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REVIEW ARTICLE

An update of management of insomnia in patients with chronic orofacial pain

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In this review, we discuss the management of chronic orofacial pain (COFP) patients with insomnia. Diagnostic work-up and follow-up routines of COFP patients should include assessment of sleep problems. Management is based on a multidisciplinary approach, addressing the factors that modulate the pain experience as well as insomnia and including both non-pharmacological and pharmacological modalities. Parallel to treatment, patients should receive therapy for comorbid medical and psychiatric disorders, and possible substance abuse that may be that may trigger or worsen the COFP and/or their insomnia. Insomnia treatment should begin with non-pharmacological therapy, to minimize potential side effects, drug interactions, and risk of substance abuse associated with pharmacological therapy. Behavioral therapies for insomnia include the following: sleep hygiene, cognitive behavioral therapy for insomnia, multicomponent behavioral therapy or brief behavioral therapy for insomnia, relaxation strategies, stimulus control, and sleep restriction. Approved U.S. Food and Drug Administration medications to treat insomnia include the following: benzodiazepines (estazolam, flurazepam, temazepam, triazolam, and quazepam), non-benzodiazepine hypnotics (eszopiclone, zaleplon, zolpidem), the melatonin receptor agonist ramelteon, the antidepressant doxepin, and the orexin receptor antagonist suvorexant. Chronic orofacial pain can greatly improve following treatment of the underlying insomnia, and therefore, re-evaluation of COFP is advised after 1 month of treatment.

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Keywords: pain; orofacial pain; sleep; sleep medicine; sleep disorders; insomnia; cognitive behavioral therapy (CBT)

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Introduction

Orofacial pain (OFP) includes a heterogeneous group of conditions, such as dental, mucosal, musculoskeletal, neurovascular, and neuropathic pains (Sharav and Benoliel, 2015) Epidemiological studies have shown that orofacial pain (OFP) is prevalent in the general population, at around 17–26%, (excluding dental pain), of which 7–11% is 'chronic' OFP (COFP) (Benoliel *et al*, 2008). Chronic pain, in contrast to acute pain which allow organisms to protect themselves from injury, has no biological advantage and has been associated with significant emotional distress (Sharav and Benoliel, 2015).

Recent findings demonstrate the importance of the emotional brain (i.e., the corticolimbic system) in the modulation of acute pain and in the prediction and amplification of chronic pain (Vachon-Presseau *et al*, 2016).

Chronic OFP syndromes are associated with significant morbidity and high levels of healthcare utilization (Sharav and Benoliel, 2015). Indeed, the dichotomized graded chronic pain scale (GCPS) status is predictive of the total cost of health care over the last 6 months, emphasizing the impacts of persistent orofacial pain (Durham *et al*, 2016). Sleep is a rhythmic physiological necessity regulated by homeostatic and circadian processes (AASM, 2014). Humans require both acute pain and sleep for survival and impairments in the regulation of these systems have negative impacts on health and well-being (Finan *et al*, 2013). For example, sleep disturbances are often early markers of ongoing neurodegeneration (Abbott and Videnovic, 2016). Sleep medicine is a rapidly evolving field that encompasses many aspects of human health. Sleep disorders are medical conditions that prevent a person from getting restful sleep, resulting in daytime sleepiness and dysfunction (AASM, 2014). Over 50 million Americans are affected by a chronic sleep disorder (AASM, 2014, Sharav and Benoliel, 2015). The international classification of sleep disorders (ICSD-3) is the most widely used classification system for sleep disorders (AASM, 2014). Its recently published third edition includes seven major categories: insomnia, sleep-related

breathing disorders, central disorders of hypersomnia, circadian rhythm sleep–wake disorders, parasomnias, sleep-related movement disorders, and other sleep disorders (AASM, 2014). The ICSD-3 divides the seven major categories into 60 diagnoses, and it also includes an appendix for classification of sleep disorders associated with medical and neurologic disorders (AASM, 2014).

Insomnia is considered one of the most common medical complaints, affecting 10% to 30% of the United States population, with over five million office visits per year in the United States alone, costing $92.5 to $107.5 billion annually, in both healthcare utilization and absenteeism (Ford *et al*, 2014; Maness and Khan, 2015).

Studies of acute and chronic pain in humans and animals have shown a bidirectional relationship between poor sleep and pain. Specifically, a reciprocal relationship between COFP and poor sleep has been demonstrated (Almoznino *et al*, 2016). In other words, there is a vicious cycle, where pain leads to sleep difficulties that exacerbate the pain (Almoznino *et al*, 2016). Treatment of one can be helpful for the other, for example, treatment of underlying sleep disorders reduces craniofacial pain such as headaches (Carra *et al*, 2012). However, sleep impairment is a stronger predictor of pain, than the converse (Finan *et al*, 2013).

Considering that sleep disturbances, in particular insomnia, are common in COFP patients (Almoznino *et al*, 2016), we aim to provide an update on the management of insomnia in COFP patients, relevant to professionals treating dental and orofacial pain.

Insomnia

Definition of insomnia requires three main components present for at least three nights per week for at least 3 months: persistent sleep difficulty (difficulty initiating or maintaining sleep, waking earlier than desired, resistance to going to bed on appropriate schedule, difficulty sleeping without a parent or caregiver), adequate sleep opportunity, and associated daytime dysfunction (AASM, 2014). Insomnia is more common in women, older adults, and shift workers, and affected people often experience fatigue, poor cognitive function, mood disturbance, and distress or interference with behavioral, social, occupational, educational, academic, or other important areas of functioning (Qaseem *et al*, 2016). The consequences of insomnia include the following: impaired performance, increased risk of car crashes as well as injuries at home and at work, decreased quality of life and a statistically significant risk of range of medical conditions such as: heart disease, hypertension, neurological disease, stroke, gastrointestinal problems, cancer, dyslipidemia, obesity, and diabetes, with an overall increased risk of mortality (adjusted hazard ratio 1.58–2.74; Kay-Stacey and Attarian, 2016; Vedaa *et al*, 2016). Moreover, a bidirectional relationship exists between insomnia and psychiatric disorders, in particular with anxiety and depression (Vedaa *et al*, 2016).

It should be noted that complex medical conditions may not only be a result of insomnia, but may coexist with insomnia, with a higher prevalence in those with heart disease, hypertension, diabetes, stomach ulcers, arthritis, asthma, neurological problems, and menstrual problems (Budhiraja *et al*, 2011). Moreover, medications conventionally used in the treatment of COFP may also cause sleep deprivation, especially when drug abuse is present (Almoznino *et al*, 2016).

The ICSD-3 includes three types of insomnia: short-term insomnia (symptoms present for <3 months), chronic insomnia (symptoms at least three times per week for at least 3 months), and other insomnia (symptoms not meeting the criteria for the short term or chronic types; AASM, 2014). In short-term insomnia, the cause may be a stressful situation, uncomfortable new medical symptom (e.g., pain, urinary frequency, cough, nasal congestion), and/or exogenous factors, such as medications,new sleep environment, Jet lag, and clock change (Sutton, 2014). Short-term insomnia often resolves when patients adapt to the stressor or develop adequate coping mechanisms, although in some cases it may evolve into chronic insomnia (AASM, 2014).

Screening for sleep disorders in patients with COFP

The diagnostic work-up and follow-up of COFP patients should include assessment of sleep problems. An algorithm for identifying and monitoring of patients with insomnia and COFP is presented in Figure 1.

Insomnia is a clinical diagnosis (Schutte-Rodin *et al*, 2008), and therefore, only requires a sleep history to confirm or exclude it. However, a medical history and physical examination should be performed to determine whether the insomnia is associated with another medical condition, psychiatric illnesses, medications (including drug abuse), alcohol, and poor life style. A personal or family history of insomnia, easy arousability, poor self-reported health, and chronic pain are risk factors associated with the onset of insomnia (Maness and Khan, 2015).

COFP history and patterns (Sharav and Benoliel, 2015) should be assessed in relation to the sleep/wake cycle using pain and sleep diaries for at least a few weeks, and patients should be asked to indicate whether their insomnia existed prior to the onset of the COFP (Rains and Pocета, 2012).

COFP is diagnosed by assessment of pain complaints and thorough clinical examination according to the ICHD-3 guidelines (2013) and according to a recent comprehensive review by Sharav and Benoliel (2015).

Validated sleep measurements should be employed, such as visual analog scale (VAS) or numeric scales, or sleep questionnaires such as the Pittsburgh Sleep Quality Index (PSQI), Insomnia severity index, 'BEARS' sleep screening tool, Epworth sleepiness scale (ESS) and a wide variety of other questionnaires reviewed elsewhere (Medarov *et al*, 2013). It is recommended to include instruments measuring different facets of sleep disturbances (Klingman *et al*, 2016).

Reports from partners or caregivers and parents (for child patients), regarding sleep habits, excessive daytime sleepiness, restless sleep, periodic limb movements, tooth grinding sounds, temporomandibular joint sounds, snoring, witnessed apneas, substance use (e.g., alcohol, tobacco,

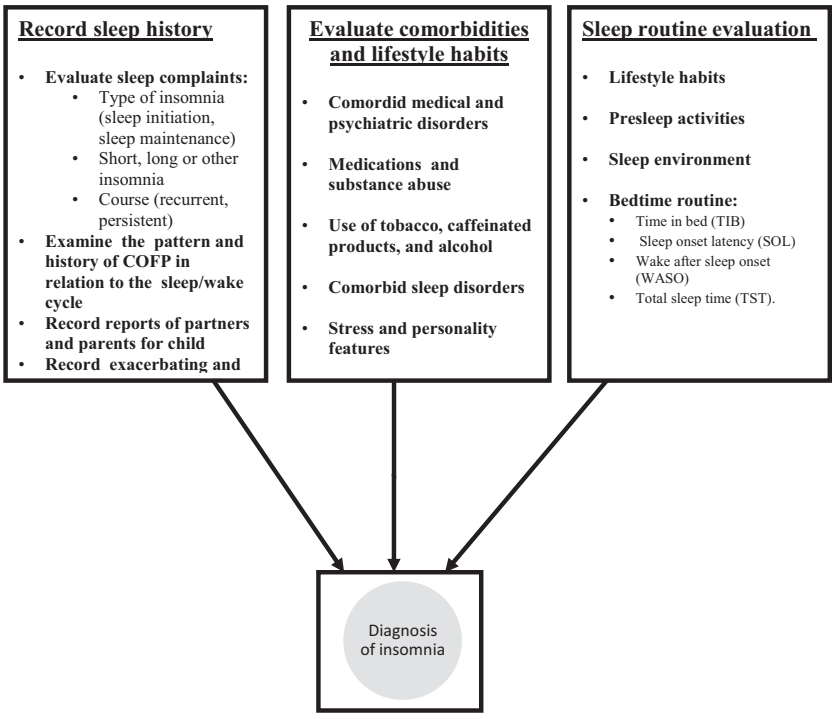

Figure 1 Identifying and monitoring of patients with insomnia and chronic orofacial pain (COFP)

caffeine), and other habits are important to collect (Ramakrishnan and Scheid, 2007; Huynh *et al*, 2014).

In approximately 5% of patients with chronic insomnia, degraded sleep caused by another sleep disorder can be a factor in the insomnia (Ohayon, 2002). Sleep disorders associated with insomnia include the following: obstructive sleep apnea, restless legs syndrome, and circadian rhythm sleep–wake disorders (Ohayon, 2002; Krell and Kapur, 2005). To assess comorbid sleep disorders, further diagnostic investigations by a sleep medicine specialist may be needed, including full-night polysomnographic study, actigraphy electroencephalogram (EEG), and neuroimaging (Ramakrishnan and Scheid, 2007). Inclusion of new tools that may be helpful for the sleep specialist better evaluate insomnia could be additive (Finan *et al*, 2016).

Managing sleep disorders in patients with COFP

An algorithm for management of patients with insomnia and COFP is presented in Figure 2. COFPs including headaches can greatly improve following treatment of the underlying sleep disorders (Carra *et al*, 2012). Therefore, re-evaluation of COFP is recommended after 1 month of sleep disorder treatment (Rains and Poceta, 2006). A combination of management modalities is usually employed due to the overlap between sleep disorders that often exists (Almoznino *et al*, 2016).

If screening and assessment by the dentist (according to Figure 1) reveals COFP and comorbid sleep disorders, such as insomnia, the patient should be referred to specialists as needed. COFP is managed by an orofacial pain specialist (Sharav and Benoliel, 2015) and sleep disorders should be managed by a sleep medicine specialist. These specialists work in collaboration, in a team with oral and maxillofacial surgeons, family doctors, and specialists in internal medicine, neurology, pulmonology, ENT (ear, nose, and throat), anesthesiology, and psychologists/psychiatrists (Huynh *et al*, 2014; Almoznino *et al*, 2016). This interdisciplinary approach is based on the bio-psycho-social model of disease, implying that the management of sleep disorders in patients with COFP should take into account the factors that modulate the COFP as well as sleep disorders.

(Stiefel and Stagno, 2004; Sharav and Benoliel, 2015). Brousseau *et al* suggested a four-step management algorithm for the assessment and treatment of sleep problems in patients with chronic pain: (1) evaluation for primary sleep disorder; (2) review of sleep hygiene; (3) behavioral and cognitive strategies; and (4) pharmacological interventions (Brousseau *et al*, 2003).

An abortive or prophylactic individualized management approach, tailored to the COFP and sleep disorders, should be adopted. Discussion of specific medications used for the management of COFP in is beyond the scope of this review, and a comprehensive treatment approach can be found elsewhere (Sharav and Benoliel, 2015).

Management of insomnia in COFP patients

Patients should receive therapy for comordid medical and psychiatric disorders and/or substance abuse that may trigger or worsen the COFP and/or insomnia (Stiefel and Stagno, 2004). Treatment of insomnia in an individual with comorbid medical disorder may improve of both conditions (Asnis *et al*, 2016). However, when treatment of the comorbid disorder does not relieve insomnia, the symptoms of insomnia *per se* have to be managed (Mayer *et al*, 2011). It should be noted that patients who do not

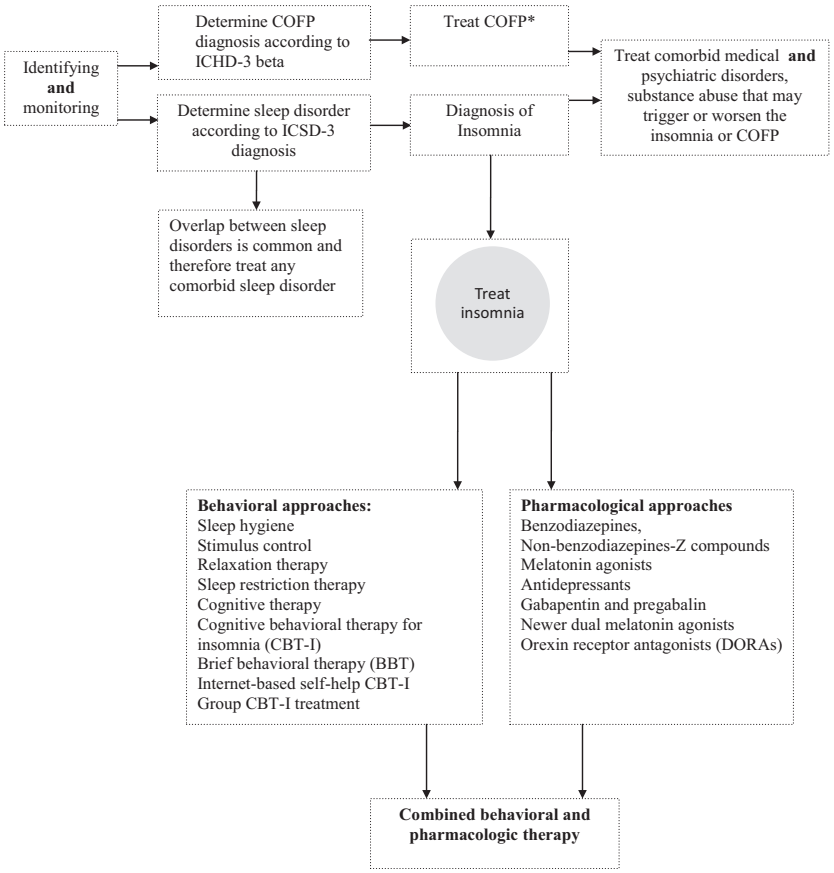

Figure 2 Algorithm for management of patients with insomnia and chronic orofacial pain (COFP). *Discussion of individual drugs used for the management of chronic orofacial pain is beyond the scope of this review, and we refer the reader to the relevant textbook by Sharav and Benoliel, 2015

receive treatment from their physician for insomnia frequently seek over-the-counter remedies and have an increased risk of substance abuse (Roehrs *et al*, 1999). The two most widely accepted treatment options for insomnia are cognitive behavioral therapy for insomnia (CBT-I) and hypnotic medications (Asnis *et al*, 2016; Qaseem *et al*, 2016; Kay-Stacey and Attarian, 2016).

There has been also an increasing body of literature that integrative medicine may be of benefit for patients with insomnia. Mind–body interventions such as hypnotherapy, meditation, guided imagery, mindfulness-based stress reduction, biofeedback, yoga, traditional Chinese practices (e.g., qi gong, tai chi), and music therapy represent safe and cost-effective treatment options for insomnia and other sleep-quality disturbances (Lam *et al*, 2015; Kligler *et al*, 2016; Lin *et al*, 2016; Qaseem *et al*, 2016).

Behavioral approach

According to the American College of Physicians management of insomnia should begin with non-pharmacological treatment (grade: strong recommendation, moderate-quality evidence), due to potential side effects, drug interactions and risk of substance abuse associated with pharmacological treatment (Ramakrishnan and Scheid, 2007; Qaseem *et al*, 2016). In particular, non-pharmacological modalities should be used in specific conditions such as pregnancy and lactation, difficulties in swallowing pills, and in patients averse to the pharmacological approach (Asnis *et al*, 2016). Moreover, studies comparing hypnotic medications to CBT-I demonstrated similar short-term outcomes but better long-term outcomes (up to 1 year) with CBT-I after discontinuing treatments, suggesting a learned carry-over effect for CBT-I (Asnis *et al*, 2016; Morin *et al*, 2009; Kay-Stacey and Attarian, 2016).

Behavioral modalities for insomnia include sleep hygiene, cognitive behavioral therapy for insomnia (CBT-I), multicomponent behavioral therapy or brief behavioral therapy (BBT) for insomnia; and other interventions, such as stimulus control, relaxation strategies, and sleep restriction (Kay-Stacey and Attarian, 2016; Qaseem *et al*, 2016).

CBT-I is a multicomponent treatment that utilizes a variety of behavioral interventions and cognitive restructuring approaches, including cognitive therapy, behavioral interventions (such as sleep restriction and stimulus control), and educational interventions (such as sleep hygiene; Finan *et al*, 2014; Qaseem *et al*, 2016). CBT-I is typically conducted by a sleep psychologist or other behavioral sleep medicine specialist, over a 5-h period (4–6 weeks) and a maintenance treatment can be administered monthly (Morin *et al*, 2009; Asnis *et al*, 2016).

CBT interventions have also been used for pain, termed cognitive behavioral therapy for pain (CBT-P), and hybrid behavioral therapies, combining elements for both pain and sleep work synergistically on sleep and pain symptoms (Finan *et al*, 2014).

A recent meta-analysis of group CBT-I demonstrated medium-to-large effect sizes for sleep onset latency, sleep efficiency, and wake after sleep onset and small effect sizes for pain outcomes (Koffel *et al*, 2014). CBT-I is

effective in the treatment of insomnia secondary to chronically painful medical conditions such as fibromyalgia, mixed chronic pain conditions, back pain, and arthritis and osteoarthritis (Roehrs, 2009; Sharav and Benoliel, 2015).CBT-I strategies not only change sleep patterns, but may also improve pain in adults (Vitiello *et al*, 2009). CBT-I approaches used for pain management in headaches (Lipchik and Nash, 2002) and TMD (Ferrando *et al*, 2012) were beneficial. Indeed, poor sleep hygiene contributes to sleep problems among chronic migraine patients (Calhoun *et al*, 2006), and this was modified by behavioral sleep interventions, which reduced headache frequency and the headache index, and chronic migraine reverted to episodic migraine (Calhoun and Ford, 2007). Headache improvement was proportionate to the number of sleep behaviors changed (Calhoun *et al*, 2006). However, unlike the results among adults, a randomized controlled trial of online CBT-P among youth with chronic pain demonstrated improvement in pain with no changes in sleep outcomes (Fales *et al*, 2015).

Disadvantages of behavioral and cognitive interventions include lack of insurance coverage, high initial cost, few trained therapists, and decreased effectiveness in older adults (Ramakrishnan and Scheid, 2007; Kay-Stacey and Attarian, 2016). Moreover, the success of the therapy is related to the experience of the individual implementing it (Kay-Stacey and Attarian, 2016). Due to these disadvantages, to date, CBTI-I is used in only 1% of chronic insomniacs, while pharmacotherapy is usually the primary treatment (Asnis *et al*, 2016; Riemann *et al*, 2011). Advantages and disadvantages of CBT-I and pharmacological approaches to treat insomnia are presented in Table 1.

An alternative, lower cost, and readily accessible option is bibliotherapy, which is based on self-help books with or without therapist guidance, with significant symptomatic improvements in comorbid and primary insomnia or Internet-based self-help CBT treatments for insomnia or group CBT-I treatment (Koffel *et al*, 2015; Kay-Stacey and Attarian, 2016; Qaseem *et al*, 2016).

Table 1 Advantages and disadvantages of cognitive behavioral therapy for insomnia (CBT-I) and pharmacological approaches to treat insomnia

	Advantages	*Disadvantages*
Cognitive behavioral therapy for insomnia (CBT-I)	Harms sparsely reported but likely small because of non-invasive nature of therapy A learned carry-over effect Better long-term outcomes Suitable in specific conditions such as: • Pregnancy and lactation • Difficulties in swallowing pills • Patients avoiding medications	Lack of insurance coverage High initial cost Few trained therapists Decreased effectiveness in older Success-related experience
Pharmacological approaches	Act quickly, usually after first dose Usually covered by insurance Lower initial cost	Side effects Drug interactions Risk of substance abuse Physical and psychological addiction with long-term use and withdrawal difficulties

Pharmacological approach

In contrast to CBT-I which takes weeks, hypnotic medications act quickly, usually after the first dose and therefore many clinicians prefer medication (Asnis *et al*, 2016). Approved U.S. Food and Drug Administration (FDA) medications for insomnia treatment include the following: benzodiazepines, non-benzodiazepine sedatives, the recently approved orexin receptor antagonist suvorexant, the melatonin receptor agonist ramelteon, and the antidepressant doxepin (Qaseem *et al*, 2016).

The FDA recommends lower doses of hypnotics in women and in older or debilitated adults, as well as short-term use of these drugs (4–5 weeks), with the skills learned in CBT-I used to manage insomnia long term (Qaseem *et al*, 2016). According to the FDA, patients with insomnia that does not remit within 7–10 days of treatment should be further evaluated. (Qaseem *et al*, 2016). However, it should be noted that none of the medications used in the treatment insomnia have been approved by any medical agency in the context of comorbid neurological disease and are therefore off-label (Mayer *et al*, 2011). Moreover, the use of medication prior to the initiation of behavioral therapy appears to be less effective (Kay-Stacey and Attarian, 2016). Risks of pharmacological interventions include side effects, as well as physical and psychological addiction with long-term use. Therefore, pharmacological interventions are only indicated when non-pharmacological measures do not produce the desired improvement, or when insomnia persists after treatment of an underlying medical condition (Kay-Stacey and Attarian, 2016; Qaseem *et al*, 2016). Another management approach includes combination therapy, where CBT-I and a medication are initiated together (usually for 6–8 weeks), then the medication is tapered off or used per-demand, while continuing CBT (Morin *et al*, 2009). However, combination therapy offers no short-term major advantage and only minimal long-term advantage (Morin *et al*, 2009).

Selection of sedative hypnotic is based on the type of insomnia and the duration of effect: Short-acting medication (duration of effect $\leq$8 h) is indicated in patients with sleep onset insomnia, longer-acting medication is recommended in sleep maintenance insomnia, and Zaleplon and a sublingual tablet of zolpidem are recommended for patients with awakening in the middle of the night, with the constraint that they will be taken only if the patient has at least 4 h in bed remaining (Kay-Stacey and Attarian, 2016).

In COFP, a combination of pharmacological therapies may be used as needed. For example, when the tricyclic antidepressant often used in COFP patients cause disturbed sleep, a benzodiazepine hypnotic or non-benzodiazepine sedatives may be used. Our experience is that in

patients with comorbid anxiety, benzodiazepines give rapid control of anxiety and seems to accelerate the effects of antiepileptic drugs.

A summary of the FDA-approved medications to treat insomnia is presented in Table 2.

Benzodiazepines

There are five FDA-approved benzodiazepines for insomnia (estazolam, flurazepam, quazepam, temazepam, and triazolam; Asnis *et al*, 2016; Qaseem *et al*, 2016). Benzodiazepines are frequently used in patients with chronic pain and sleep disturbances (Stiefel and Stagno, 2004). A survey of patients with chronic pain reported that 42% used benzodiazepines not only for sleep, but also for muscle relaxation, treatment of anxiety, and pain relief (King and Strain, 1990). Other studies on benzodiazepines failed to show a significant improvement in sleep in individuals with chronic pain conditions (King and Strain, 1990; Nielsen *et al*, 2015).

Benzodiazepines do not significantly alter pain, although some evidence of the efficacy of benzodiazepines in treating pain has been found in chronic tension headache, temporomandibular disorders (TMD) (Mujakperuo *et al*, 2010), burning mouth syndrome (BMS) (Spanemberg *et al*, 2014), and tic douloureux (Nielsen *et al*, 2015). Indeed, in other studies, Triazolam improved sleep but failed to alter pain in TMD patients (DeNucci *et al*, 1998).

Due to their potential side effects, benzodiazepines should be used at the lowest dose and for short periods (maximum 4 weeks), and daytime sedation, adverse effects, rebound insomnia, as well as dependence and

Table 2 FDA-approved medications to treat insomnia

Pharmacological class	*FDA-approved medications*	*Indications*	*Disadvantages*
Benzodiazepines	Estazolam, Flurazepam, Quazepam, Temazepam Triazolam	Insomnia Sedative/hypnotic Muscle relaxation Anxiolysis Pain relief Anticonvulsant	Daytime sedation, drowsiness, dizziness or lightheadedness Rebound insomnia Dependence and withdrawal difficulties Respiratory suppression at high doses with co-administration of other drugs/substances (e.g., alcohol) Dementia Increased risk for falls, hip fractures, and mobility problems in older adults Temazepam associated with an increase in incident cancer cases
Non-benzodiazepines—"Z compounds"	Zolpidem Extended release Zolpidem Zaleplon Eszopiclone	As effective as benzodiazepines in insomnia treatment, but have less overall adverse effects May reduce narcotic consumption Middle of the night awakenings	FDA labels warn of daytime impairment, "sleep driving," behavioral abnormalities, and worsening depression. Highest for extended release and more prevalent in woman (eliminates slowly than men) and older adults. Observational studies have shown that hypnotic drugs may be associated with infrequent but serious adverse effects, such as dementia, serious injury, and fractures
Melatonin agonists	Ramelteon	Circadian rhythm sleep disorder Insomnia Benzodiazepines withdrawal in elderly with insomnia Preventive therapy in primary headaches Analgesic effect	Dizziness Somnolence (similar to placebo) Fatigue Headache Unpleasant taste Nausea New cognitive or behavioral abnormalities Complex behaviors, such as "sleep driving" Exacerbation of depression and suicidal ideation in primarily depressed patients
Antidepressants	Doxepin	Doxepin: Sleep maintenance insomnia Antidepressants: Pain relief in COFP conditions Preventive therapy in primary headaches Useful in the management of COFP patients with comorbid insomnia and depression	Sedation Fatigue Weakness Lethargy Dry mouth Constipation Blurred vision Headache
Orexin receptor antagonist	Suvorexant	Sleep onset and sleep maintenance insomnia	Because it is new to the market, fewer postmarket data are available and no trials have yet compared it with the other hypnotic drugs. Somnolence Cognitive and behavioral changes, such as amnesia, anxiety, hallucinations, and other neuropsychiatric symptoms Complex behaviors, such as "sleep driving"; worsening of depression, including suicidal thinking in persons with depression Daytime impairments Sleep paralysis; Hypnagogic/hypnopompic hallucinations

withdrawal difficulties should be closely monitored (Stiefel and Stagno, 2004; Ramakrishnan and Scheid, 2007). Careful medication selection to avoid dependence and respiratory suppression is critical in patients with pain, because of frequent co-administration of opioids, antiepileptic agents, neuropathic agents, and muscle relaxants (Fine, 2015).

Non-benzodiazepines hypnotics

The non-benzodiazepine "Z compounds" are as effective as benzodiazepines with less overall adverse effects (Ramakrishnan and Scheid, 2007). Non-benzodiazepine hypnotics approved by the FDA for the treatment of insomnia include zolpidem (Ambien), zolpidem extended release (Ambien CR), zaleplon (Sonata), and eszopiclone (Lunesta; Qaseem *et al*, 2016).

Interestingly, occasional side effects of these drugs include headaches (Lieberman, 2007). Zolpidem was shown to reduce narcotic consumption, fatigue level, and postoperative pain following knee arthroscopy (Krenk *et al*, 2014). Regarding chronic pain conditions, zolpidem, but not zopiclone, improved some sleep parameters in patients with fibromyalgia, but neither drug improved pain (Roehrs, 2009). A case of a patient with chronic resistant facial pain, who took high-dose zolpidem for pain relief and encountered serious withdrawal effects was reported (Krueger *et al*, 2005).

Melatonin

Melatonin is FDA approved to treat circadian rhythm sleep disorder in blind children and adults (Ramakrishnan and Scheid, 2007). Levels of melatonin have been found to be low in migraine and in cluster headache (Bougea *et al*, 2016); therefore, these patients may derive beneficial hypnotic and antinociceptive benefit from melatonin (Nesbitt *et al*, 2014; Bougea *et al*, 2016). Moreover, melatonin is usually a well-tolerated medication with few side effects and it appears to be safe when used short term (3 months or less; Qaseem *et al*, 2016). Some studies have supported the use of melatonin for preventive therapy in primary headaches and migraines (Nagtegaal *et al*, 1998; Nesbitt *et al*, 2014; Bougea *et al*, 2016), in particular in CH, where melatonin treatment is thought to reset the circadian pacemaker (Bougea *et al*, 2016). Several case reports on hemicrania continua, an indomethacin-responsive headache reported a positive response to melatonin (Rozen, 2015). Melatonin has a similar chemical structure to indomethacin, and the addition of melatonin to indomethacin may allow around 45% of patients to have complete or partial relief of their headache with the subsequent ability to reduce or eliminate their indomethacin dosage (Rozen, 2015). Melatonin also has analgesic effects in patients with fibromyalgia and irritable bowel syndrome (Wilhelmsen *et al*, 2011).

A randomized control trial which studied the analgesic and sedative effects of melatonin in TMD demonstrated that melatonin lowered pain scores and reduced analgesic consumption (Vidor *et al*, 2013). Furthermore, the effect of melatonin on pain appears to be independent of changes in sleep quality (Vidor *et al*, 2013).

Antidepressants

The tricyclic antidepressants (TCAs) are the main class of antidepressants used in headache treatment, with amitriptyline being the most studied (Nesbitt *et al*, 2014). Antidepressants can also cause sedation by blocking acetylcholine, histamine, norepinephrine, and serotonin (Ramakrishnan and Scheid, 2007). However, antidepressants have been shown to improve and disturb sleep, and the sedating effect tends to be short-lived and other side effects are common (Nesbitt *et al*, 2014). Moreover, data on the use of antidepressants in the management of sleep in patients with pain disorders are limited (Roehrs, 2009). A Cochrane review concluded that serotonin–norepinephrine reuptake inhibitors (e.g., duloxetine and milnacipran) produced a small improvement in pain symptoms, but were no more effective than a placebo in relieving sleep symptoms in patients with fibromyalgia, and insomnia was a frequently reported side effect (Hauser *et al*, 2013). Recently, the antidepressant, doxepin, a selective histamine receptor antagonist, was approved by the U.S. food and drug administration (FDA) for the treatment of insomnia at 3 and 6 mg doses (Yeung *et al*, 2014). Some types of antidepressants may be useful in the management of COFP patients with comorbid insomnia and depression (Stiefel and Stagno, 2004; Ramakrishnan and Scheid, 2007).

Gabapentin and pregabalin

These anticonvulsant agents are commonly used in COFP conditions (Sharav and Benoliel, 2015). A systematic review concluded that pregabalin is beneficial in the treatment of sleep disturbances and pain symptoms in patients with fibromyalgia (Straube *et al*, 2010). Sustained improvement in sleep interference in patients with painful diabetic peripheral neuropathy and postherpetic neuralgia occurred rapidly (within 1 day for some patients) in response to treatment with pregabalin (Parsons *et al*, 2014). Significant reductions in pain and pain-related sleep interference were observed when pregabalin was used in the treatment of neuropathic pain (Anastassiou *et al*, 2011).

Orexin receptor antagonist

Orexinergic neurons promote arousal in areas such as the locus coeruleus, tuberomammillary nucleus, basal forebrain, dorsal raphe nucleus, and cerebral cortex (Kay-Stacey and Attarian, 2016). Antagonists that reversibly block the action of endogenous peptides at both the orexin 1 and orexin 2 receptors (OX1 R and OX2 R), termed dual orexin receptor antagonists (DORAs), inhibit activation of the arousal system (Kay-Stacey and Attarian, 2016). Suvorexant is a reversible DORA that was FDA approved for use in insomnia in 2014 (Kay-Stacey and Attarian, 2016; Qaseem *et al*, 2016). It is thought to be effective in treatment of sleep onset and sleep maintenance insomnia; however, no trials have yet compared it with the other hypnotic drugs (Kay-Stacey and Attarian, 2016). Based on preclinical studies, DORAs are also being developed for primary headache disorders (Nesbitt *et al*, 2014).

Conclusions

Principles of management of COFP and insomnia were highlighted in the present review. This update is relevant to professionals treating dental and orofacial pain because of the importance of dealing and managing serious side effects and consequences. Patients with COFP and insomnia should be identified and monitored. Management is based on a comprehensive, multidisciplinary pain management approach, addressing the factors that modulate the pain experience as well as insomnia. Treatment includes both non-pharmacological and pharmacological modalities, in order to limit serious side effects and consequences.

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Conflicts of interest

None to declare.

Author contribution

G.A. was involved in article's conception and design, drafted the manuscript and provided final approval of the version to be published. Y.H. and Y.S. revised the manuscript and provided final approval of the version to be published. R.B. drafted the manuscript and provided final approval of the version to be published.

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