies reporting them to be effective and others refuting (32,33). The stabilization splint is one of the most widely used appliance. A systematic review and meta-analysis suggested that it may provide short term relief and its effect in long term may be similar to other therapeutic modalities but recommended more well-designed studies. The systematic review suggested that there may be more improvement with physical functioning while using usual treatment including splints for MMD (33). Although the exact mechanism of action is still enigmatic, it may work as a behavioral interventional modality, distribute load, and protect the teeth and joint from high loading.

Injections and dry needling

Trigger point injections with substances such as local anesthetics, corticosteroids, Botox, nerve blocks and dry needling have been offered as treatment options for TMDs. There is no consensus regarding these. However, low quality evidence with statistical insignificance suggests trigger point injections with local anesthetics may offer slightly better results immediately and dry needling may be more effective 3–6 months (34). Botox may be used in resistant cases and may have better effects at 2–6 months in comparison to short term at 4–6 weeks (35) and multi session is often more beneficial in comparison to a single session (36). Trigger point injections for difficult muscles may be done under high definition ultrasound guidance (37).

Among nerve blocks, a recent innovation was the twin block injection introduced in 2014 and studies suggest it may be effective in myogenous TMDs (38,39). Further randomized controlled trials dwelling into this area may further shed light into its efficacy.

Physiotherapy

Physiotherapy modalities include dry needling, low-level laser therapy, myofascial release, deep tissue massage, ischemic compression, and temporomandibular joint (TMJ) mobilization. Systematic reviews and meta-analyses have shown that manual therapy may improve range of motion, reduce pain, and increase pain pressure threshold (40-42). However, a systematic review reported inconclusive results due to risks of bias and study heterogeneity (43).

Complementary therapy and psychotherapy

Acupuncture: systematic reviews have concluded that there is low to weak evidence for the use of acupuncture in MMD, symptomatic TMD, and chronic neck pain (44-46). However, a recent meta-analysis concluded that there is moderate evidence for its efficacy in head and neck myofascial pain, and that it may be a safe alternative (47). Traditional acupuncture may provide similar benefits comparable to laser acupuncture in combination with occlusal splints (48).

In chronic neck MMD, exercise has been shown to be beneficial in the short and long term. Mobility and mixed exercises may improve range of motion and reduce pain in TMDs. Additional benefits may be conferred by coming stretching with strength training (49). A study on chronic MMD patients reported less efficient exercise induced hypoalgesia in patients with MMD and delayed response to mechanical temporal summation following non-strenuous aerobic exercises. Nasri-Heir *et al.* reported that chronic masticatory pain patients with reduced pain modulation may exhibit a delayed hypoalgesia to mechanical stimulation following nonstrenuous aerobic exercises suggesting a role of endogenous pain modulation system (50).

Yoga, massage, tai-chi, meditation, mindfulness practices, cognitive behavioural therapy, and mind-body practices may have beneficial effects on pain, mood disorders, function, and sleep in several chronic pain conditions (46,51). At present very few behavioral modification techniques are used in the management of TMDs and it is suggested that more techniques can be explored for their effect on management of TMDs (52). Biofeedback has also found to be effective in reducing masticatory muscle activity and may have beneficial effects in MMD (53). Hypnosis/relaxation therapies have low level of evidence with a high risk of bias indicating. It may be beneficial on pain and mouth opening (54). Acceptance and commitment therapies may also help in improvement of health related quality of life (55).

Musculoskeletal disorders and orofacial pain/ headaches

Headache is also frequently reported with TMDs.

Headache associated with TMD is more prevalent in patients with myogenous TMD. This type of headache may bear semblance to migraine, may be more frequent and may evoke masticatory muscle pain on clinical examination (56).

The spectrum: from local to systemic

It is now recognised that several chronic pain conditions may overlap each other with shared underlying pathophysiologic mechanisms and risk factors. A study by Ohrbach and colleagues (57) on five COPCs (TMD, headache, irritable bowel syndrome, low back pain and fibromyalgia); reported that in musculoskeletal disorders, the presence of an additional COPC may result in additive pain augmentation of up to 25%. They also reported that the pain intensity was proportional to the number of comorbid COPC. In addition, pain interference scores were augmented by up to 150% by the presence of other COPCs, and this interference increased up to a maximum number of four COPCs and decreased at five COPCs. Thus, it is paramount that symptoms of TMDs not be considered in isolation and importance should be given for identification of other systemic conditions that may have an impact on TMDs (58).

Fibromyalgia is a multi-symptom generalised chronic pain disorder. The prevalence and incidence of the condition varies and has been attributed to variations in diagnostic criteria for fibromyalgia and sampling strategies. The prevalence varies between 0.5–12%. The incidence is 3.2% and increases in patients with additional pain symptoms or rheumatologic diseases. There is a higher prevalence in females 3:1 (59).

Fibromyalgia is a chronic multi-symptom disorder, involving multiple chronic conditions with overlapping pain presentations. Fatigue and sleep disturbances are hallmarks of fibromyalgia. Risk factors include personal history with chronic pain in different regions of the body: central nervous system (CNS) symptoms including problems with mood, sleep, memory, and fatigue; strong familial chronic pain history; and environmental, physical, medical and psychological stressors including trauma, illness, infections (59-61).

The condition is associated with multiple medical (irritable bowel syndrome, interstitial cystitis, chronic pelvic pain, chronic orofacial pain, rheumatologic disease), sleep (central and obstructive sleep apnoea, restless leg syndrome), psychiatric (major mood disorders, substance abuse, and anxiety) disorders, and other comorbidities including chronic fatigue syndrome, obesity, and allergy (rhinitis, urticaria) (59-61).

Orofacial pain symptoms commonly comorbid with fibromyalgia include TMD, migraine, headache disorders, chronic headaches, and otologic symptoms.

The pathogenesis of fibromyalgia has still not been completely elucidated, and there are still several areas of ongoing research. Some of the proposed mechanisms include augmented pain processing leading to central sensitization, decreased descending pain modulation, enhanced pain facilitation, diffuse enhancement in processing of sensory stimuli, alterations in neurotransmitters, reorganization of neural networks with connections between pain and non-painful networks, and peripheral sensitization contributing to nociceptive inputs to CNS. The role of the immune system, microglia, inflammation and autonomic nervous system are also under consideration (59). Future research may elucidate specific mechanisms and enable more mechanism specific management strategies.

Over the years, several classification systems for screening and diagnosis have been proposed, mainly for research purposes with limited application in a clinical setting. Since 2011, criteria for clinical and research settings have been proposed with the 2010 and 2011 AAPT criteria, and subsequent 2016 criteria and its revision (62-64). The AAPT diagnostic criteria require presence of pain in >6 sites among nine possible sites, moderate to severe fatigue, and sleep disturbances, present for a minimum period of 3 months. Muscle and soft tissue tenderness, dyscognition, hypervigilance, and musculoskeletal stiffness are additional important clinical features.

Certain systemic conditions can mimic fibromyalgia and need to be included in the differential diagnosis of fibromyalgia. Several endocrine (such as hypothyroidism, hyperparathyroidism, Cushing syndrome, and Addison's disease), rheumatologic (rheumatoid arthritis, polymyalgia rheumatica, polyarticular osteoarthritis, systemic lupus erythematosus, spondyloarthropathy, polymyositis, and osteomalacia), infectious (hepatitis, Lyme disease) and neurologic conditions (neuropathy and multiple sclerosis), vitamin D deficiency, and medications (statins, opioids, aromatase inhibitors, bisphosphonates) can mimic fibromyalgia, and workup for fibromyalgia should include exclusion of these conditions (59).

Multidisciplinary multimodal treatment is the most widely accepted approach. Self-identification of coping strategies is very important. In most cases, the symptoms remained constant with mild changes over long term. Level

A recommendations include drug therapy (short term amitriptyline 10–50 mg/day), psychotherapy [cognitive behavioural therapy (CBT)], and physiotherapy (mild to moderate aerobic exercise at least 2–3 times/week for at least 30 min, muscle strength training and relaxation after aerobic exercises).

Level B recommendations include patient education and pharmacotherapy, such as cyclobenzaprine or short-term antiepileptic medications. Of the antiepileptic medications, pregabalin is preferred. In cases of co morbid depression and anxiety, SNRIs (duloxetine in particular) and SSRIs (fluoxetine or paroxetine) are recommended (65).

Although several management strategies have been described; there is still lack of well designed, well controlled, high quality randomized controlled trials with strict diagnostic criteria and methodological criteria. This has led to significant bias and controversial results in many scientific studies. Future studies should focus on use of rigid methodological criteria to enable definitive conclusions.

Current and future directions—ends of a spectrum-MMD and fibromyalgia-QST and somatosensory profiles

QST may be an adjunct diagnostic aid to differentiate TMJD from MMD. Electrical detection threshold has been reported to be reduced in the auriculotemporal nerve territories in arthrogenous TMDs and elevated in MMD (26). Some studies have reported that this effect may extend to contralateral side and extra territorial regions suggesting central mechanisms (66).

A study comparing somatosensory profiles in TMD patients and fibromyalgia patients suggested two subsets of TMD patients (a sensitive group, and an insensitive group resembling healthy controls); the sensitive group showed more evoked and ongoing differences in pain perception with extensive changes in the hand dorsum, cheek and trapezius area, and exhibited similarities in pain sensitivities to the same stimuli as fibromyalgia (dynamic mechanical allodynia, and hyperalgesia to pin prick, blunt pressure, and cold) but did not fulfill criteria for fibromyalgia. Thus, the sensitive group exhibited similarities to fibromyalgia and underlying central sensitization. Furthermore, an overlap of trigger and tender points was reported in 44% of TMD and 64% of fibromyalgia patients in the same study suggesting similar underlying mechanisms in sensitive TMD and fibromyalgia patients. However, sensitive and insensitive TMD patients did not significantly differ in their psychological profile. A systematic review on thermal modalities in fibromyalgia patients concluded that cold pain threshold was significantly reduced compared to controls; other thermal modalities were also altered in fibromyalgia patients (67,68).

Role of altered pain processing, central, peripheral sensitization in myofascial pain and fibromyalgia?

Pain pathways may be significantly altered in chronic pain conditions such as TMD and fibromyalgia. There may be augmentation of pain processing mechanisms and decrease in the functioning of pain modulatory pathways both at the level of the brain and spine (69). Suppression of descending modulation, interhemispheric disinhibition, and disinhibition of motor cortex has also been reported in TMDS and MMDs (50). In contrast in fibromyalgia, there may be reduction in pain threshold, elevated detection threshold and dysfunctional diffuse noxious inhibitory controls DNIC (70).

Conclusions

MMDs and fibromyalgia are complex conditions. First line management for MMD may include patient education, counselling, home care, risk factor and behavioral modification, pharmacotherapy, short term intra oral appliances, nerve blocks, trigger point injections, physiotherapy, psychotherapy. Distinction of acute and chronic MMDs, localized *vs.* systemic forms, degree of peripheral and central sensitization and preventing transition of acute to chronic MMD, is crucial to management. Fibromyalgia is a global systemic disorder and management of MMDs in Fibromyalgia is primarily palliative and multidisciplinary or interdisciplinary management may have enhanced success rates. Precision medicine may enhance success rates. ICD-11 chronic primary and chronic secondary pain may be helpful as these allow for separation of surgical *vs.* non-surgical diagnoses.

Precision medicine with individualized treatment—is it the answer?

Until a decade ago, the focus of pain was exclusively on anatomical corelates. However, recent studies have shown that biopsychosocial, phenotypic, and genotypic clustering may enable developing precision treatments with enhanced

success rates. Future studies should explore these arenas.

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