HHS Public Access

Author manuscript

Clin Chest Med. Author manuscript; available in PMC 2022 August 04.

Published in final edited form as:

Clin Chest Med. 2022 June ; 43(2): 353–371. doi:10.1016/j.ccm.2022.02.013.

Sleep Deficiency in Obstructive Sleep Apnea

Olurotimi Adekolu, MD[a], **Andrey Zinchuk, MD, MHS**[b,*]

[a]Starling Physicians, 533 Cottage Grove Road, Bloomfield, CT 06002, USA;

[b]Section of Pulmonary, Critical Care and Sleep Medicine, Department of Internal Medicine, Yale School of Medicine, 300 Cedar Street, The Anlyan Center, 455SE, New Haven, CT 06519, USA

Keywords

Sleep deficiency; Obstructive sleep apnea (OSA); Insomnia; COMISA; Circadian misalignment; Periodic limb movements of sleep (PLMS); Cognitive behavioral therapy for insomnia (CBT-I)

INTRODUCTION

Obstructive sleep apnea (OSA) is the most common sleep disordered breathing syndrome, with prevalence ranging from 9% to 38% in the general population.[1] OSA is highly burdensome because it contributes to psychiatric, metabolic, and cardiovascular diseases (CVDs), such as depression, diabetes, hypertension, and stroke,[1–4] and importantly impairs daytime function by potentiating sleep deficiency. The National Institutes of Health defines sleep deficiency as abnormalities in sleep duration, circadian alignment, sleep quality, and sleep-related disorders.[5]

Sleep deficiency in OSA may be a direct consequence of upper airway obstruction, leading to hypoxemia, arousals from sleep, and sympathetic activation. These events result in poor quality sleep and decreased sleep duration, extensively described in prior literature.[6,7]

Sleep deficiency in OSA, however, is also closely linked to comorbid disorders. These disorders may contribute to poor sleep directly or through interactions with OSA. Conditions such as insomnia, circadian misalignment, periodic limb movements of sleep (PLMS) can all impact sleep quantity and quality in patients with OSA hence worsening sleep deficiency. Here, we discuss these relationships as they relate to sleep deficiency in individuals with OSA.

COMORBID INSOMNIA AND OBSTRUCTIVE SLEEP APNEA

Epidemiology

Difficulty initiating, maintaining, or early termination of sleep associated with daytime symptoms (e.g., fatigue) or functional impairment are diagnostic characteristics of the insomnia disorder. These are also common in those with OSA. For example, a recent systematic metanalysis by Zhang and colleagues[8] examined the co-occurrence of insomnia

*Corresponding author. andrey.zinchuk@yale.edu.

symptoms and insomnia disorder in patients with OSA (apnea-hypopnea index [AHI] ≥ 5; n = 28,252). Insomnia was defined based on the insomnia severity index (ISI) score of 15 or higher,[9] *Diagnostic Statistical Manual Mental Disorders*, 5th edition, or the International Classification of Sleep Disorders (ICSD) criteria,[10,11] or physician diagnosis.[12] The prevalence of insomnia was 38% (95% confidence interval, 15%–64%).[8] Difficulty maintaining sleep was the most common presenting symptom (42%). However, other signs such as short sleep duration owing to difficulty falling asleep and early morning awakenings occurred in 18% and 21% of patients with OSA, respectively. In contrast with previous studies,[13] OSA severity did not influence the prevalence of insomnia, suggesting that clinicians should assess for insomnia in all patients with OSA, regardless of the AHI.

Pathophysiology

The co-occurrence of insomnia and OSA may be related to each disorder perpetuating the other (Fig. 1).[14] Insomnia may increase susceptibility to apneic episodes. Physiologic arousal is heightened in insomnia patients, as evidenced by elevated cortisol, metabolic rate, electroencephalography (EEG) activity, and prolonged sleep latency.[15–23] This state of hyperarousal increases the propensity for lighter sleep, which in turn increases the vulnerability to apneic episodes.[24] Indeed, a low arousal threshold, or propensity to awaken easily from a respiratory stimulus, is more common in those with comorbid insomnia and OSA (COMISA) versus OSA alone.[25] In those with a low arousal threshold, ventilatory over-shoots during arousals lead to greater CO_2 reduction with resultant worsening in upper airway muscle tone and propensity for airway obstruction during sleep.[26] Data suggest that reducing arousability by pharmacotherapy or cognitive behavioral therapy for insomnia (CBT-I) may decrease the AHI.[27,28]

Conversely, OSA contributes to insomnia symptoms. The repetitive arousals and postarousal awakenings may be perceived as recurrent wakefulness during sleep and promote maladaptive cognition about sleep. Repetitive nights of sleep difficulties may activate the sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA) axis.[29] The consistent association of the bedroom environment, the time of night, and the unmet desire to fall asleep along with sympathetic nervous system/HPA axis activation can become conditioned and underlie the development of psychophysiological or conditioned insomnia.[29,30]

How deeply a patient sleeps as measured by the odds ratio product (ORP) may be an intrinsic trait that influences an individual’s tendency for arousal when exposed to internal or external stimuli and may be a pathogenic mechanism linking OSA and insomnia. The ORP quantifies the moment-to-moment sleep depth using EEG signal processing from standard polysomnography. An ORP of 2.5 indicates complete alertness/wakefulness, whereas 0 indicates deep sleep/zero likelihood of arousal. Younes and Giannouli[25] investigated the mechanistic origin of excessive wakefulness (defined as a sleep efficiency of <80%) observed in both conditions. They measured the ORP in healthy controls and people referred for polysomnography with and without OSA, PLMS disorder (PLMD), and insomnia symptoms. They found that ORP was higher in those with insomnia symptoms (65% of participants) than those without. Sleep depth in the first 9 seconds after arousal was also

lighter, increasing the risk for subsequent arousals.[25] Notably, those with excessive night wake time exhibited a higher ORP than those without, regardless of the comorbid OSA or PLMD. These findings suggest that an individual's sleep propensity is an important determinant of excessive wake time and is not solely owing to disorders characterized by repetitive arousals, such as OSA and PLMD.

Clinical Characteristics and Consequences of Comorbid Insomnia and Obstructive Sleep Apnea

Like all patients suffering from insomnia, those with COMISA have difficulty falling asleep, maintaining sleep owing to frequent awakenings or early morning awakenings, and nonrestorative sleep. Difficulty maintaining sleep is the most common COMISA symptom.[31,32] Individuals with this symptom are older, have a higher body mass index, AHI, and more daytime sleepiness as measured by the Epworth sleepiness score compared with those with other symptoms.[31,33,34] Difficulty initiating sleep, in contrast, is associated with lower OSA severity[34] and is more common in women with COMISA who smoke and manifest poor physical and mental quality of life.[31] Particular attention should be paid to those suffering from mood disorders, chronic pain, and post-traumatic stress disorder, which predict severe insomnia (ISI scores of 23.1 ± 2.6) and are treatable precipitating and perpetuating factors.[35]

COMISA is associated with adverse consequences, including higher use of sedative and psychotropic medications, greater daytime impairments, and poorer physical and mental quality of life.[31,36,37] Those with COMISA have lower adherence to continuous positive airway pressure (CPAP) therapy (OR, 0.81; $P = .02$) and decreased clinical response to mandibular advancement devices than individuals who have OSA alone.[32,38] CPAP therapy in COMISA improves middle-of-the-night sleep maintenance but may also be associated with the emergence of early morning awakenings.[33]

Both OSA and insomnia are also linked to CVD. The shared mechanistic pathways (Fig. 2) suggest the risk from COMISA may be increased compared with each condition alone.[39–46] OSA's negative intrathoracic pressure swings increase transmural pressure of thoracic structures and left ventricular afterload. These changes impede stroke volume, increase myocardial oxygen demand and arrhythmogenesis.[47] Hypoxia leads to pulmonary vasoconstriction, pulmonary hypertension, and right heart dysfunction.[47–49] Insomnia, in contrast, is associated with dysregulation of the hypothalamic–pituitary–adrenal axis. The HPA axis is in turn associated with an increased heart rate, blood pressure, dyslipidemia, and mediators of the CVD pathway, such as impaired glucose metabolism and diabetes.[50–52] Both sleep apnea and insomnia share the pathways of excessive arousals, autonomic dysregulation, increased systemic inflammation, insulin resistance, atherogenesis, and endothelial dysfunction[44,47,48,53–56] Although all these factors are plausible mechanisms for increased risk of CVD in COMISA, further work is needed to determine if this plausibility translates into observed increased CVD risk in COMISA compared with OSA and insomnia alone.

Diagnosis and Treatment

The COMISA-specific diagnostic criteria are yet to be established. Thus, identifying this condition relies on the presence of insomnia and OSA according to current guidelines (*Diagnostic Statistical Manual Mental Disorders*, 5th edition/ICSD and ICSD, respectively).[10,11] A general medical/psychiatric questionnaire, assessment of sleepiness (e.g., Epworth sleepiness score), insomnia severity measures (e.g., ISI), sleep logs (or actigraphy) in addition to polysomnography or polygraphy are essential to diagnosis and management.[57,58]

Similar to diagnosis, although there are well-established guidelines for treating OSA and insomnia, such guidelines do not exist for COMISA. CPAP therapy is the most common treatment for OSA, with oral appliances, surgery, or upper airway stimulation used in some cases.[59,60] CPAP use, however, is hampered by poor adherence to therapy in those with insomnia symptoms.[61–65] CBT-I is the recommended first-line treatment for insomnia. Recent data suggest that a combination of CBT-I with CPAP therapy may improve outcomes in COMISA.[57,66,67] Tables 1 and 2 summarize the observational and clinical trial studies on the treatment of patients with COMISA. Elsewhere in this article, we highlight the findings of the most recent, randomized clinical trials addressing the effect of CBT-I, its delivery method, and when it might be best to administer CBT-I in relation to the initiation of OSA therapy on patient-centered outcomes in COMISA.

Alessi and colleagues[68] compared the effect of concurrent delivery of a 5-session combined CBT-I and behavioral CPAP adherence program administered by trained sleep coaches versus a sleep education control program on insomnia symptoms and CPAP use at 6 months. The CBT-I/adherence intervention was delivered to 125 adult veterans (96% male) with insomnia and an AHI of 15 or more per hour. Compared with sleep education alone, the CBT-I group showed a greater improvement in actigraphy-measured sleep onset latency and efficiency, a clinically significant 6-point decrease in the ISI and 78- and 48-minute greater adherence to CPAP therapy at the 3- and 6-month follow-ups, respectively.[68] Notably, a study by Bjorvatn and colleagues[69] shows that the delivery of CBT-I via a self-help book is not sufficient to derive benefits among patients with COMISA.

To determine if CBT-I administered before OSA therapy can improve outcomes, Sweetman and colleagues compared CBT-I to treatment-as-usual before positive airway pressure (PAP) therapy in 145 patients with COMISA.[70] The CBT-I group demonstrated higher PAP treatment acceptance (99% vs 89%; $P = .034$), nightly adherence to PAP (61 minutes higher; $P = .023$), and greater improvement in insomnia at 6 months (ISI 18.5 vs 9.0; $P = .001$). Notably, the authors identified a 15% increase in sleepiness the week after administering sleep restriction as a part of CBT-I that returned to pretreatment levels in the subsequent weeks.[71] Thus, it may be important to inform patients that a transient worsening in sleepiness may occur, but overall, sleep deficiency will improve.

Finally, Ong and colleagues[72] conducted a 3-arm randomized controlled trial among 121 adults with COMISA comparing the timing of CBT-I and PAP initiation (PAP alone vs CBT-I concurrent with PAP vs CBT-I followed by PAP). Compared with PAP alone, the 2 CBT-I treatment arms reported a significantly greater decrease from baseline in insomnia

severity. They had a greater percentage of participants categorized as good sleepers and remitters from insomnia. No significant differences were found between the CBT-I followed by PAP versus concurrent CBT-I/PAP arms on any outcome measure.

In summary, CBT-I, when used with CPAP in patients with COMISA, is more efficacious than CPAP alone.[70,72] Although no data support CBT-I use before versus along with PAP initiation, it is clear that treating insomnia and OSA at least concurrently is needed to improve important patient outcomes.

Owing to the limited availability of qualified CBT-I providers, sedative-hypnotics are often used in patients with COMISA.[73] There are concerns about worsening airway collapsibility in COMISA with hypnotics. Notably, however, the nonbenzodiazepine hypnotics such as eszopiclone or zolpidem do not worsen airway collapsibility among patients with nonsevere OSA.[74,75] In an unselected OSA population, eszopiclone also improved the effectiveness of CPAP titration and initial CPAP adherence (21% more nights and 1.1 more hours per night of CPAP use) at 6 months compared with placebo.[76,77] A notable finding from Sweetman and colleagues' work is that the CBT-I group exhibited a decrease in the AHI that was 7.5 events/h greater than in the control group, suggesting that addressing mechanisms of insomnia and improving sleep quality may also improve OSA control.[28] Targeting patients with OSA and low arousal threshold, which can present as insomnia and responds to nonbenzodiazepine hypnotics, may be an effective way to make therapy for COMISA more precise.[78]

Future Directions

Research is needed to elucidate the relationship between the mechanisms of insomnia and respiratory events. The concept of sleep depth as measured by the ORP is promising. It may be used to investigate the interplay between sleep depth, wakefulness, and upper airway obstruction, especially during treatment with CBT-I, PAP, or both. Insomnia is a disorder of hyperarousal, yet it is unknown whether a low arousal threshold in OSA leads to insomnia or insomnia manifests with a low arousal threshold, or both. The findings of CBT-I reducing OSA severity require validation. When administered with PAP, understanding whether sedative-hypnotics improve OSA severity, sleep quality, and function in those with COMISA is needed. Importantly, whether such use of hypnotics in COMISA is safe in the long term, especially in vulnerable populations, such as the elderly and those on opioid therapy, should be addressed. Finally, data on the efficacy of other treatment combinations such as CBT-I and oral appliance orupper airwaystimulation therapy, can help to inform the treatment approaches for those who cannot tolerate PAP.

CIRCADIAN MISALIGNMENT IN OBSTRUCTIVE SLEEP APNEA

Circadian rhythms are patterns of behavior and physiology that follow a 24-hour cycle under the control of a self-sustaining molecular oscillator (i.e., circadian clock) that is entrained by external cues such as the solar light–dark cycle and timing of sleep–wake, eating, and exercise.[79] Circadian misalignment includes complex conditions that are characterized by mismatches in timing among solar day–night, the central clock, peripheral clocks, and behaviors such as sleep or feeding.[79] These misalignment phenomena are common in shift

workers, individuals who are forced by social and occupational constraints to adhere to a schedule that does not conform to their natural chronotype (social jet lag) and during travel across time zones.

Epidemiology

To our knowledge, no studies have examined the prevalence of circadian misalignment among individuals with OSA. Recent data do suggest that a bidirectional relationship may exist between circadian misalignment and OSA and contribute to sleep deficiency in individuals who suffer from both.

Pathophysiology

Circadian changes in respiratory control and arousability across the 24-hour period may contribute to sleep apnea pathogenesis. Simulations show that circadian changes can augment sleep-induced periodic breathing, a manifestation of high loop gain, in the evening compared with daytime naps.[80] Using a forced desynchrony protocol, Butler and colleagues identified circadian rhythms in the frequency and duration of respiratory events in NREM sleep. At an average clock time of 22:30 (30° from dim light melatonin onset [DLMO]), the AHI was highest, and the duration of apneas and hypopneas was shortest in contrast to the average lowest AHI and longest event duration at an average clock time of 5:30 (135° from DLMO).[81] These changes may be mediated through an increase in arousal threshold, which increases from the onset to the end of a nocturnal sleep period.[82]

OSA, in contrast, may lead to circadian misalignment. For example, circadian variation of oxygen saturation level that helps to synchronize key components of the molecular clock, including the Period and Clock genes,[83] is likely to be disrupted by hypoxia caused by OSA. Hypoxia lengthens the period and dampens the amplitude of circadian rhythmicity of the mammalian molecular clock and can also induce misalignment between peripheral clocks and between peripheral and central clock as observed in mice.[84,85] Such studies provide glimpses of the relationships between circadian rhythms and OSA, and much remains to be elucidated.

Clinical Characteristics and Consequences of Circadian Misalignment in obstructive sleep apnea

Patients with sleep deficiency owing to circadian misalignment in OSA may present with a delay or advance of their major sleep episode with respect to their desired sleep timing. Extreme difficulty with falling asleep at desired bedtimes and waking up at the required or desired times characterize a delayed rhythm. In contrast, the inability to stay awake during evening hours with an undesirably early wake time characterizes an advanced rhythm. Circadian misalignment can worsen excessive daytime sleepiness and depressive symptoms, common features of OSA that confer a great portion of the disability and lost quality of life associated with the disorder.[86,87] Individuals with delayed phase may also present with insomnia symptoms (an inability to fall asleep at conventional evening times) with implications discussed elsewhere in this article. The assessment of circadian timing is, therefore, needed for the success of OSA treatment.

Diagnosis and Treatment

Melatonin-based measurement of the circadian phase is not practical in a clinical setting. Therefore, actigraphy accompanied by a sleep diary as part of the initial assessment of patients with OSA who present with symptoms suggestive of circadian misalignment is important. These data may help to identify individuals who are most likely to benefit from a chronotherapeutic intervention, in addition to CPAP therapy.

Interventions for circadian rhythm disorders include timing of sleep-wake periods, physical activity/exercise, medications, and light therapy (the most effective circadian cue) to phase shift and/or promote sleep or wakefulness. Short amounts (30–60 minutes) of appropriately timed light therapy effectively realigns individuals' circadian rhythm, with associated improvements in sleep duration, self-reported sleep quality, insomnia symptoms, and fatigue.[88] Light therapy is also effective in acutely decreasing sleepiness, fatigue, and increasing alertness.[89–93] Benefits of exercise are multifold in patients with OSA who also have obesity. Buxton and colleagues[94] showed that acute bouts of high-intensity exercise after the DLMO can significantly delay the circadian phase. In contrast, early evening exercise before the DLMO can lead to phase advancement.[94,95] Baehr and colleagues[96] showed that combining bright light therapy and exercise can potentiate their phase-shifting effects.

Future Directions

Much of this discussion is based on research in patients without OSA. This is in part due to the lack of readily applied circadian biomarkers. For example, 24-hour blood, urinary, or salivary melatonin level measurements are impractical in most settings. Developing noninvasive measures can help to define the type of circadian disturbance among patients with OSA and its impact on treatment efficacy and CPAP adherence. Studies assessing the utility of treating circadian misalignment on patient-centered outcomes, such as daytime sleepiness, insomnia, and quality of life are needed.

PERIODIC LIMB MOVEMENTS OF SLEEP IN OBSTRUCTIVE SLEEP APNEA

PLMS are repetitive movements, typically in the lower extremities involving an extension of the toe and flexion of the ankle, knee, and even the hip. PLMS are often associated with a cortical arousal or an awakening.[97] These events can fragment and reduce the duration of sleep already compromised by OSA. Increasing evidence suggests that PLMS are associated with sympathetic activation, inflammation, endothelial dysfunction, and increased cardiovascular risk in those with OSA[98–103] However, the pathophysiology of the relationship between PLMS and OSA and its clinical implications (independent vs synergistic effects) remain understudied, leaving uncertainty about consequences and management. PLMS often coexist with restless leg syndrome (RLS). Because RLS is more readily identified and treated independently of sleep-disordered breathing, we focus the discussion in this section on sleep deficiency associated with PLMS in OSA.

Epidemiology

The reported prevalence of PLMS in OSA ranges widely (8%–59%) and depends on cut-offs of AHI and PLM index (PLMI) used to define OSA and PLMS.[104–106] Similarly, the frequency of PLMS in OSA is different in sleep clinic compared with community populations. In a diverse sleep clinic cohort of 849 patients with OSA (AHI of ≥10/h) randomized to CPAP or sham (Apnea Positive Pressure Long-term Efficacy Study, APPLES), the prevalence of PLMS (PLMI of ≥15/h) was 15%.[107] The prevalence of PLMS increases markedly with age. Among individuals 65 years or older with OSA (AHI of ≥15/h) in community cohorts, PLMS are observed in 52% of women and 60% of men (unpublished data from Study of Osteoporotic Fractures[108] and Outcomes of Sleep Disorders in Older Men Study[109] cohorts). PLMI is underestimated in those with severe OSA because PLMS are not scored when adjacent to respiratory events. Studies in sleep clinic populations show that, in individuals with OSA and PLMS, a PLMI of 15 or more per hour persists in 65% to 76% after adequate CPAP titration.[106,110] Notably, in 9% to 22% of patients with OSA free of limb movements, PLMS emerge after CPAP use,[106,110] suggesting that monitoring for PLMS as a potential cause of residual symptoms may be warranted. Risk factors include low iron stores; chronic lung, heart, and kidney disease; neurologic disorders (e.g., multiple sclerosis, Parkinson's disease); and psychoactive substances (e.g., caffeine, antidepressants, antihistamines).

Pathophysiology

The pathophysiology of PLMS is discussed in detail elsewhere.[111] Whether PLMS contribute to the pathogenesis of OSA, are a consequence of respiratory events, or are independent but co-occurring phenomena remains to be understood. Recent studies suggest that a low arousal threshold, a causative trait of OSA, may be a potential mechanism linking PLMS and OSA, whereby the cortical and subcortical arousability observed in PLMS[112] may manifest as a low arousal threshold. In 1 study, 59% of individuals with OSA-PLMS exhibited a low arousal threshold compared with 20% among those with OSA alone, findings also observed in another, independent cohort.[104] In contrast, other work suggests that PLMS may be a consequence of undertreated OSA, with persistent PLMS heralding ongoing airway obstruction (elimination of hypopneas but persistent flow limitation) that improves at higher CPAP pressures.[101] Other studies, including secondary analyses of the APPLES trial, show that PLMI after titration or 6 months of therapy did not differ between sham or in-laboratory titrated CPAP arms (−4.2 ± 25.4 vs −4.8 ± 25.0; $P = .9$).[107] Similar findings in observational studies showing greater rates of PLMS emergence rather than resolution after CPAP titrations suggest that PLMS and OSA may simply co-occur.[106,110]

Clinical Characteristics and Consequences of Periodic Limb Movements of Sleep in Obstructive Sleep Apnea

PLMS may manifest as repeated awakenings, unrefreshing sleep, reports of movements by a bed partner, as well as fatigue, depression, anxiety, and RLS. Without objective testing (e.g., PSG on PAP or at-home PLMS monitors), however, one is unlikely to detect PLMS, as demographics, baseline sleep study data, and clinical history only have weak predictive value for PLMI of 15 or more per hour.[113]

Evidence is accumulating that PLMS are associated with adverse consequences in OSA. These include impaired sleep quality (prolonged latency, lower efficiency, and duration) before OSA treatment (independently of AHI) and on CPAP, identified in the APPLES study.[107] These changes did not translate into increased subjective or objective sleepiness, however. Notably, other daytime symptoms such as insomnia and fatigue associated with PLMS in non-OSA samples[114] (and common in OSA) were not reported in this study. Both PLMS and OSA are associated with cyclical alternating pattern. EEG subtypes related to arousals increased sympathetic activation,[111] and heart rate, and blood pressure elevations.[115,116] PLMS may potentiate each of these when associated with respiratory events.[115,116] Small studies also show that inflammation and arterial stiffness are increased in those with PLMS and OSA versus those with OSA or PLMS alone,[99,100] suggesting synergistic effects.

PLMS are associated with increased risk of prevalent hypertension,[117] atrial fibrillation,[118] and incident CVD, and all-cause mortality, independently of the AHI.[119] Few studies, however, have addressed the potential interactive effects of PLMS and OSA. In a cohort of US veterans, a cluster of patients with predominantly mild OSA an elevated PLMI (median of 64/h) was at an increased risk of incident diabetes (adjusted hazard ratio, 2.26; 95% confidence interval, 1.06–4.83)[98] and CVD or death (adjusted hazard ratio, 2.36; 95% confidence interval, 1.61–3.46) compared with a mild cluster.[103] These findings are yet to be replicated, and the impact of therapy for OSA or PLMS on cardiovascular outcomes is unknown.

Diagnosis and Treatment

Objective monitoring is required to diagnose PLMS, and scoring criteria are defined in the American Academy of Sleep Medicine manual.[120] Other approaches to define PLMS and respiratory-related limb movements that may be more relevant in OSA have been proposed.[121–123] The ICSD defines PLMD as a PLMI of more than 15/h and the lack of another explanation for clinical or functional disturbance being observed. Current guidelines suggest the treatment of PLMS in those with OSA should only be considered if they persist after treatment. This approach, however, is challenged by recent findings that in more than 60% of patients with OSA and PLMS, the movements persist after adequate CPAP titration,[106,110] CPAP does not decrease PLMS severity over 6 months, and that movements are associated with impaired sleep quality.[107] These observations raise the question of whether PLMS and OSA should be treated in parallel, or at least monitoring for PLMS be done in those with impaired sleep quality or residual daytime symptoms after OSA therapy.

Approaches to therapy for PLMS are analogous to those for RLS. Addressing modifiable factors (e.g., insufficient sleep opportunity, iron storage deficiency, antihistamine, and caffeine use) is important before instituting pharmacotherapy (e.g., alpha-2-delta calcium channel ligands, dopamine agonists). Although it is conceptually appealing to use these therapies to improve sleep quality, to our knowledge, no study has assessed whether treatment of PLMS improves sleep or cardiovascular outcomes in OSA.

Future Directions

The key unknowns in those with OSA and PLMS include establishing causal relationships (or lack thereof) between limb movement and respiratory events. This factor is likely to be addressed by signal analysis studies examining the timing and consequences (e.g., autonomics, cortical arousability) of both events and randomized interventional trials targeting PLMS in those with OSA. Moreover, although these data suggest potential synergy between PLMS and OSA in risk of intermediate outcomes and CVD, studies aiming to establish whether the risk in OSA is modified by PLMS and in which groups (e.g., elderly, without prevalent CVD) are needed. Finally, assessing whether PLMS specific therapies improve patient-centered outcomes in OSA is a domain ripe for exploration.

SUMMARY

Sleep deficiency in patients with OSA can be captured under the domains of short sleep duration, poor quality sleep, circadian misalignment, and influenced by other sleep-related disorders. Conditions including chronic insomnia, circadian misalignment, and PLMS should be considered when evaluating sleep deficiency in patients with OSA.

DISCLOSURES

Dr Odekolu has nothing to disclose. Dr A. Zinchuk is supported by the Parker B. Francis Fellowship Award and by the National Heart, Lung and Blood Institute's K23 Award 1K23HL159259.

REFERENCES

1. Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 2017;34:70–81. [PubMed: 27568340]
2. AlGhanim N, Comondore VR, Fleetham J, et al. The economic impact of obstructive sleep apnea. Lung 2008;186(1):7–12. [PubMed: 18066623]
3. Hillman DR, Murphy AS, Antic R, et al. The economic cost of sleep disorders. Sleep 2006;29(3): 299–305. [PubMed: 16553015]
4. Song SO, He K, Narla RR, et al. Metabolic consequences of obstructive sleep apnea especially Pertaining to diabetes Mellitus and insulin sensitivity. Diabetes Metab J 2019;43(2):144–55. [PubMed: 30993938]
5. National heart LaBI. Sleep Deprivation and deficiency. NHLBI. 2022. Available at: https://www.nhlbi.nih.gov/health-topics/sleep-deprivation-and-deficiency. Accessed July 31, 2022.
6. Strollo PJ, Rogers RM. Obstructive sleep apnea. N Engl J Med 1996;334(2):99–104. [PubMed: 8531966]
7. Malhotra A, White DP. Obstructive sleep apnoea. Lancet 2002;360(9328):237–45. [PubMed: 12133673]
8. Zhang Y, Ren R, Lei F, et al. Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev 2019;45:1–17. [PubMed: 30844624]
9. Cho YW, Kim KT, Moon HJ, et al. Comorbid insomnia with obstructive sleep apnea: clinical characteristics and risk factors. J Clin Sleep Med 2018;14(3):409–17. [PubMed: 29458695]
10. Diagnostic and statistical manual of mental disorders: DSM-5. 5th edition. Arlington, VA: American Psychiatric Association; 2013.
11. American Academy of Sleep Medicine. International classification of sleep disorders. 3rd edition. Darien, IL: American Academy of Sleep Medicine; 2014.

12. Saaresranta T, Hedner J, Bonsignore MR, et al. Clinical phenotypes and comorbidity in European sleep apnoea patients. PloS one 2016;11(10): e0163439. [PubMed: 27701416]
13. Bjorvatn B, Lehmann S, Gulati S, et al. Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea. Sleep Breath 2015;19(4):1387–93. [PubMed: 25855469]
14. Luyster FS, Buysse DJ, Strollo PJ Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. J Clin Sleep Med 2010;6(2):196–204. [PubMed: 20411700]
15. Rodenbeck A, Hajak G. Neuroendocrine dysregulation in primary insomnia. Revue neurologique 2001;157(11 Pt 2):S57–61. [PubMed: 11924040]
16. Rodenbeck A, Huether G, Rüther E, et al. Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. Neurosci Lett 2002; 324(2):159–63. [PubMed: 11988351]
17. Vgontzas AN, Bixler EO, Lin H-M, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. J Clin Endocrinol Metab 2001; 86(8):3787–94. [PubMed: 11502812]
18. Campbell SS, Murphy PJ. Relationships between sleep and body temperature in middle-aged and older subjects. J Am Geriatr Soc 1998;46(4):458–62. [PubMed: 9560068]
19. Bonnet MH, Arand D. 24-Hour metabolic rate in insomniacs and matched normal sleepers. Sleep 1995;18(7):581–8. [PubMed: 8552929]
20. Bonnet MH, Arand D. Physiological activation in patients with sleep state misperception. Psychosomatic Med 1997;59(5):533–40.
21. Freedman RR. EEG power spectra in sleep-onset insomnia. Electroencephalography Clin Neurophysiol 1986;63(5):408–13.
22. Perlis ML, Smith MT, Andrews PJ, et al. Beta/Gamma EEG activity in patients with primary and secondary insomnia and good sleeper controls. Sleep 2001;24(1):110–7. [PubMed: 11204046]
23. Lichstein KL, Wilson NM, Noe SL, et al. Daytime sleepiness in insomnia: behavioral, biological and subjective indices. Sleep 1994;17(8):693–702. [PubMed: 7701180]
24. Ratnavadivel R, Chau N, Stadler D, et al. Marked reduction in obstructive sleep apnea severity in slow wave sleep. J Clin Sleep Med 2009;5(6):519–24. [PubMed: 20465017]
25. Younes M, Giannouli E. Mechanism of excessive wake time when associated with obstructive sleep apnea or periodic limb movements. J Clin Sleep Med 2020;16(3):389–99. [PubMed: 31992415]
26. Younes M Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 2004;169(5):623–33. [PubMed: 14684560]
27. Eckert DJ, Owens RL, Kehlmann GB, et al. Eszopiclone increases the respiratory arousal threshold and lowers the apnoea/hypopnoea index in obstructive sleep apnoea patients with a low arousal threshold. Clin Sci (Lond) 2011;120(12):505–14. [PubMed: 21269278]
28. Sweetman A, Lack L, McEvoy RD, et al. Cognitive behavioural therapy for insomnia reduces sleep apnoea severity: a randomised controlled trial. ERJ Open Res 2020;6(2).
29. Lack L, Sweetman A. Diagnosis and treatment of insomnia comorbid with obstructive sleep apnea. Sleep Med Clin 2016;11(3):379–88. [PubMed: 27542883]
30. Mercer JD, Bootzin RR, Lack LC. Insomniacs' perception of wake instead of sleep. Sleep 2002; 25(5):559–66.
31. Björnsdóttir E, Janson C, Gíslason T, et al. Insomnia in untreated sleep apnea patients compared to controls. J Sleep Res 2012;21(2):131–8. [PubMed: 21988168]
32. Wickwire EM, Smith MT, Birnbaum S, et al. Sleep maintenance insomnia complaints predict poor CPAP adherence: a clinical case series. Sleep Med 2010;11(8):772–6. [PubMed: 20673741]
33. Bjornsdottir E, Janson C, Sigurdsson JF, et al. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway pressure treatment. Sleep 2013; 36(12):1901–9. [PubMed: 24293765]
34. Chung KF. Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. Respiration 2005;72(5):460–5. [PubMed: 16210883]

35. Wallace DM, Wohlgemuth WK. Predictors of insomnia severity index Profiles in United States veterans with obstructive sleep apnea. J Clin Sleep Med 2019;15(12):1827–37. [PubMed: 31855168]
36. Krakow B, Melendrez D, Ferreira E, et al. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. Chest 2001;120(6): 1923–9. [PubMed: 11742923]
37. Gupta MA, Knapp K. Cardiovascular and psychiatric Morbidity in obstructive sleep apnea (OSA) with insomnia (sleep apnea Plus) versus obstructive sleep apnea without insomnia: a case-control study from a Nationally Representative US sample. PLOS ONE 2014;9(3):e90021. [PubMed: 24599301]
38. Machado MA, de Carvalho LB, Juliano ML, et al. Clinical co-morbidities in obstructive sleep apnea syndrome treated with mandibular repositioning appliance. Respir Med 2006;100(6):988–95. [PubMed: 16278081]
39. Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342(19):1378–84. [PubMed: 10805822]
40. Shahar E, Whitney CW, REdline S, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 2001;163(1): 19–25. [PubMed: 11208620]
41. Arzt M, Young T, Finn L, et al. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med 2005;172(11):1447–51. [PubMed: 16141444]
42. Phillips B, Mannino DM. Do insomnia complaints cause hypertension or cardiovascular disease? J Clin Sleep Med 2007;3(5):489–94. [PubMed: 17803012]
43. Lanfranchi PA, Pennestri M-H, Fradette L, et al. Nighttime blood pressure in normotensive subjects with chronic insomnia: implications for cardiovascular risk. Sleep 2009;32(6):760–6. [PubMed: 19544752]
44. Vgontzas AN, Liao D, Bixler EO, et al. Insomnia with objective short sleep duration is associated with a high risk for hypertension. Sleep 2009; 32(4):491–7. [PubMed: 19413143]
45. Vgontzas AN, Liao D, Pejovic S, et al. Insomnia with objective short sleep duration is associated with type 2 diabetes: a population-based study. Diabetes care 2009;32(11):1980–5. [PubMed: 19641160]
46. Schwartz S, Anderson WM, Cole SR, et al. Insomnia and heart disease: a review of epidemiologic studies. J psychosomatic Res 1999;47(4): 313–33.
47. Somers VK, Javaheri S. Cardiovascular effects of sleep-related breathing disorders. Sleep Breathing Disord E-Book. 2016;270.
48. Javaheri S, Barbe F, Campos-Rodriguez F, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. J Am Coll Cardiol 2017;69(7):841–58. [PubMed: 28209226]
49. Kholdani C, Fares WH, Mohsenin V. Pulmonary hypertension in obstructive sleep apnea: is it clinically significant? A critical analysis of the association and pathophysiology. Pulm Circ 2015;5(2):220–7. [PubMed: 26064448]
50. Le-Ha C, Herbison CE, Beilin LJ, et al. Hypothalamic-pituitary-adrenal axis activity under resting conditions and cardiovascular risk factors in adolescents. Psychoneuroendocrinology 2016;66:118–24. [PubMed: 26802599]
51. Rosmond R, Bjorntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. J Intern Med 2000;247(2):188–97. [PubMed: 10692081]
52. Javaheri S, Redline S. Insomnia and risk of cardiovascular disease. Chest 2017;152(2):435–44. [PubMed: 28153671]
53. Parthasarathy S, Vasquez MM, Halonen M, et al. Persistent insomnia is associated with mortality risk. Am J Med 2015;128(3):268–275 e262. [PubMed: 25447616]
54. Irwin MR. Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol 2015;66:143–72. [PubMed: 25061767]
55. King CR, Knutson KL, Rathouz PJ, et al. Short sleep duration and incident coronary artery calcification. JAMA 2008;300(24):2859–66. [PubMed: 19109114]

56. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol 2004;43(4):678–83. [PubMed: 14975482]
57. Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;04(05):487–504.
58. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009;05(03):263–76.
59. Epstein LJ, Kristo D, Strollo P Jr, et al. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009;5(3):263–76. [PubMed: 19960649]
60. Kushida CA, Chediak A, Berry RB, et al. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med 2008;4(2):157–71. [PubMed: 18468315]
61. Sawyer AM, Gooneratne NS, Marcus CL, et al. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev 2011;15(6):343–56. [PubMed: 21652236]
62. Rotenberg BW, Murariu D, Pang KP. Trends in CPAP adherence over twenty years of data collection: a flattened curve. J Otolaryngology-Head Neck Surg 2016;45(1):1–9.
63. Barthlen GM, Lange DJ. Unexpectedly severe sleep and respiratory pathology in patients with amyotrophic lateral sclerosis. Eur J Neurol 2000; 7(3):299–302. [PubMed: 10886313]
64. Smith S, Dunn N, Douglas J, et al. Sleep onset insomnia is associated with reduced adherence to CPAP therapy. Sleep Biol Rhythms 2009;7:A74.
65. Suraiya S, Lavie P. P394 Sleep onset insomnia in sleep apnea patients: influence on acceptance of nCPAP treatment. Sleep Med 2006;(7):S85.
66. Qaseem A, Kansagara D, Forciea MA, et al. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of physicians. Ann Intern Med 2016;165(2): 125–33. [PubMed: 27136449]
67. Sweetman A, Lack L, Lambert S, et al. Does comorbid obstructive sleep apnea impair the effectiveness of cognitive and behavioral therapy for insomnia? Sleep Med 2017;39:38–46. [PubMed: 29157586]
68. Alessi CA, Fung CH, Dzierzewski JM, et al. Randomized controlled trial of an integrated approach to treating insomnia and improving the use of positive airway pressure therapy in veterans with comorbid insomnia disorder and obstructive sleep apnea. Sleep 2021;44(4).
69. Bjorvatn B, Berge T, Lehmann S, et al. No effect of a self-help book for insomnia in patients with obstructive sleep apnea and comorbid chronic insomnia - a randomized controlled trial. Front Psychol 2018;9:2413. [PubMed: 30555398]
70. Sweetman A, Lack L, Catcheside PG, et al. Cognitive and behavioral therapy for insomnia increases the use of continuous positive airway pressure therapy in obstructive sleep apnea participants with comorbid insomnia: a randomized clinical trial. Sleep 2019;42(12).
71. Sweetman A, McEvoy R, Smith S, et al. The effect of cognitive and behavioral therapy for insomnia on week-to-week changes in sleepiness and sleep parameters in insomnia patients with comorbid moderate and severe sleep apnea: a randomized controlled trial. Sleep 2020;43(7): zsaa002. [PubMed: 31927569]
72. Ong JC, Crawford MR, Dawson SC, et al. A randomized controlled trial of CBT-I and PAP for obstructive sleep apnea and comorbid insomnia: main outcomes from the MATRICS study. Sleep 2020;43(9).
73. Krakow B, Ulibarri VA, Romero E. Persistent insomnia in chronic hypnotic users presenting to a sleep medical center: a retrospective chart review of 137 consecutive patients. J nervous Ment Dis 2010;198(10):734–41.
74. Carberry JC, Fisher LP, Grunstein RR, et al. Role of common hypnotics on the phenotypic causes of obstructive sleep apnoea: paradoxical effects of zolpidem. Eur Respir J 2017;50(6).

75. Rosenberg R, Roach JM, Scharf M, et al. A pilot study evaluating acute use of eszopiclone in patients with mild to moderate obstructive sleep apnea syndrome. Sleep Med 2007;8(5):464–70. [PubMed: 17512799]
76. Lettieri CJ, Quast TN, Eliasson AH, et al. Eszopiclone improves overnight polysomnography and continuous positive airway pressure titration: a prospective, randomized, placebo-controlled trial. Sleep 2008;31(9):1310–6. [PubMed: 18788656]
77. Lettieri CJ, Shah AA, Holley AB, et al. Effects of a short course of eszopiclone on continuous positive airway pressure adherence: a randomized trial. Ann Intern Med 2009;151(10):696–702. [PubMed: 19920270]
78. Schmickl CN, Lettieri CJ, Orr JE, et al. The arousal threshold as a Drug Target to improve continuous positive airway pressure adherence: secondary analysis of a randomized trial. Am J Respir Crit Care Med 2020;202(11):1592–5. [PubMed: 32673496]
79. Baron KG, Reid KJ. Circadian misalignment and health. Int Rev Psychiatry 2014;26(2):139–54. [PubMed: 24892891]
80. Stephenson R A theoretical study of the effect of circadian rhythms on sleep-induced periodic breathing and apnoea. Respir Physiol Neurobiol 2004;139(3):303–19. [PubMed: 15122996]
81. Butler MP, Smales C, Wu H, et al. The circadian system contributes to apnea lengthening across the night in obstructive sleep apnea. Sleep 2015; 38(11):1793–801. [PubMed: 26039970]
82. Sforza E, Krieger J, Petiau C. Nocturnal evolution of respiratory effort in obstructive sleep apnoea syndrome: influence on arousal threshold. Eur Respir J 1998;12(6):1257–63. [PubMed: 9877474]
83. Adamovich Y, Ladeuix B, Golik M, et al. Rhythmic oxygen levels reset circadian clocks through HIF1α. Cell Metab 2017;25(1):93–101. [PubMed: 27773695]
84. Wu Y, Tang D, Liu N, et al. Reciprocal regulation between the circadian clock and hypoxia signaling at the genome level in mammals. Cell Metab 2017; 25(1):73–85. [PubMed: 27773697]
85. Manella G, Aviram R, Bolshette N, et al. Hypoxia induces a time-and tissue-specific response that elicits intertissue circadian clock misalignment. Proc Natl Acad Sci 2020;117(1):779–86. [PubMed: 31848250]
86. Smagula SF, Ancoli-Israel S, Blackwell T, et al. Circadian rest–activity rhythms predict future increases in depressive symptoms among community-dwelling older men. Am J Geriatr Psychiatry 2015;23(5):495–505. [PubMed: 25066948]
87. Maglione JE, Ancoli-Israel S, Peters KW, et al. Depressive symptoms and circadian activity rhythm disturbances in community-dwelling older women. Am J Geriatr Psychiatry 2014;22(4): 349–61. [PubMed: 23567424]
88. Van Maanen A, Meijer AM, van der Heijden KB, et al. The effects of light therapy on sleep problems: a systematic review and meta-analysis. Sleep Med Rev 2016;29:52–62. [PubMed: 26606319]
89. Phipps-Nelson J, Redman JR, Dijk D-J, et al. Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. Sleep 2003;26(6): 695–700. [PubMed: 14572122]
90. Viola AU, James LM, Schlangen LJ, et al. Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scand J work, Environ Health 2008;297–306. [PubMed: 18815716]
91. Lockley SW, Evans EE, Scheer FA, et al. Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep 2006;29(2):161–8. [PubMed: 16494083]
92. Smolders KC, De Kort YA, Cluitmans P. A higher illuminance induces alertness even during office hours: findings on subjective measures, task performance and heart rate measures. Physiol Behav 2012;107(1):7–16. [PubMed: 22564492]
93. Beaven CM, Ekström J. A comparison of blue light and caffeine effects on cognitive function and alertness in humans. PloS one 2013;8(10):e76707. [PubMed: 24282477]
94. Buxton OM, Lee CW, L'Hermite-Balériaux M, et al. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. Am J Physiology-Regulatory, Integr Comp Physiol 2003; 284(3):R714–24.

95. Buxton OM, L'Hermite-Balériaux M, Hirschfeld U, et al. Acute and delayed effects of exercise on human melatonin secretion. J Biol rhythms 1997; 12(6):568–74. [PubMed: 9406031]
96. Baehr EK, Eastman CI, Revelle W, et al. Circadian phase-shifting effects of nocturnal exercise in older compared with young adults. Am J Physiology-Regulatory, Integr Comp Physiol 2003;284(6): R1542–50.
97. American Academy of Sleep M. International classification of sleep disorders. 3rd edition. Darien, IL: Diagnostic and Coding Manual; 2014.
98. Ding Q, Qin L, Wojeck B, et al. Polysomnographic phenotypes of obstructive sleep apnea and incident type 2 diabetes: results from the DREAM study. Ann Am Thorac Soc 2021;18(12):2067–78. [PubMed: 34185617]
99. Drakatos P, Higgins S, Pengo MF, et al. Derived arterial stiffness is increased in patients with obstructive sleep apnea and periodic limb movements during sleep. J Clin Sleep Med 2016;12(2): 195–202. [PubMed: 26414977]
100. Murase K, Hitomi T, Hamada S, et al. The additive impact of periodic limb movements during sleep on inflammation in patients with obstructive sleep apnea. Ann Am Thorac Soc 2014;11(3):375–82. [PubMed: 24433139]
101. Seo WH, Guilleminault C. Periodic leg movement, nasal CPAP, and expiratory muscles. Chest 2012; 142(1):111–8. [PubMed: 22241760]
102. Wu MN, Lai CL, Liu CK, et al. Basal sympathetic predominance in periodic limb movements in sleep after continuous positive airway pressure. Sleep Breath 2018;22(4):1005–12. [PubMed: 29335917]
103. Zinchuk AV, Jeon S, Koo BB, et al. Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. Thorax 2018; 73(5):472–80. [PubMed: 28935698]
104. Wang Q, Li Y, Li J, et al. Low arousal threshold: a potential Bridge between OSA and periodic limb movements of sleep. Nat Sci Sleep 2021;13: 229–38. [PubMed: 33658878]
105. Lee SA, Kim SJ, Lee SY, et al. Clinical characteristics of periodic limb movements during sleep categorized by continuous positive airway pressure titration polysomnography in patients with obstructive sleep apnea. Sleep Breath 2022;26(1):251–7. [PubMed: 33973111]
106. Aritake-Okada S, Namba K, Hidano N, et al. Change in frequency of periodic limb movements during sleep with usage of continuous positive airway pressure in obstructive sleep apnea syndrome. J Neurol Sci 2012;317(1–2):13–6. [PubMed: 22498043]
107. Budhiraja R, Javaheri S, Pavlova MK, et al. Prevalence and correlates of periodic limb movements in OSA and the effect of CPAP therapy. Neurology 2020;94(17):e1820–7. [PubMed: 31882530]
108. Spira AP, Blackwell T, Stone KL, et al. Sleep-disordered breathing and cognition in older women. J Am Geriatr Soc 2008;56(1):45–50. [PubMed: 18047498]
109. Zhao YY, Blackwell T, Ensrud KE, et al. Sleep apnea and obstructive airway disease in older men: outcomes of sleep disorders in older men study. Sleep 2016;39(7):1343–51. [PubMed: 27091524]
110. Ren R, Huang G, Zhang J, et al. Age and severity matched comparison of gender differences in the prevalence of periodic limb movements during sleep in patients with obstructive sleep apnea. Sleep Breath 2016;20(2):821–7. [PubMed: 26174846]
111. Ferri R, Koo BB, Picchietti DL, et al. Periodic leg movements during sleep: phenotype, neurophysiology, and clinical significance. Sleep Med 2017;31:29–38. [PubMed: 28341521]
112. Figorilli M, Puligheddu M, Congiu P, et al. The clinical importance of periodic leg movements in sleep. Curr Treat Options Neurol 2017;19(3):10. [PubMed: 28349352]
113. Moro M, Goparaju B, Castillo J, et al. Periodic limb movements of sleep: empirical and theoretical evidence supporting objective at-home monitoring. Nat Sci Sleep 2016;8:277–89. [PubMed: 27540316]
114. Hardy De Buisseret FX, Mairesse O, Newell J, et al. While Isolated periodic limb movement disorder significantly impacts sleep depth and efficiency, Co-morbid restless leg syndrome mainly Exacerbates perceived sleep quality. Eur Neurol 2017; 77(5–6):272–80. [PubMed: 28391285]

115. Yang CK, Jordan AS, White DP, et al. Heart rate response to respiratory events with or without leg movements. Sleep 2006;29(4):553–6. [PubMed: 16676789]
116. Li X, Covassin N, Zhou J, et al. Interaction effect of obstructive sleep apnea and periodic limb movements during sleep on heart rate variability. J Sleep Res 2019;28(6):e12861. [PubMed: 31131533]
117. Dean DA, Wang R, Jacobs DR, et al. A systematic assessment of the association of polysomnographic indices with blood pressure: the Multi-Ethnic Study of Atherosclerosis (MESA). Sleep 2015;38(4):587–96. [PubMed: 25348124]
118. Xie J, Chahal CAA, Covassin N, et al. Periodic limb movements of sleep are associated with an increased prevalence of atrial fibrillation in patients with mild sleep-disordered breathing. Int J Cardiol 2017;241:200–4. [PubMed: 28457559]
119. Kendzerska T, Kamra M, Murray BJ, et al. Incident cardiovascular events and death in individuals with restless legs syndrome or periodic limb movements in sleep: a systematic review. Sleep 2017; 40(3).
120. Berry RBB R, Gamaldo CE, Harding SM, et al. The AASM manual for the scoring of sleep and associated events: rules terminology and technical pecifications, Version 2.1. Darien, IL: American Academy of Sleep Medicine; 2014. www.aasmnet.org.
121. Ferri R, Fulda S, Allen RP, et al. World Association of Sleep Medicine (WASM) 2016 standards for recording and scoring leg movements in polysomnograms developed by a joint task force from the International and the European Restless Legs Syndrome Study Groups (IRLSSG and EURLSSG). Sleep Med 2016;26:86–95. [PubMed: 27890390]
122. Aritake S, Blackwell T, Peters KW, et al. Prevalence and associations of respiratory-related leg movements: the MrOS sleep study. Sleep Med 2015;16(10):1236–44. [PubMed: 26429752]
123. Manconi M, Zavalko I, Bassetti CL, et al. Respiratory-related leg movements and their relationship with periodic leg movements during sleep. Sleep 2014;37(3):497–504. [PubMed: 24587572]
124. Nguyen XL, Chaskalovic J, Rakotonanahary D, et al. Insomnia symptoms and CPAP compliance in OSAS patients: a descriptive study using Data Mining methods. Sleep Med 2010;11(8): 777–84. [PubMed: 20599419]
125. Nguyên XL, Rakotonanahary D, Chaskalovic J, et al. Insomnia related to sleep apnoea: effect of long-term auto-adjusting positive airway pressure treatment. Eur Respir J 2013;41(3):593–600. [PubMed: 22835611]
126. Pieh C, Bach M, Popp R, et al. Insomnia symptoms influence CPAP compliance. Sleep Breath 2013; 17(1):99–104. [PubMed: 22311553]
127. Wallace DM, Shafazand S, Aloia MS, et al. The association of age, insomnia, and self-efficacy with continuous positive airway pressure adherence in black, white, and Hispanic U.S. Veterans. J Clin Sleep Med 2013;9(9):885–95. [PubMed: 23997701]
128. Glidewell RN, Renn BN, Roby E, et al. Predictors and patterns of insomnia symptoms in OSA before and after PAP therapy. Sleep Med 2014;15(8): 899–905. [PubMed: 25011662]
129. Wohlgemuth WK, Chirinos DA, Domingo S, et al. Attempters, adherers, and non-adherers: latent profile analysis of CPAP use with correlates. Sleep Med 2015;16(3):336–42. [PubMed: 25441752]
130. Eysteinsdottir B, Gislason T, Pack AI, et al. Insomnia complaints in lean patients with obstructive sleep apnea negatively affect positive airway pressure treatment adherence. J Sleep Res 2017; 26(2):159–65. [PubMed: 27976438]
131. Fung CH, Martin JL, Josephson K, et al. Efficacy of cognitive behavioral therapy for insomnia in older adults with Occult sleep-disordered breathing. Psychosom Med 2016;78(5):629–39. [PubMed: 27136498]
132. Krakow B, McIver ND, Ulibarri VA, et al. Retrospective, nonrandomized controlled study on autoadjusting, dual-pressure positive airway pressure therapy for a consecutive series of complex insomnia disorder patients. Nat Sci Sleep 2017;9: 81–95. [PubMed: 28331381]

KEY POINTS

- Sleep deficiency in patients with obstructive sleep apnea includes abnormal quality, timing, and duration of sleep, and the presence of other sleep disorders.
- Obstructive sleep apnea occurring alongside insomnia is termed comorbid insomnia and obstructive sleep apnea and affects about one-third of patients with obstructive sleep apnea.
- Cognitive behavioral therapy for insomnia concurrent with the treatment of upper airway obstruction improves patient-centered outcomes in comorbid insomnia and obstructive sleep apnea.
- Despite their potential impact, the relationship between obstructive sleep apnea and circadian misalignment (pathogenesis, patient symptoms, and function) is understudied.
- Periodic limb movements of sleep are common in obstructive sleep apnea and are associated with poor sleep quality in those with obstructive sleep apnea that does not improve with positive airway pressure.

CLINICS CARE POINTS

- Patients with OSA should be assessed for symptoms of insomnia.
- Co-occurence of OSA and insomnia (COMISA) is associated with greater daytime impairments, poorer physical and mental health outcomes.
- Treating insomnia concurrently with OSA in patietns with COMISA improves patient-centered outcomes (CPAP adherence and daytime function).
- Clinical trials examining concurrent treatment of periodic limb movements or circadian misalignment in patients with OSA do not exist. However, addressing these sources of sleep deficiency, indepedently of OSA, may help ameliorate sleep deficiency in OSA patients.

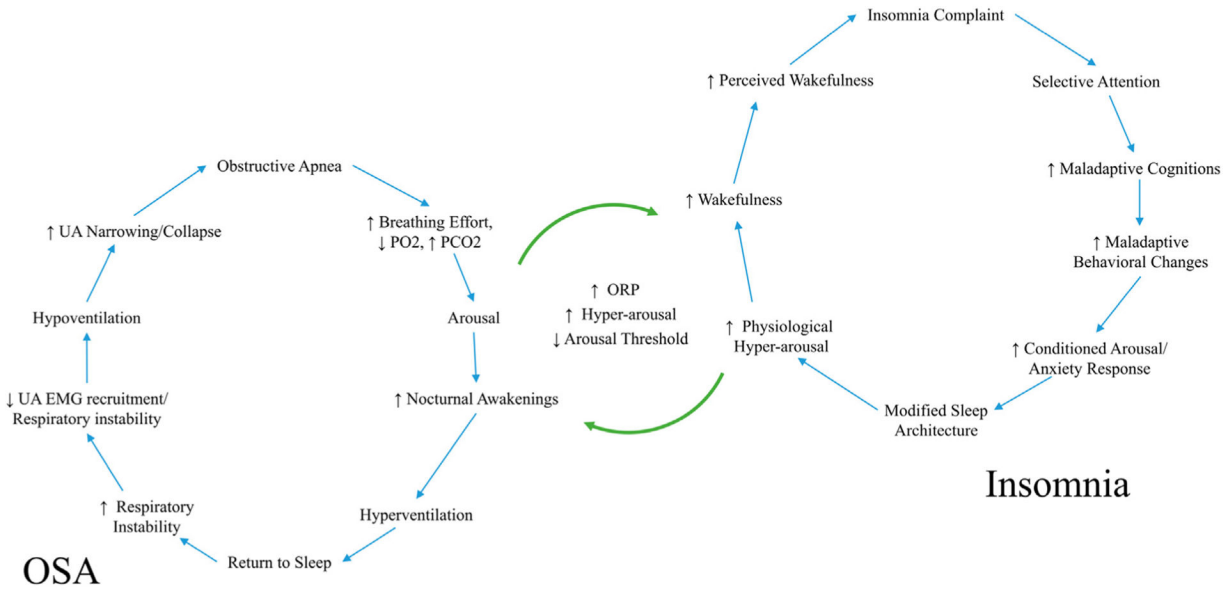

Fig. 1.

Potential mechanisms by which OSA and insomnia interact. The physiologic hyperarousal of insomnia may manifest as a low arousal threshold and contribute to respiratory instability in OSA. The frequent arousals and sleep fragmentation from OSA may lead to a conditioned response to arousal and insomnia. The low sleep depth, reflected by the high ORP, may be the intrinsic trait that links OSA and insomnia, with increased susceptibility to arousal, destabilized sleep, and excessive wake time. EMG, electromyographic; P_{O_2}, partial pressure of oxygen; P_{CO_2}, partial pressure of carbon dioxide; UA, upper airway. (*From* Eckert DJ, Sweetman A. Impaired central control of sleep depth propensity as a common mechanism for excessive overnight wake time: implications for sleep apnea, insomnia and beyond. J Clin Sleep Med. 2020 Mar 15;16(3):341 – 343.)

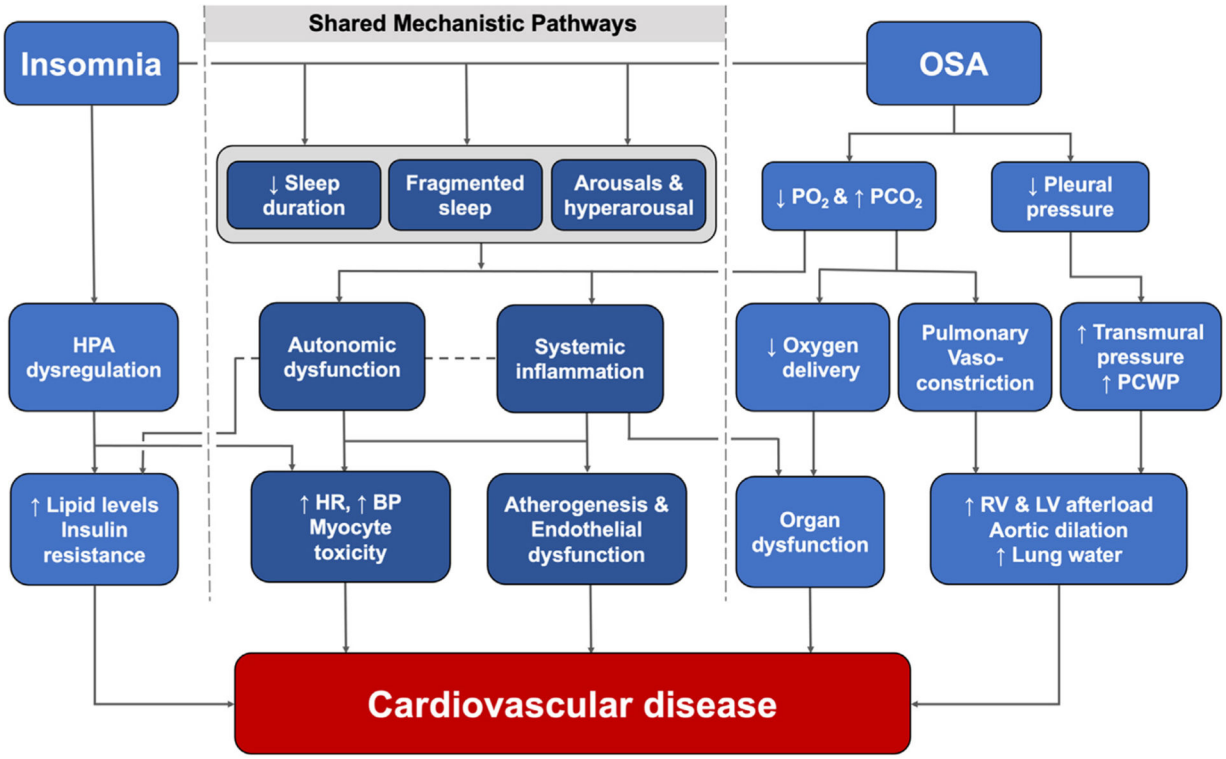

Fig. 2.

Potential mechanistic pathways for cardiovascular disease in COMISA. BP, blood pressure; HR, heart rate; LV, left ventricle; PCWP, pulmonary capillary wedge pressure; RV, right ventricle.

Table 1

Observational studies examining the impact of insomnia on therapy outcomes in patients with OSA

Study	Design/Setting	Sample Size	Baseline Characteristics (Mean ± SD)	Exposure/Control	Outcome(s)	Findings
Nguyen et al,[124] 2010	Prospective cohort/ sleep clinic (France)	148	Age (years) 54.8 ± 11.8 BMI (kg/m^2) 29.1 ± 6.3 AHI (#/h) 39.0 ± 21.3	High (ISI ≥15) vs low (ISI < 15) insomnia groups	CPAP use at 1 and 6 mo	Insomnia groups did not predict CPAP use or CPAP cessation rates
Wickwire et al,[32] 2010	Retrospective cohort/sleep clinic (USA)	232	Age 53.6 ± 12.4 BMI 43.4 ± 7.7 AHI 41.8 ± 27.7	Initial (DIS), middle (DMS), and early morning insomnia (EMA) via self-report	CPAP use: average hours/night, and Adherence: ≥4 h/night CPAP use in 70% of the nights in the last 4 wk	Prevalence: DMS (23.7%), EMA (20.6%), DIS (16.6%). DMS associated with a 12 mins/night lower CPAP use and 19% lower adherence (Odds ratio 0.81)
Bjornsdottir et al,[33] 2013	Prospective cohort/ University hospital (Iceland)	705	Age 54.9 ± 10.2 BMI 33.7 ± 5.6 AHI 45.5 ± 20.5	DIS, DMS, EMA insomnia (Basic Nordic Sleep Questionnaire)	Adherence to PAP: 53% APAP 43% CPAP 3% BiPAP 1% ASV Change in Insomnia subtype prevalence in patients using or not using CPAP at 24 mo	Prevalence of DIS, DMS and EMA Insomnia at baseline: 12.9%, 59.4% and 23.3% in PAP users and 20.8%, 59.1% and 36.6% in non-PAP users. DIS insomnia at baseline predicted PAP non adherence at 24 mo. DIS and EMA insomnia at baseline were less likely to adhere to PAP therapy.
Nguyen et al,[125] 2013	Prospective cohort/ sleep clinic (France)	80	Age 54.9 ± 10.6 BMI 30.5 ± 6.0 AHI 45.0 ± 24.6	N/A patients with OSA receiving APAP therapy	Change in ISI score from baseline to 24 mo Responders: ≥ 9-point decline on ISI over 24-mo	Overall ISI decreased from 14 to 8. Of the 39 with Insomnia (ISI ≥ 15), 51% had a decrease in ISI of ≥9 points from baseline to 24-mo
Pieh et al,[126] 2013	Prospective cohort/ sleep center (Germany)	73	Age 55.1 ± 11.5 BMI 30.8 ± 5.0 AHI 39.2 ± 26.7	Insomnia. RIS	Parameters influencing CPAP adherence	Insomnia scores correlate with 6-mo CPAP adherence: Adherence declines by 2.6 h/night per 1 SD of RIS score
Wallace et al,[127] 2013	Retrospective cross-sectional/Veteran Affairs sleep clinic (USA)	248	Age 59 ± 11 y BMI 33.0 ± 5.0 AHI 40.0 ± 30.0	Factors influencing CPAP adherence	CPAP Adherence	Black race-ethnicity, insomnia symptoms, and self-efficacy associated with mean daily CPAP use. Adherence decreases by 1 h/night per 10-unit ISI increase
Glidewell et al,[128] 2014	Retrospective cohort/sleep center (USA)	68	Age 47.5 ± 12.4 BMI 32.2 ± 7.3 AHI 34.7 ± 32.2	PAP therapy	Change in ISI score	Lower baseline ISI scores, higher baseline RDI and PAP use predict marked reduction of ISI scores (decrease to none/mild) on PAP therapy; 55% had persistent (moderate or worse) insomnia, exhibited 1.1 h/night lower PAP use
Wohlgemuth et al,[129] 2015	Retrospective cohort/Veteran Affairs sleep clinic (USA)	207	Age 58.4 ± 11.9 BMI 32.4 ± 5.0 AHI 40.0 ± 29.4	CPAP therapy	CPAP user profiles/ subtypes Predictors of CPAP subgroup membership	Three subgroups were identified and labeled nonadherers, attempters, and adherers. A 1-unit increase in the ISI score increased the likelihood of being an attempter by 9% (OR, 1.09) and a nonadherer by 16% (OR, 1.16).

Study	Design/Setting	Sample Size	Baseline Characteristics (Mean ± SD)	Exposure/Control	Outcome(s)	Findings
Eysteinsdottir et al,[130] 2017	Prospective cohort/ sleep clinic (Iceland)	796	Age 54.4 ± 10.6 BMI 33.5 ± 5.7 AHI 44.9 ± 20.7	None	CPAP adherence	Initial and late insomnia predicted CPAP cessation at 1 y only in participants with a BMI of 30 kg/m^2. Higher BMI, AHI and Epworth sleepiness score predicted adherence.
Fung et al,[131] 2016	Prospective cohort/ Veteran Affairs sleep clinic (USA)	134	Age > 60 y BMI AHI < 15/hour	CBT-I (vs sleep education)	Changes in sleep quality (Pittsburgh Sleep Quality Index) Sleep latency, duration	CBT-I improved sleep onset latency and sleep quality regardless of presence of OSA (AHI <5 vs AHI 5 to <15/h)
Krakow B et al,[132] 2017	Retrospective cohort/sleep clinic (USA)	302	Age 53.4 ± 14.2 BMI 31.6 ± 8.0 AHI 32.0 ± 28.2 Complex insomnia defined as those who failed CPAP owing to intolerance or emergence of treatment-emergent central apneas	Advanced PAP devices (auto BPAP/ ASV)	Changes in ISI	Total weekly hours of PAP use correlated inversely with change in ISI scores. In full PAP users (≥20 h/wk, 82% of sample) ISI scores improved by 0.7, 0.9, and 0.7 SDs for DIS, DMS, and EMA subtypes. No difference between ASV and auto-BPAP
Sweetman A et al,[67] 2017	Retrospective cohort/sleep center (Australia)	141	Age 51.7 ± 15.7 BMI 26.3 ± 4.9 AHI 14.3 ± 8.0	CBT-I	Change in insomnia and other patient-centered outcomes at 3 mo	A 10-unit decrease in the ISI score A 58-min increase in the duration of sleep A 19% improvement in sleep efficiency Marked improvement in stress, depressive, and anxiety symptoms

Abbreviations: AHI, apnea-hypopnea index; APAP, auto positive airway pressure; ASV, Adaptive-Servo ventilator; BiPAP, bilevel positive airway pressure; BMI, body mass index; COMISA, comorbid insomnia and obstructive sleep apnea; DIS, difficulty initiating sleep; DMS, difficulty maintaining sleep; EMA, early morning awakening; RIS, Regensburg Insomnia Scale.

Nonadherers used CPAP for an average of 37 min nightly, used CPAP 18.2% of nights, and used CPAP for more than 4 h 6.2% of nights. Attempters used CPAP for 156 min on average, used CPAP 68.2% of nights, and used CPAP for more than 4 h 29.3% of nights. Adherers used CPAP for 392 min, used CPAP 95.4% of nights, and used CPAP for more than 4 h 86.2% of nights.

Table 2

Recent randomized controlled trials on CBT-I and PAP therapy in patients with COMISA

Study	Sample	Characteristics	Control	Intervention(s)	Outcome(s)	Findings
Alessi et al,[68] 2021	125	US Veterans Overall Age (years) 63.2 ± 7.1 Male 96%	5 weekly sleep education sessions delivered with CPAP use.	5 weekly CBT-I and CPAP adherence program delivered by a sleep coach.	Primary: CPAP adherence at 3 mo Subjective (D from diary) and objective (A from actigraphy) measures at 3 mo: SOL-D, SE-D, SE-A, WASO-D	CBT-I vs control: 3.2 vs 1.9 h/night CPAP use Greater improvement in SOL-D 16.2 min SE-D 10.5% SE-A 4.4% WASO-D no difference Findings persisted at 6 mo
Bjorvatn et al,[69] 2018	164	Control vs intervention Age (years) 57.0 ± 12.1 vs 55.0 ± 11.6 Male 75% vs 68% BMI 31.9 ± 5.6 vs 32.3 ± 6.0 kg/m^2 AHI 24.9 ± 18.1 vs 25.6 ± 19.9/h	Sleep hygiene advice with CPAP	Delivered self-help CBT-I book with CPAP	Primary: Insomnia severity based on the BIS and ISI. Secondary: CPAP adherence	There was significant improvement in BIS and ISI scores in both groups, no effect of intervention compared with control. No difference in CPAP adherence.
Ong et al,[72] 2020	121	Overall Age (years) 50.0 ± 13.1 Female 53% OSA severity: Mild (51%, 43.2%) Moderate/severe (67%, 56.8%)	CPAP only group	CBT-I before CPAP and CBT-I concurrently with CPAP	Primary: CPAP adherence over 90 d (≥4 h on ≥70% of nights for 30 d) Secondary: ISI and PSQI scores and others	No differences in primary outcome between intervention groups vs control group. Significant decrease in ISI scores and improvement in PSQI scores in intervention vs control groups. No differences between intervention groups.
Sweetman et al,[70] 2019	145	Control vs intervention Age (years) 59.1 ± 9.9 vs 57.3 ± 9.9) BMI 34.5 ± 6.3 vs 36.2 ± 6.5 kg/m^2 AHI 33.2 ± 19.8 vs 35.8 ± 23.9/h	Treatment as usual	Four session CBT-I before CPAP therapy	Primary: Average CPAP adherence over 6 mo Secondary: CPAP acceptance, insomnia severity, diary sleep metrics, daytime function and others	CBT-I group with 1 h/night greater CPAP adherence 10% greater CPAP acceptance Significant improvement in ISI scores No differences in diary measured sleep metrics No differences in functional outcomes

Abbreviations: BIS, Bergen Insomnia Scale;; PSQI, Pittsburgh Sleep Quality Index; SE-a, sleep efficiency by 7-day actigraphy; SE-d, sleep efficiency by sleep diary; SOL-d, sleep onset latency by sleep diary; WASO-d, wake after sleep onset by sleep diary

A good sleeper is defined as a PSQI total score of less than 5 at the study end point; insomnia remission is defined as an ISI score of less than 8 at the study end point; insomnia response is defined as a decrease in the ISI score of more than 7 points from baseline to the study end point.