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Toward an Enhanced Understanding of Relationship Between Insomnia and Painful Temporomandibular Disorder: An Integrative Review

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Abstract

Sleep is essential for vital health because it improves physiological and psychological resiliency. Insomnia symptoms predispose individuals to chronic painful temporomandibular disorders (TMD) or worsen the condition. Individuals suffering from painful TMD, and insomnia are often associated with psychological health problems. These conditions when coexisting can lead to marked impairment in function and quality of life. This review discussed the clinical relationship between insomnia and painful TMD as well as overlapping psychological factors driving the onset and interaction of both disorders. Additionally, we shed light on clinical assessment components and effective management strategies such as cognitive behavioral therapy, pharmacological interventions, and other non-intervention approaches which may help the clinician to manage insomnia in patients with painful TMD. Taken together, this review would aid in the development of tailored treatments and improved quality of life for patients suffering from insomnia and painful TMD.

Keywords: Temporomandibular disorders, insomnia, chronic pain

INTRODUCTION

Pain is a common complaint in clinical practice that affects individuals' physiological and psychological states. It is a global health problem that causes long-term disability.[1] In patients with chronic orofacial pain, recurrent dental pain and temporomandibular disorders (TMDs) are the most common conditions that are more challenging to treat.[2] The TMDs are a cluster of musculoskeletal conditions that affect masticatory muscles and temporomandibular joint and/or associated structures. It afflicts approximately 10%-15% of the population at a clinically significant level, with symptoms severe enough to warrant medical attention.[3] Epidemiological studies have shown that TMD affects 5%-12% of general population, with "Orofacial Pain Prospective Evaluation and Risk Assessment Study (OPPERA)" reporting an annual incidence of 3.9% in adults.[4,5] The TMD etiology is multifactorial. In the last decades, risk factors of TMD had shifted from biomechanical factors to biopsychosocial factors.[6] The exact pathophysiological mechanisms of TMD are currently unclear, although they are thought to be a combination of peripheral and central mechanisms.[7]

The presentation of TMD is diverse, and the symptoms may vary from mild, transient, recurrent, self-limiting to severe disabling, impacting the individual's quality of life.[3] The most predominant symptom of TMD is pain which includes typical diagnoses such as myalgia, myofascial pain, myofascial pain with referral, arthralgia, and headache attributed to TMD.[4] Patients with painful TMD frequently have overlapping conditions such as headaches, depression, sleep disturbances, and fibromyalgia. Approximately, one-third to two-thirds of patients with chronic musculoskeletal pain report sleep disturbances.[8] Sleep disorders that may have an impact on TMD are insomnia, sleep-related breathing disorders such as obstructive sleep apnea (OSA), and sleep-related movement disorders.

Insomnia is one of the most commonly reported sleep disorders which has been connected with both pain and psychological traits. Insomnia, described as a persistent difficulty initiating or maintaining sleep, includes frequent awakenings and

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difficulties or inability to return sleep. It is a chronic condition that manifests in patients when sleep onset does not occur after 30 minutes at least 3 times per week for a period of 3 months or more, and there must be daytime impairment to meet the diagnostic criteria.[9,10] However, insomnia can occur for a short period of time lasting less than 3 months with recognizable stressors such as physical, psychosocial, and interpersonal triggers.[11] Insomnia can be classified as a primary sleep disorder or a secondary sleep disorder with a coexisting psychological medical condition, mental disorder, or substance abuse. Female sex, older age, and lower socioeconomic and marital status are typical risk factors. Common signs and symptoms include fatigue, cognitive problems, decreased productivity, increased absenteeism, behavioral issues, and ongoing worry.[10] It is also a risk factor for medical conditions such as metabolic syndrome, diabetes, hypertension, coronary heart diseases, gastroesophageal reflux disease, and thyroid disorders.[12]

Sleep is increasingly being recognized as a plausible target for a range of chronic pain conditions including TMD. In chronic pain patients, insomnia is highly prevalent, with 53% to 90% having a clinically significant degree of insomnia.[13] When insomnia and painful TMD coexist they can severely limit daily functional activities as well as profoundly affect patient's quality of life and impose a significant personal economic burden. Furthermore, treatment outcomes of painful TMD are worst when insomnia and other conditions such as depression, substance dependence, and somatization are combined.[14,15] It is challenging for the clinician to determine whether chronic, painful TMD actually worsens insomnia or whether amplification of painful TMD occurs as a result of insomnia. Previous research demonstrated a bidirectional relationship between insomnia and chronic pain, in particular painful TMD.[7,16,17] Evidence suggesting a relationship between insomnia and orofacial pain implies that insomnia predisposes individuals to new-onset painful TMD, rather than the inverse of it.[17,18]

A clinician's objective in the management of painful TMD is to resolve the symptom and address underlying comorbid issues. Undiagnosed insomnia in patients with painful TMD can be a barrier to effective pain management.[13] This raises the question of whether managing sleep should be explored as one option to manage painful TMD and other associated conditions. Therefore, understanding the intricacy of painful TMD and insomnia, recognizing them as distinct conditions, and examining their similarities as well as the consequences associated with them will enable the clinician to address this combination (Figure 1). The objective of this review is to provide clinicians with a better understanding of the relationship between insomnia and painful TMD, along with a brief discussion on common psychological and behavioral factors related to both conditions. Importantly, the review also covers screening for insomnia in patients with painful TMD and management strategies. By targeting this troublesome combination, the overall goal is to enhance the development of tailored treatments and improve the quality of life for patients suffering from painful TMD.

Psychological and Behavioral Risk Factors in Insomnia and Painful Temporomandibular Disorder

Sleep and pain are 2 separate processes that involve a range of molecular and behavioral changes. More detailed description on the mechanism of sleep and pain are provided in other reviews.[7,10,19-22] Depression and anxiety are the most

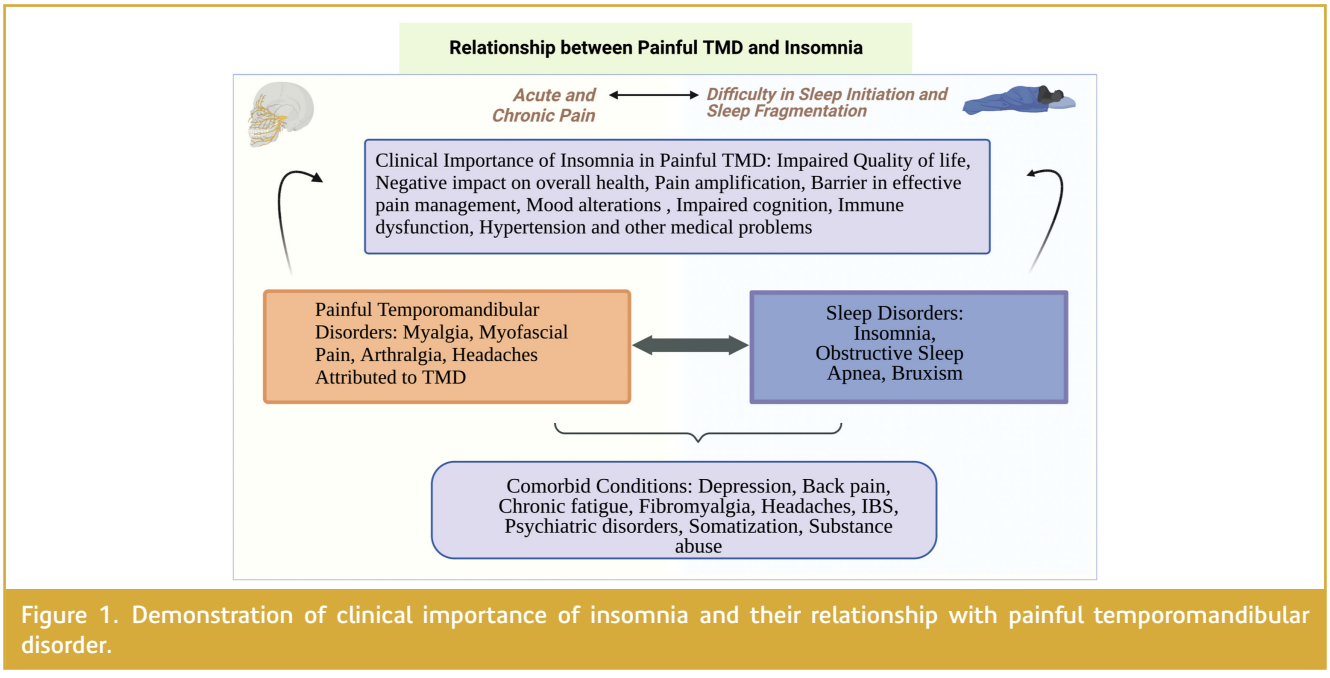

Figure 1. Demonstration of clinical importance of insomnia and their relationship with painful temporomandibular disorder.

common types of distress presented at the orofacial pain clinic.[23] Similarly, patients with a diagnosis of insomnia report comorbid psychosocial issues. Given this, we provide a brief overview of the effects of depression, anxiety, and emotional distress in insomnia and chronic, painful TMD (Figure 2).

Anxiety and depression are highly co-occurring within the TMD population, particularly in patients with myofascial pain, and managing stress and depression can effectively improve painful TMD.[24,25] Previous studies have investigated the possibility that pain may be indirectly influenced by sleep-related psychosocial factors.[24-28] For instance, depression, negative emotions, and anxiety may all contribute to the insomnia reported by patients with chronic pain.[26,27] Furthermore, several cognitive processes may contribute to the severity of sleep disturbance including pain-related dysfunctional beliefs and attitudes about sleep.[29] Pain catastrophizing or rumination has also been shown to be a risk factor for sleep disturbance in patients with chronic, painful TMD and indirectly influences pain severity and interference through sleep disturbance.[30,31]

Pain has both sensory and emotional-affective components. Research generally supported the idea that negative emotions experienced at bedtime affect sleep quality.[32] A growing literature also suggests that insomnia and painful TMD may be related to emotional dysregulation.[33-35] For instance, physical components such as environmental light, temperature, and posture play an important role in sleep, and if not appropriate, these external factors lead to insomnia.[33] Moreover, equally important are intrinsically experienced factors including danger, fear, anxiety, arousal, stress, tension, sadness, stressful life events, and adverse childhood experiences that may also lead to insomnia and painful TMD.[34] Major life events, stressful or emotional experiences, increases the severity and duration of disrupted sleep and painful TMD.[35] Generally, emotionally stimulating encounters tend to be better recalled than the neutral ones. This long-term retainment of emotional experiences over neutral experiences leads to stronger activation of noradrenergic, adrenergic, and glucocorticoid signaling, integrated in the basolateral complex of the amygdala.[34,35] It further leads to sleep disturbances and pain amplification.

Additionally, stressful life events (physical or psychological) could have the capability to change the activity of stress-regulatory systems (i.e., the hypothalamic–pituitary–adrenal axis (HPA)). The HPA axis is interrelated with the immune system in such a way that pro-inflammatory cytokines activate the HPA axis resulting in increased production of cortisol which eventually suppresses the inflammation.[36] In patients with chronic, painful TMD who have underlying stressful events this interaction between the HPA axis and immune system is weak, and dysfunction of the HPA axis leads to reduced sensitivity of the glucocorticoid receptor and cortisol and low-grade inflammation.[36] Moreover, this also leads to monoamine depletion, which increases pain perception by reducing the descending inhibitory drive in response to nociceptive input.[37] Similarly, studies revealed that deep sleep is associated with decreased cortisol levels and awakening to elevated levels. Subsequently, sleep disturbances resulted in elevated plasma cortisol levels, which could lead to HPA

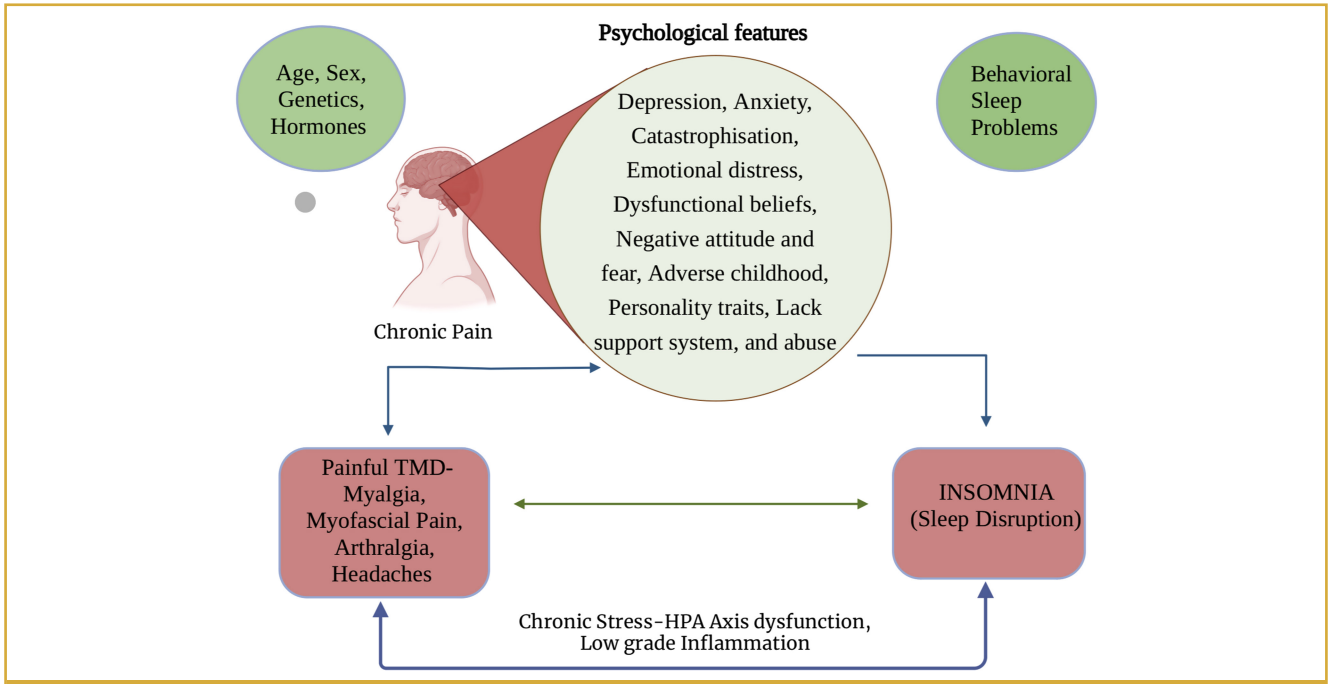

Figure 2. Psychological factors in insomnia and painful temporomandibular disorder.

dysfunction.[38] Among individuals suffering from insomnia symptoms, a hyperreactivity of the HPA axis to stressors have been reported.[39] The hyperactivity mediates the relationship between inadequate sleep and higher pain sensitivity. This implies that dysregulation of the HPA axis responses may indeed serve as a marker for the risk of chronic, painful TMD linked to insomnia.

Furthermore, patients with chronic pain are often underactive and report low level of physical activities.[22] In general, engaging in physical activity elevates the levels of adenosine, a sleep-promoting neurochemical that increases pressure to fall asleep. To cope up with their pain, chronic pain patients may spend a significant portion of their day lying down and perform their daily tasks in the bedroom environment.[22] These behaviors may exacerbate sleep disturbances and decrease the sleep drive. Indeed, patients with chronic pain and insomnia engage in more safety-seeking behaviors than those with pain or insomnia alone.[40] Overall these observations of emotional dysregulation and behavioral changes in individuals with insomnia and painful TMD may aid investigators in developing a new approach for the management of this comorbid condition. Future studies should definitely establish whether these variables mediate the connection between sleep disruption and pain.

Clinical Studies on Relationship Between Insomnia and Painful Temporomandibular Disorder

Generally, the process of sleep is driven by the combination of circadian and homeostatic mechanisms modulated by genetic and environmental variables. Suprachiasmatic nuclei govern the circadian process which is regulated by external cues, predominantly light–dark cycle. Another process called as homeostatic is the pressure or need for sleep in relation to the amount of time since the last restful night's sleep.[41,42] Studies have shown the influence of sleep homeostatic mechanisms and the circadian clock on a number of objective and subjective sleep and alertness-related characteristics.[42-44] Evidence from sleep deprivation experiments has suggested that under normal conditions, sleep homeostatic pressure will benefit sleep, and good sleep will strengthen circadian clock functioning. While, several nights of disturbed sleep or night to night variability in sleep quality may result in a less functioning circadian clock, typically insomnia.[42-44] Various experimental, clinical, and review studies have already investigated the relationship between chronic pain and insomnia.[45-48] Despite differences in sample characteristics, design, and instruments used to assess sleep and pain, micro-longitudinal and longitudinal analyses indicate a more consistent relationship in which sleep disruptions are linked to increased pain.

Epidemiological studies have shown that patients with orofacial pain had a relative risk of 3.7 (95% CI, 2.9-4.9) for a sleep disturbance.[49] The TMD-sleep impairments relationship was thoroughly investigated by the OPPERA study, which is one of the largest study designed to identify the risk factors for TMD in pain-free participants using subjective Pittsburg Sleep Quality Index (PSQI).[50] It is observed that TMD incidence was twice as high in participants whose baseline subjective sleep quality was poor (demographically adjusted Hazard ratio of 2.04; 95% CI, 1.55-2.70).[50] Literature suggests that sleep disturbances increase the risk of new onset of chronic, painful TMD in pain-free individuals as well as sleep disturbances may worsen the long-term prognosis of existing painful TMD and headaches.[51] Furthermore, good sleep seems to improve the long-term prognosis of individuals with tension-type headache, migraine, and chronic musculoskeletal pain such as painful TMD.[51]

The most common sleep disturbance in TMD patients is insomnia, and changes in the severity of insomnia are good indicators of alterations in pain.[9] A recent study observed that one-third of patients seeking care at an orofacial pain unit including TMD had sleep disturbances, with 37% of studied patients responding positively to a screening questions for insomnia.[52] This is consistent with the findings of a Polysomnography (PSG) study conducted on TMD patients, which revealed that 36% of patients suffered from insomnia of whom 26% had primary insomnia.[53,54] Studies have also examined the relationship of sleep disturbances secondary to TMD.[55,56] Pain has been found to increase the risk of insomnia in patients who have coexisting mood disorder or familial history of insomnia.[57] Painful TMD generally does not cause sleep interruptions; however, in 1 study, up to 24% of individuals with a high muscle tenderness score reported awakening because of pain.[55] In another study, patients with myofascial pain reported considerably worse quality of sleep than those with controls.[56] Overall, TMD patients frequently reported sleep disorders, with up to 70% reported criteria for at least 1 sleep disorder and 43% reported 2 or more,[58,59] while insomnia patients commonly reported other medical comorbidities and mental disorders. In fact, the risk ratio for incident depression among individuals with insomnia is estimated at 2.10 (95% CI, 1.86-2.38), which is also a common risk factor for painful TMD[60] (Table 1).

The incidence and prevalence of TMD in individuals with insomnia or vice versa still varies. Factors such as variation in sampling strategies, lack of clinical confirmation through validated diagnostic criteria, presence of other coexisting conditions, incidence prevalence bias, and other factors have all led to these variabilities which should be accounted in future studies. These data suggest that insomnia is one of the risk factors contributing to chronic, painful TMD. When developing a treatment plan for patients with chronic, painful TMD, insomnia and other comorbidities should be taken into consideration.

Table 1. Summary of Major Studies Showing Relationships Between Insomnia and Painful Temporomandibular Disorders

Author	Objective of the Study	Inference
Macfarlane et al[49]	Association between orofacial pain and sleep disturbances - a cross-sectional population study	In patients with orofacial pain, the strongest association was observed for a sleep disturbance with a risk factor of 3.7
Smith et al[54]	Relationship between sleep onset insomnia symptoms and chronic pain	High rate of primary insomnia in chronic pain may be linked with central pain sensitivity as well as reciprocal interaction between sleep and pain observed
Benoliel et al[55]	Analyze whether pain-related awakening occurs with persistent orofacial pain or whether it is related to severity	Persistent pain often induces pain-related awakening in both patients with myofascial pain and trigeminal neuralgia
Quartana et al[53]	Temporal association between naturalistic fluctuations in insomnia and pain in TMD	Naturally occurring fluctuations in insomnia severity are prospectively associated with daily TMD pain
Sneer et al[56]	Comparison of sleep quality in patients with myofascial pain and disc displacement vs asymptomatic controls	Sleep quality impairments are more common among patients with myofascial pain than disc displacement
Sanders et al[50]	Prospective cohort study (OPPERA) analyzes sleep disturbances as a risk factor for TMD	Patient with disturbed sleep quality have greater incidence for first-onset TMD
Lei et al[59]	Prevalence of sleep disturbances in TMD population	TMD patients frequently reported sleep disturbances and psychological distress
Schmitter et al[58]	Sleep disturbances among TMD patients and controls	Sleep disturbances occur most often in patients with myofascial pain
Rener-Sitar et al[57]	Self-reported sleep quality in TMD cases and controls	Sleep quality is impaired in TMD patients with pain-related diagnosis and even more in patients with dysfunctional pain
Cruz et al[52]	Prevalence of insomnia in orofacial pain population	One in 3 patients reported sleep disturbances with half of them had insomnia
Cao et al[60]	Relationship between acute/chronic TMD and sleep and psychological disturbances	Chronic pain TMDs are associated with higher sleep disturbances

OPPERA, Orofacial Pain Prospective Evaluation and Risk Assessment Study; TMD, temporomandibular disorders.

Clinical Assessment of Insomnia in Painful Temporomandibular Disorder

The descriptive history and clinical assessment should be given special attention when diagnosing TMD. Additional diagnostic imaging may be required in some cases to render a definitive TMD pain diagnosis and rule out other pathology.[61] The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) includes pain history questionnaires as well as validated clinical examination criteria for diagnosis of TMD. It also offers Axis II questionnaires for evaluating psychosocial and behavioral aspects that may have an impact on the onset and persistence of patient's TMD.[4] Recently, the International classification of orofacial pain has provided a comprehensive description of pain conditions affecting orofacial region including TMD along with structured diagnostic criteria.[62,63]

There should be regular questions about sleep health. By definition, insomnia is subjective in nature and demands careful questioning to better understand the problem and ultimately tailor the best treatment plan. A clinician should attempt to address the underlying psychological or psychiatric problems, medications history (both prescription and non-prescription), and other medical problems that may be contributing to sleep disturbances and viewed as risk factor for painful TMD.[17] Additionally, clinicians should also look for other sleep disorders such as OSA, restless leg syndrome, periodic limb movement, and narcolepsy which might hinder the treatment plan as well as the prognosis of individuals with painful TMD.

A sleep history should record sleep habits as well as risk factors for insomnia. Although sleep patterns vary from person to person, a clinician should ask about a patient's bedtime routine, sleep events, and behaviors that might be connected to sleep.[64] The initial screening questions for insomnia include difficulty initiating or maintaining sleep, early morning awakening, or simply unrefreshed sleep. This includes sleep/wake schedule, bedtime routine, nocturnal behavior, daytime dysfunction, comorbidities, and lifestyle habits. The 3-P (Predisposing, Precipitating, and Perpetuating) model can help a clinician in the assessment of insomnia. The "3-P" occurs in temporal order: factors predisposing an individual to insomnia, factors precipitating an acute episode of insomnia, and factors perpetuating the insomnia from acute to chronic. Predisposing factors include genetic and personality traits leading to physiologic and cognitive hyperarousal. Precipitating factors are the triggers after which the insomnia cycle begins and are typically stressful events. Perpetuating factors allow the insomnia to continue even when the trigger is removed.[10,15,65] These factors include behaviors and thoughts that may appear to offer short-term relief yet cause long-term harm (Figure 3).

Additionally, in patients with chronic, painful TMD and sleep disturbances, a subjective and objective assessment

is warranted. Subjective assessment is usually measured through sleep-wake diaries, questionnaires, which are easily administered and cost-effective, thus facilitating the feasibility of this measurement. Some of the commonly used validated tools for practitioners to obtain a standard history include the PSQI, Epworth Sleepiness Scale, Insomnia Severity Index (ISI), and Sleep Assessment Questionnaire These questionnaires include a series of questions about daytime dysfunction, medication use, daytime latency, sleep quality, duration, and efficiency.[10] The 8-item Patient Reported Outcome Measurement Information System for Sleep Disturbance Short Form is another measure.[66] The ISI allows for initial evaluation and can also be used to assess treatment outcomes.[10] If the responses on the ISI indicate that insomnia may be an issue and there is suspicion that painful TMD, anxiety, or even depression is present then the use of other questionnaires (PHQ-4, PHQ-9, and GAD-7) may be helpful. Positive screening results may prompt the clinician to offer treatment or to refer the patient to a specialist.

Objective assessment of sleep quality is measured through PSG. The PSG evaluation comprehends a series of biophysiological changes, including Electroencephalogram (EEG), eye movements, muscle activity, heart rhythm, and respiratory function. It is a gold standard in diagnosing sleep disorders such as sleep-disordered breathing or periodic limb movement.[67] It involves expensive equipment and resources including overnight stay, therefore limiting its applicability. The role of PSG in the diagnosis of insomnia is limited specifically in which insomnia is based on self-report. This is due to the fact that traditional PSG data indexes do not accurately reflect the sleep issues that about 40% of individuals with insomnia experience.[68] The PSG can be helpful to rule out other possible explanations for poor sleep, such as OSA; therefore, it may be indicated when there is concern for sleep apnea or when the patient is not responding to treatment as expected.

An alternative method is actigraphy which consists of a device, typically worn on the wrist that records movement

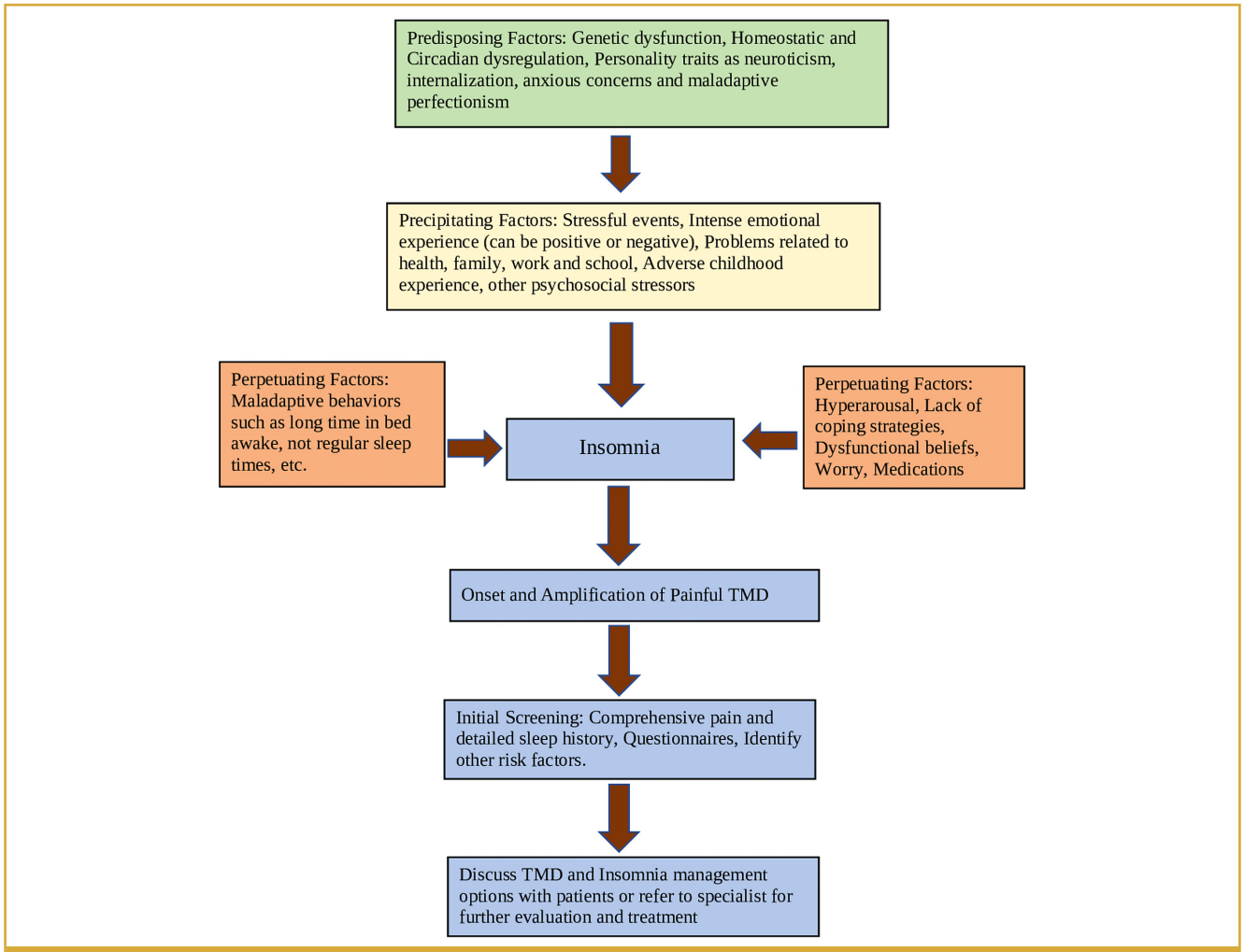

Figure 3. Illustration of the screening approach to insomnia in patients with painful temporomandibular disorder.

and employs an algorithm to estimate sleep and wake periods. Actigraphy has reasonable reliability with PSG in good sleepers but not in individuals with sleep difficulty. Actigraphy is not required in the evaluation of insomnia; however, it can be useful for a patient whose sleep log or history is not reliable or when circadian disorders are suspected.

Exclusive of screening methods, many researchers are performing investigative methods to understand the relationship between insomnia and pain using brain imaging. These methods are EEG-derived sleep parameters and neuroimaging methods, which provide better spatial resolution than EEG and allow the investigation of the morphometry [magnetic resonance imaging (MRI)], neurochemical (magnetic resonance spectroscopy), and functional aspects (functional MRI (fMRI), Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT) of the human brain during wakefulness and sleep.[69] Thus, increasingly sensitive methods are needed to uncover the neurobiological factors underlying the subjective experience of insomnia and TMD pain.

Management of Insomnia in Painful Temporomandibular Disorder

Typically, mechanism-based treatments are optimal; however, identifying the mechanism behind insomnia and painful TMD is challenging. For many patients, the goals of therapy should be tailored toward an improved quality of life, which might be more realistic than meaningful pain reduction. An appropriate TMD management strategy should aim to alleviate the main signs and symptoms of this condition. As a result, for painful TMD a multidisciplinary treatment approach is recommended.[70] Conservative treatments for TMD include education and reassurance, self-care, oral appliances, physical therapy and ergonomic modifications, therapeutic exercise, dry needling and acupuncture, stress management, and relaxation techniques when indicated. Other treatments in such a framework can include steroids, non-steroidal anti-inflammatory drugs (NSAIDs), opioid and non-opioid pharmacological therapies, injectable pharmacotherapies, psychological therapies, integrative treatments, and non-surgical interventional and surgical procedures. Typically, conservative treatment approach is preferred over surgery because it is less invasive and usually results in satisfactory clinical outcomes in mild to moderate TMD. While, according to the literature approximately 10%-15% of all individuals undergoing treatment for TMD require surgical intervention.[70] There is a spectrum of surgical procedures ranging from arthrocentesis and arthroscopy to more complex open joint surgical procedures arthrotomy or joint replacement (Figure 4).

When treating TMD pain, patients can benefit from strategies targeting insomnia or from treatments that can help to manage both insomnia and pain such as cognitive behavioral therapy. Ideally, an individualized management approach should be implemented considering several aspects and characteristics of the individual, such as comorbidities, existing treatments medications, and genetics. The goals of insomnia are to improve quantitative and qualitative sleep aspects of sleep to reduce distress, and anxiety associated with poor sleep and to improve daytime function.[71] Management of insomnia generally falls under 2 broad categories as cognitive-behavioral treatments for insomnia (CBT-I) and medication management. Patients often prefer non-pharmacological approaches but two-thirds of patients taking medications report at least moderate satisfaction. Patients often try other approaches including reading, relaxation, proper sleep hygiene, and over-the-counter remedies such as alcohol, antihistamines, and herbal preparations (Table 2).[69,72]

Cognitive Behavioral Therapy

Insomnia can be perpetuated by maladaptive behaviors, thoughts, and beliefs. Cognitive-behavioral therapy (CBT) for insomnia are multifaceted that incorporate behavioral interventions. This treatment comprises advice on sleep–wake behavior, stimulus control and sleep restriction, relaxation and cognitive techniques which means reframing the patient's ideas and preconceived notions on sleep. It is typically delivered in 6-8 individual sessions by qualified healthcare professionals.[10,15] The efficacy of CBT-I has been shown in meta-analyses of randomized controlled trials. It has been shown to be equal to pharmacotherapy during acute treatment and more effective for long-term treatment. Recent developments in CBT-I include abbreviated behavioral treatments, internet-based versions, and stepped-care models ranging from self-help to individualized psychotherapy. Initial combined CBT-I and pharmacotherapy, followed by CBT-I alone may produce the best outcomes.[10] The American Academy of Sleep Medicine (AASM) has released recommendations that with a high and moderate degree of clinical certainty, support the efficacy of behavioral therapies, stimulus control therapy, relaxation training, cognitive therapy, sleep hygiene and sleep restriction to treat insomnia. More recently, mindfulness-based interventions have also been added. These guidelines state that the majority of patients will benefit from multicomponent cognitive therapy which combines all of the aforementioned strategies. Others, however ought to be used in accordance with clinical judgment.[72,73]

The CBT can also be focused on pain (CBT-P) in painful TMD patients and hybrid models of CBT for both sleep and pain have been proposed as an effective treatment strategy. Common CBT-P components include psychoeducation on pain, relaxation/mindfulness exercises, activity pacing, training to improve pain-related communication, cognitive restructuring, and coping strategies for pain flare-ups. Although their long-term efficacy remains unclear, a recent meta-analysis demonstrated that combining CBT-I and CBT-P can lead to significant effects on pain intensity at post-treatment versus

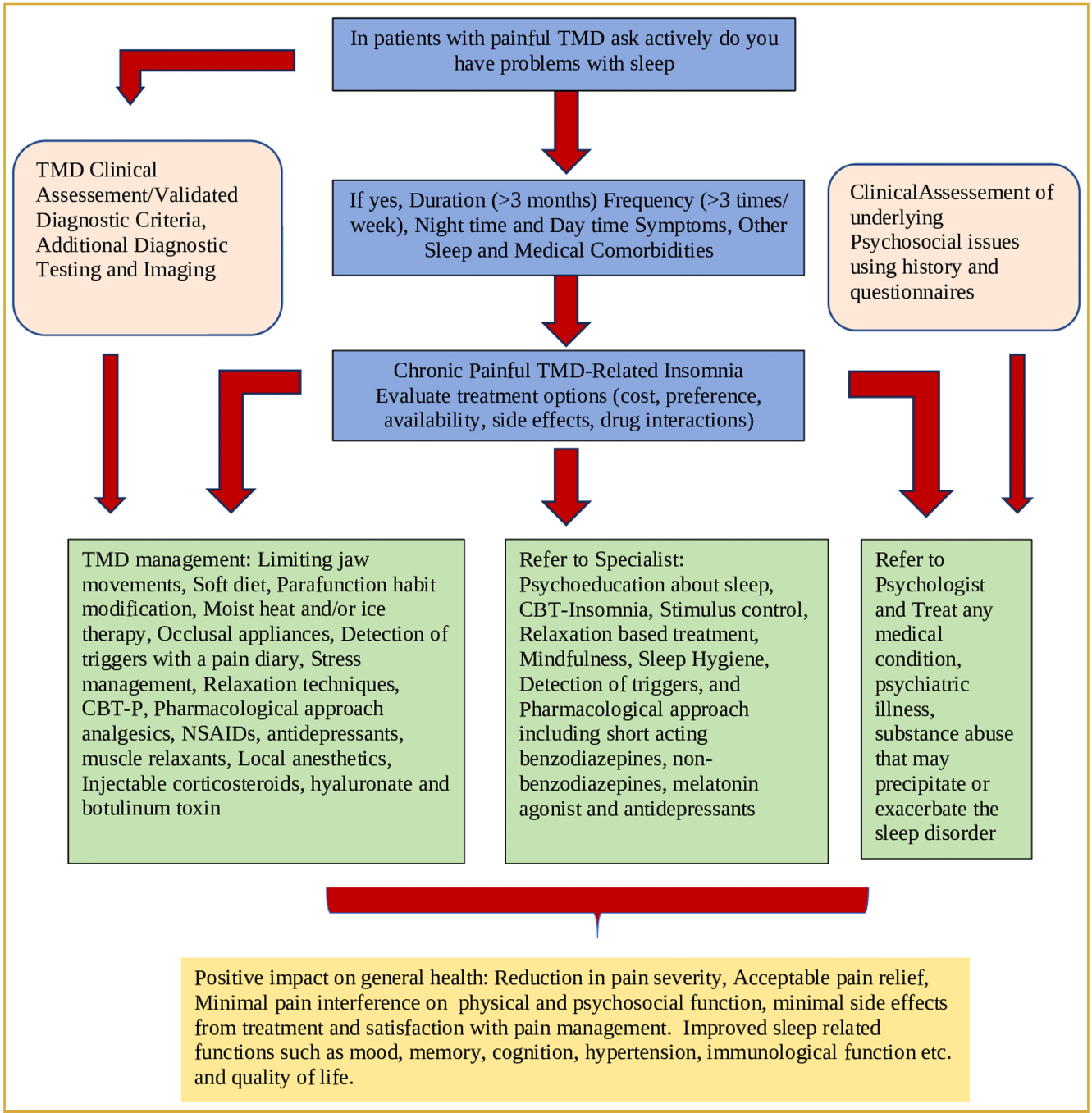

Figure 4. Treatment options for the management of insomnia and painful temporomandibular disorder.

control, but not at follow-up. However, these effects on pain were similar to trials using CBT-I alone.[10,74] Future studies should utilize longer follow-up periods and compare the effects of hybrid treatment in patients with chronic pain and sleep disturbances in order to investigate the effectiveness of hybrid treatment.

Pharmacotherapy

For patients suffering from insomnia, there are different classes of medications. The effect of medications are usually immediate and can a have lower cost than CBT but may be accompanied by side effects, drug–drug interactions, short-term efficacy, and a risk of addiction. The most widely

Table 2. Clinical Implications on Insomnia and Painful Temporomandibular Disorders

Clinical Implications
1. A comprehensive sleep history is an essential component of diagnosing insomnia in patients with painful TMD.
2. Predisposing, precipitating, and perpetuating of insomnia and painful TMD should be thoroughly evaluated to aid in diagnosis and treatment planning.
3. Early diagnosis and management of insomnia are likely to greatly improve the prognosis, improve the quality of life, and reduce health care costs.
4. Screen for other concomitant sleep disorders such as obstructive sleep apnea, sleep bruxism, and other medical conditions that exacerbate the pain and affect treatment outcomes.
5. Individualized and multidisciplinary team approaches are necessary for every patient.
6. Manage painful TMD and insomnia in the context of biopsychosocial interventions, and if necessary, consider pharmacological and other interventions.
7. Patient should undergo routine revaluations to check for any side effects, negative impacts, or long-term consequences of both insomnia and painful TMD treatments.
8. Promote basic research to expand knowledge on mechanism between insomnia and painful TMD.
9. Recognizing how sleep deprivation and related psychological changes contribute to the transition from acute to chronic pain.
10. Provide appropriate referral to sleep specialist, primary physician, and other specialist if needed.

TMD, temporomandibular disorder.

prescribed classes of medication for insomnia are hypnotics, sedative antidepressants, melatonin agonists, orexin antagonists, and antihistaminic and antipsychotics.

The sedative hypnotics include benzodiazepines and benzodiazepine receptor agonists medications. These medications act by facilitating the Gamma-Aminobutyric Acid (GABA) activity in the cortex, hippocampus, thalamus, hypothalamus, basal ganglia, and brainstem where sleep is thought to be promoted by the inhibition of glutamine and monoaminergic arousal.[10,75] According to meta-analyses of randomized controlled trials, benzodiazepines and benzodiazepine receptor agonists are safe and effective for short-term or acute insomnia treatments.[76] However, their safety and efficacy are substantially restricted by the development of tolerance and an elevated risk of dependency with long-term use.[75] The benzodiazepine receptor agonists that clinicians use for chronic insomnia are zolpidem, zaleplon, and eszopiclone which reduce sleep latency and improve sleep maintenance. The risk of sedation is common with all the hypnotics hence, they should be used as a short measure. Currently, 5 benzodiazepine estazolam, flurazepam, quazepam, triazolam, and temazepam are approved by Food and Drug Administration (FDA) and only triazolam and temazepam recommended by the AASM for use in chronic insomnia.[10,71,75] Other medications, sedating antidepressants which included doxepin and trazodone may have 2-fold benefit due to high prevalence of insomnia in depressed patients. It has low abuse potential and cost-effective which makes it appealing. The AASM, however, does not recommend it due to a lack of evidence of efficacy and the possibility of harm outweighs benefits. Another class of drugs is melatonin agonists, which are used to treat insomnia with a component of circadian rhythm disorder component. The mechanism of action of melatonin agonist is biological clock manipulation. Two drugs in this family, ramelteon and tasimelteon have indications for the treatment of sleep disorders.[10,71,75]

A novel pharmacological approach, dual orexin receptors antagonist drugs such as suvorexant, lamborexant, and daridorexant have indications for treatment of insomnia.[10] These medications avoid risk of dependency and encourage sleep by inhibiting the orexin alerting system which is thought to be a neuronal system that promotes continuous wakefulness and separates wake and sleep periods. This is in contrast with other pharmacological approaches such as benzodiazepines which strengthen the sleep drive by the augmentation of GABA activity.[10]Another promising therapeutic target is the adrenergic neurotransmitter system, an important arousal pathway with an under-explored drug development potential for insomnia. Some clinical evidence also suggests that antihypertensive drugs with alpha-adrenergic antagonistic properties can induce sleep.[9,10,48] Alternative pharmacological approach is to directly block wake-promoting amine and cholinergic transmission. Antihistamines (diphenhydramine, doxylamine, hydroxyzine) and tricyclic antidepressants (with anticholinergic and antihistamines properties) have been increasingly used over the past decades, although few data support this treatment option.[10]

Patients with TMD are typically treated with drugs based on scientific evidence. Although a number of drugs are frequently given to treat TMD, many of them lack evidence for this specific disorder. Corticosteroids, NSAIDs, muscle relaxants, anxiolytics, opiates, tricyclic anti-depressants (TCAs), gabapentin, and lidocaine patches are among the most commonly used drugs. Some of these medications are used to treat arthralgia while others are used to treat myalgia or myofascial pain. Additionally, injectable pharmacotherapies such as local anesthetics, corticosteroids, sodium hyaluronate injections, and botulinum toxin are used for the management of painful TMD.[70,77]

Evidence suggests that benzodiazepines, such as diazepam and clonazepam can help with sleep improvement and pain outcomes in groups with chronic pain including TMD. The TCAs in low doses, such as amitriptyline or nortriptyline, have shown to be effective in reducing pain and improving sleep quality in different chronic pain populations. These drugs do not cause addiction. However, these compounds are associated with substantial side effects, such as rebound insomnia after withdrawal, liver dysfunction, and heart rhythm disturbances. Further studies are needed to explore the

effectiveness of antihistamines and antidepressants in TMD pain and insomnia.[69,70,77,78,79]

Anticonvulsant medications such as pregabalin and gabapentin may also be good options for managing chronic pain. Other medications that may be effective in improving sleep and pain in TMD are the muscle relaxant cyclobenzaprine, melatonin, and selective serotonin and norepinephrine reuptake inhibitor duloxetine. In general, opioid should be avoided as much as possible, due to the risk of addiction, central sleep apnea, and deleterious effect on insomnia.[77-80]

Alternative Management Strategies

In chronic TMD pain patients with insomnia, a combination of CBT-I and CBT-P and short-term pharmacotherapy, hypnosis, physical exercise, music therapy, yoga, mindfulness, or traditional Chinese medicine are other alternatives to improve pain and sleep disturbance.[69] There are other alternative strategies that include the use of non-invasive neurostimulation, such as transcranial magnetic stimulation and transcranial direct current stimulation, which have shown promising results in chronic pain and insomnia. These techniques can induce local activity changes in selected areas of cortex and could modulate pain and insomnia via corticothalamic cortical feedback loops. Another approach is the transformation of descriptive recordings of brain activity patterns, such as EEG or real-time fMRI signals, via biofeedback.[69] Further trials are needed to determine if neuro-feedback can be considered to be an effective treatment for insomnia and chronic pain. Moreover, it is critical to understand the limitations of each treatment approach as well as other constraints such as limited access to care, cost, and the possibility of patient noncompliance due to the long duration of treatment. Furthermore, when treating insomnia in patients with painful TMD, providers must weigh the long-term effects of pain and sleep deprivation against the potential risks of their interventions.

Finally, dental practitioners can play a significant role in the early detection of sleep disturbances in patients with pain, thereby reducing consequences and improving clinical

Table 3. Behavioral and Pharmacotherapy for Insomnia

1. Behavioral Treatment for Insomnia	
Therapeutic Approach	**Intervention**
Cognitive therapy	Restructuring maladaptive thought process about sleep
Stimulus control	Conditioning the bed and bedroom to be associated with sleep
Relaxation	Reduce stress and tension
Sleep restriction	Increasing sleep drive to overcome the level of arousal
Mindfulness	Teaching nonjudgmental awareness to help reduce worry about sleep
Sleep hygiene	A collection of behaviors and actions that should be avoided or adopted to improve sleep quality
Multicomponent CBT	Using all interventions listed above in combination
2. Pharmacotherapy	
Common Medications	**Dosage and Side effects**
A) Nonbenzodiazepines Receptors Agonists	
Zolpidem	5 mg, 10 mg, 6.5 mg, 12.5 controlled release; Dizziness, drugged state, allergic reaction, diarrhea, nausea, headache, somnolence, visual disturbance, fatigue
Eszopiclone	1, 2, 3 mg; Taste disturbance, vomiting, dizziness, headache, migraine, respiratory tract infection
Zaleplon	5, 10 mg; Abdominal pain, dizziness, headache, paresthesias, eye pain, dysmenorrhea
B) Benzodiazepines	
Temazepam	7.5, 15, 22.5, 30 mg; Drowsiness, dizziness, lightheadedness, difficulty with coordination
Triazolam	0.125, 0.25 mg; Drowsiness, headache, dizziness, lightheadedness, paresthesias, difficulty with coordination
C) Dual Orexin Receptors Antagonists	
Suvorexant	5, 10, 15, 20 mg; Dizziness, headache, somnolence, diarrhea, xerostomia
Lemborexant	5-10 mg; Palpitations, abnormal sleep behavior, sleep paralysis, headache, lethargy
Daridorexant	25-50mg; Headache, somnolence, fatigue, dizziness, nausea
D) Melatonin and Melatonin Agonists	
Melatonin	1-3 mg, Nausea, amnesia, dizziness, headache, insomnia, somnolence
Ramelteon	1 mg; Back pain, arthralgia, weakness
E) Sedative Antidepressants	
Doxepin	3, 6 mg; Somnolence, sedation, nausea, upper respiratory tract infection, suicidal ideation, serotonin syndrome

outcomes (Table 3). While in some patients with coexisting sleep disturbances, the identification of a possible sleep disorder by the dental practitioner should be followed by referral to a sleep physician for validating the diagnosis and further management. Evaluation and treatment by a sleep specialist are appropriate when the patient fails to respond to medications and has symptoms or clinical features of another sleep disorder, such as excessive daytime sleepiness (narcolepsy, apnea), loud snoring or witnessed apneas (sleep-related breathing disorders), pronounced alteration of sleep timing (circadian rhythm sleep disorder), or unusual sleep behaviors or injury (parasomnia).[15]

CONCLUSION

The relationship between insomnia and chronic, painful TMD represents a major challenge for the clinician, specifically in refractory pain cases despite effective therapy. In such instances, diagnostic approaches may need to be modified with greater emphasis on identifying sleep disorders associated with painful TMD. Data on insomnia as a risk factor for painful TMD are demonstrated in this review. There have been a few observational and longitudinal studies that have analyzed the relationship between insomnia and painful TMD. To support the evidence that insomnia symptoms predispose individuals to chronic, painful TMD or worsen the condition, more longitudinal studies are required. Similarly, we require more micro-longitudinal studies that incorporate the use of technologies to assess the dynamic changes of sleep architecture during pain flare-ups. The influence of psychological variables on sleep and pain may reveal the mechanism for novel treatment of patients with comorbid insomnia and painful TMD. Clarifying the potential mechanisms underlying insomnia and painful TMD is critical for future research in order to develop more refined therapeutic strategies and improve both sleep and pain.

Increased awareness of insomnia and its management in patients with painful TMD is fundamentally important. Beyond the favorable clinical improvements made with regard to sleep continuity disturbance, the treatment of insomnia can also have a positive impact on general health. For instance, improving sleep-related functions such as mood, memory, cognition, hypertension, and immunological function can be achieved by restoring excellent sleep continuity and improving sleep duration. The ultimate goal is to successfully select and implement personalized treatment. This indicates the urgent need for a multidisciplinary and integrated approach which is a crucial step towards addressing these global health challenges as both conditions have demonstrated to worsen general health and place an increased burden on the individual and society.

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