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Review Article

Comorbid Insomnia and Sleep Apnea: mechanisms and implications of an underrecognized and misinterpreted sleep disorder

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ABSTRACT

Sleep-disordered breathing (SDB) and insomnia have long been recognized as important sleep disrupters often associated with increased morbidity and mortality. Although they are often seen as divergent conditions, mainly because their cardinal symptoms (excessive daytime sleepiness, and sleep loss) differ, these two sleep disorders present with many common symptoms, which may hinder diagnosis and treatment. In addition to possible bidirectional pathways between SDB and insomnia, other factors such as circadian timing may play a role. In this paper, we review the mechanisms, differential clinical aspects, and implications of Comorbid Insomnia and Sleep Apnea, sometimes termed COMISA.

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1. Introduction

It has long been known that there exists an association between sleep breathing abnormalities and insomnia. Mackenzie in 1925 in describing Cheyne Stokes Respiration (CSR) wrote: "Occasionally the periods of apnea are so complete and prolonged that the patient wakes up with a sense of great distress, sometimes so severe that he may spring out of bed in his extremity and may then have to breathe heavily and in labored fashion for many minutes." [1] Harrison in 1934 reported that heart failure patients who developed dyspnea at sleep onset invariably had CSR and arousals from sleep led to CSR [2]. Guilleminault, Eldridge, and Dement, in 1973, first described two adult male patients, with an overlap of symptoms of insomnia and central sleep apnea (CSA) [3]. Co-Morbid Insomnia and Sleep Apnea (sometimes termed COMISA) has recently emerged as a topic of interest [4].

In clinical practice, insomnia and obstructive sleep apnea (OSA) are often considered divergent conditions. Yet, insomnia is characterized by an increase in neuroexcitation, generating an increase in alertness, a rise of metabolic activity, hypothalamic–pituitary–adrenal axis involvement, heart rate elevation, and overactivation of the sympathetic nervous system, therefore leading to a high level of stimulation, both at night and during the day [5]. Frequent arousals also related to an increase in sympathetic tone and fragmented sleep associated with intermittent hypoxia, usually leads to excessive daytime sleepiness. This is an important and clinically significant finding which is observed in most of the patients [5]. Yet, despite the marked clinical divergences regarding the cardinal signs of each one, these two sleep disorders present with many common symptoms, which may hinder diagnosis and treatment. Thus, management is a challenge [6].

Insomnia can be characterized by the complaint of dissatisfaction with the quality or quantity of sleep, associated with other symptoms, such as difficulty in initiating and maintaining sleep,

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early awakenings in the morning, with difficulty to return to sleep. The consequences of insomnia often compromise daily life, particularly, academic and occupational performance. The chronic form of insomnia occurs at least three times a week for at least three months (insomnia consensus) [7] and its estimated prevalence is between 10% and 40% [8,9].

On the other hand, OSA has greater physiological effects. It is characterized by episodes of partial or total upper airway obstruction during sleep, leading to transient blood gas abnormalities, and fragmentation of sleep [5]. The prevalence of OSA is high affecting from 9 to 38% of the adult population [10]. The severity of OSA is usually classified considering the number of apneas and hypopneas (AHI) per hour of sleep. An index between 5 and 14 is considered mild sleep apnea; between 15 and 29, compatible with moderate sleep apnea; and above 30, severe sleep apnea [5]. Some patients with AHI less than 5 may have increased arousals during sleep leading to daytime symptoms – a condition called the Upper Airway Resistance Syndrome [11].

The prevalence of COMISA varies according to the definition, usually related to the condition that is valued. A high prevalence of insomnia symptoms has been observed in patients with OSA, ranging between 39% and 55%, depending on the sample used – patients presenting to a sleep clinic with a primary complains of insomnia, hypersomnia, or a representative sample from the general adult population [5]. The variation in this prevalence is also linked to insomnia characteristics and demographic variables such as age and gender. For example, insomnia is a more common presenting feature in females with OSA than males [12].

Approximately 36% of the patients have difficulty in maintaining sleep, 18% with a complaint in initiating sleep, and 21% with early awakening. It should be noted that the most common insomnia symptom in patients with OSA is difficulty in sleep maintenance [13], it is likely that this is the most representative phenotype of maintenance insomnia. Alternatively, the prevalence of OSA in patients with insomnia is 35% (AHI$\geq$ 5) and 29% (AHI$\geq$ 15) [14]. Lichstein et al. found that roughly a third of older adults with insomnia had OSA [15]. Fung et al. observed nearly half of the patients with insomnia (46.7%) had AHI $\geq$ 15 events/h; the patients had not been previously diagnosed with OSA [16]. Wallace et al. also found a link between insomnia and OSA [17].

Regarding race, Subramanian et al. confirmed female gender as being a significant risk factor for comorbid insomnia in patients with OSA, and also reported that Caucasian women had the highest rate of self-reported sleep maintenance insomnia (80%) [18]. Regarding gender, Ong et al., reported that insomnia was more common in females (53.4% of the sample was female). Over 90% of the sample was non-Hispanic, with 49% identified as White, 42% as Black or African American, 6% as Asian, 2% as more than one race, and 1% as American Indian or Alaskan Native [19].

1.1. Physiopathology

Whether there exists a causal relationship between OSA and insomnia is unclear, however, some evidence suggests a bidirectional relationship. Repetitive obstructive breathing events may be the cause of sleep fragmentation in some patients with OSA. Although the precise mechanisms by which upper airway obstruction elicits arousals in humans are still poorly understood, several mechanisms involving the autonomic nervous system (ANS) seem to be involved [20]. The ANS regulates cardiovascular function, while respiratory events influence the ANS [20,21]. Liang et al. showed that the combination of respiratory events and arousals has a greater effect on heart-rate-variability, as an expression of ANS activity than both events when occurring in isolation [22]. Moreover, the extent of their effects on the ANS is influenced by sleep stage, and thus by CNS activity. Therefore, the coupling between ANS and CNS seems to play an important role in sleep microstructure [20]. In addition, the relationships between slow-wave and fast–wave activity reflect the presence of cross-talk between subcortical and cortical brain regions [23].

Analysis of sleep microstructure may provide important insights into the differences between COMISA sub-types, as well as allow differentiation between isolated OSA, isolated insomnia, and the combination of these two diagnoses [24,25]. Sleep microstructural deviations have been readily detected either in patients with OSA [25,26] or insomnia [27,28], and evaluation of differences between these isolated conditions and sleep microarchitecture in COMISA may provide important insights into the clinical implications of this disease.

Apnea is almost always associated with cortical arousal. Bahr et al. found evidence that the microstructure of respiratory arousals may be patient specific. In other words, every individual patient experiencing an obstructive respiratory event will manifest changes in their cortical or subcortical neural arousal-associated pattern generator with a specific signature in terms of duration and intensity, aiming to ensure ventilation during sleep. However, in some individuals with OSA, this neural pattern generator may pro-actively induce arousals that seem to precede the obstructive events in OSA patients [20]. Sleep interruptions, repeatedly, and throughout the night, may be perceived as awakenings or prolonged wakefulness periods. Nocturia is a frequent complication of OSA [29]. In this context, patients feel the need to get out of bed several times. This causes sleep fragmentation. This patient may take naps and increase their caffeine intake as a form to compensate. These behaviors are also typical of insomnia, which leads to the perpetuation of insomnia associated with bad sleep habits. There may also be an increase in anxiety generated by awakenings associated with the feeling of shortness of breath [14] and a cycle that perpetuates itself in the presence of these elements.

Since OSA can be a causal factor of insomnia, treating OSA should improve insomnia complaints, however, this effect is variable and not always observed clinically. Yet, sleep maintenance difficulties tend to have a higher resolution rate when compared with complaints on initiating sleep or related to early awakenings [14,30]. Patients with not yet diagnosed OSA with comorbid insomnia may receive hypnotic medications to treat insomnia and may receive such treatment for years without improvement [31]. Yet, once OSA is recognized and treated correctly, sleep complaints may significantly improve [32].

Insomnia can also be considered a risk factor for OSA. Besides the well-known anatomical predisposition for OSA, non-anatomic factors can also play an important role in the pathophysiology [30]. The non-anatomic factors described are the responsiveness of the muscles of the upper airway, hypersensitivity of ventilatory control, and a low arousal threshold. These aspects of pathophysiology have been cited and studied more recently to describe the different endotypes and phenotypes of OSA. This last factor (arousal threshold) seems to be important in 37% of cases [33]. A low arousal threshold may lead to sleep fragmentation as documented by abrupt shifts towards higher EEG frequencies in response to the increased respiratory resistance that occurs with narrowing of the upper airway. This pathophysiological aspect can act both ways, causing insomnia in OSA, and can also be a condition that predisposes to disordered breathing in insomnia due to respiratory instability.

The use of medications aiming to increase the arousal threshold and improve sleep continuity has been suggested in OSA. Low arousal thresholds have been identified as an important phenotypic variant enhancing the risk of sleep fragmentation, and consequently leading to poor quality of sleep [34]. Since sleep

fragmentation and episodic hypoxemia mediate clinical manifestations and outcomes of OSA, the option of using sleep-inducing medications has been evaluated and needs to be based on the underlying patient's phenotype [34]. Patients who present significant hypoxemia, which is associated with increased cardiovascular risk, need to have treatment aiming primarily targeted at decreasing hypoxemia. So, sleep-promoting medications would not be indicated in such patients but should be potentially considered for those with relatively milder hypoxemia and a high arousal index [35].

Indeed, Eckert et al., demonstrated that the use of eszopiclone can significantly increase the arousal threshold and decrease the AHI without worsening of oxygen saturation or respiratory event duration. However, in this study, patients with severe hypoxemia (nadir overnight SaO 2 <70%) were excluded [34]. Trazadone can also decrease AHI in OSA patients. The mechanisms are not fully evaluated, but it was suggested that such an effect may be related to the decrease in N1 sleep, which would lead to a more stable breathing pattern [36].

The identification of phenotypes contributes to understanding the heterogeneity of OSA and insomnia. Factors such as high ventilatory response and low arousal threshold may be related to clinical aspects such as anxiety and stress, which may be associated with the perpetuation of chronic insomnia disorder [33].

Therefore, the hypothesis of a reciprocal influence between insomnia and sleep apnea can be considered. That is, through a bidirectional form, in which the consequence will be a more serious sleep disorder, higher frequency of psychiatric and cardiovascular comorbidities [5] when compared to those with one of the two disorders alone [37].

Patients with comorbid insomnia and OSA have a reduced quality of life which appears to be induced by concurrent sleepiness and disturbed mood [38]. The daytime symptoms seem to reflect the balance between OSA and insomnia daytime symptoms. Indeed, the Epworth Sleepiness Scale shows a mean score of 10 in COMISA patients compared to 11 in OSA and 8 in Insomnia [39]. Similarly, caffeine need in OSA was reported in 65,8%, and very similar in COMISA patients (63,1%), while being reduced among Insomnia patients (52,2%) [36]. The lower percentage of COMISA patients reporting regular exercise and physical activity when compared to both OSA and Insomnia [39] also suggest a higher degree of tiredness and lack of motivation.

A sensation of unrefreshing sleep, fatigue, impaired attention, concentration and memory, social and occupational dysfunction, increased propensity for accidents, and worry about sleep are also frequently reported symptoms in patients with comorbid insomnia and OSA [5]. An aspect of interest is that in patients with chronic pain, COMISA often contributes to the worsening of pain symptoms either during daytime or during sleep. Hence, this could have an important clinical impact, since pharmacologic options in pain management may require higher dosages and potentially compromise the patient's health [40].

In addition to the factors mentioned above, some studies recently published by our team suggest that the circadian matrix dictated by biological clocks may also interfere with these mechanisms, potentiating them and raising the associated risks [41–43]. In these surveys, we demonstrated, for example, that the circadian misalignment can be an important mediator in cardiovascular and metabolic risk, associated with insomnia and OSA. It is likely that by direct interference with endocrine and neurocognitive pathophysiological mechanisms, circadian dysrhythmia characteristic of both conditions may be intensified in the comorbid condition, increasing complications, particularly those related to cardiometabolic risk. Alternatively, it is also possible that this intensified interaction justifies part of the phenotypic distinction with an impact on clinical evaluation [41–43]. For the evaluation of phenotypes different techniques have been developed using cluster analysis. In the Icelandic study, the cluster of patients with OSA was characterized by disturbed sleep [44]. This group presented the highest frequencies of arterial hypertension, cardiovascular disease, and diabetes compared to the other groups [30].

1.2. Diagnostic evaluation

Krakow et al., selected 231 patients for overnight polysomnography, and clinical investigation for insomnia [14]. Of these, 211 were diagnosed with OSA, and 20 presented with upper airway resistance syndrome. They found that 115 patients reported no complaints of insomnia, and 116 patients reported clinically significant complaints of insomnia, characterizing them with the diagnosis of COMISA. Polysomnographic data, when comparing one group of OSA and other of COMISA, led to the finding of worsening of total sleep time (7.2 vs 5.6 h), sleep efficiency (92% vs 75%), and sleep latency (17 vs 65 min), respectively. The COMISA group showed greater compromise in polysomnographic data. Clinical complaints of the COMISA group: 20 patients complained of classic insomnia, and were not investigated for OSA, however, five patients complained of insomnia at the beginning of sleep, six of maintenance insomnia, and nine complained of both. Thirteen patients reported fatigue throughout the day or sleepiness. It was observed that 37% of the patients evaluated in this study used psychotropic drugs, and the patients diagnosed with COMISA, represented twice as many users of these drugs as those who had OSA alone [14].

Krakow et al., in 2013, conducted a prospective epidemiological survey to study the frequency of insomnia and sleep breathing disorders symptoms, and their co-occurrence in patients who sought care in primary care clinics [30]. Obstructive sleep apnea was assessed by questionnaire documented these symptoms: snoring, loud snoring, apneas, choking, gasping, or struggling for breath while asleep, and other trouble breathing at night. Insomnia was documented with the Insomnia Severity Index (ISI). Among the 660 participants who reported at least one symptom of insomnia: 248 (37.6%) also reported one symptom of SDB; 88 (13.3%) reported two symptoms of sleep-disordered breathing (SDB); 32 (4.9%) reported three symptoms of SDB; 22 (3.3%) reported four symptoms of SDB, and 17 (2.6%) reported all five symptoms of RSD. Thus, 50.8% of the total sample reported at least one symptom of insomnia and one symptom of SDB. ISI scores increased progressively with the increase in the number of SDB symptoms that patients presented. Patients without SDB symptoms had a mean ISI = 6.84 that was significantly lower than patients with two SDB symptoms = 9.81 (P = 0.001); three SDB symptoms had ISI = 10.36 (P = 0.001); four SDB symptoms had ISI = 11.08 (P = 0.001); and five SDB symptoms had ISI = 13.56 (P = 0.001) [30].

Smith et al., studied the impact of insomnia on the mood of OSA patients [45]. The criteria for insomnia diagnosis were: an ISI score greater than or equal to 15, with a duration of symptoms in at least 6 months, sleep onset latency, evaluated by polysomnography, over 30 min, and the presence of at least one negative daytime consequence associated with the sleep disorder. For the diagnosis of OSA overnight polysomnography was used. Mood-related results suggest that patients diagnosed with OSA alone reported 'normal' levels (that is, levels of depression, anxiety, and stress symptoms) that put them in the non-clinical range for these disorders. Patients in the Insomnia Group that also presented with OSA, reported levels suggestive of anxiety at severe levels and depression and stress at moderated levels. Therefore, they conclude that patients with COMISA seem to be associated with mood disturbance [45]. Since patients with isolated insomnia commonly complain from these psychological symptoms, it is possible they are exacerbated in patients with COMISA and contribute to a deleterious cycle.

Wallace and Wohlgemuth pointed out that the ISI questionnaire is composed of complaints related to day and night symptoms [17]. However, it should be noted that patients with OSA may have high daytime impairment on ISI measurements, in the absence of nighttime insomnia complaints, resulting in higher overall 'insomnia' scores and an incorrect COMISA classification. Overlapping symptoms can make it difficult to control insomnia symptoms after different approaches to treatment on COMISA [17]. For example, COMISA patients treated with CPAP therapy may report a reduction in daytime symptoms, which may translate into an overall reduction in "insomnia severity" questionnaire scores in the absence of improvement in nighttime symptoms. These authors propose that, when administered to patients with OSA, the ISI questionnaire should be scored according to a 'night' sub-item (comprising the first three items, ranging from 0 to 12), and a 'day' sub-item (comprising the subsequent four items, ranging from 0 to 16) [17].

Punjabi et al., demonstrated that sleep fragmentation (caused by apnea or hypopnea), hypoxemia, percentage of N2 sleep, and slow-wave sleep were independent predictors of the severity of hypersomnolence. Thus, hypersomnolence in patients with OSA seems to result from several consequences during sleep [46]. Based on this observation, Gold et al. conducted a retrospective survey, which reported a statistically significant negative correlation between AHI and insomnia [47]. They observed that patients with upper airway resistance syndrome presented more sleepiness than patients with OSA, which could be justified by the intrusion of alpha activity during NREM sleep, and may reflect a state of 'Increased arousal' during sleep that would compromise the ability to generate restorative sleep, resulting in hypersomnolence [47]. Chung et al. found that insomnia complaints at the onset of sleep occur more frequently in patients with less important upper airway collapse during sleep [38].

Both insomnia and OSA contribute to a higher risk of depression. Complaints of depression were more intense in individuals with both conditions, compared to individuals with insomnia alone [48]. Psychiatric comorbidity also has a greater association if both conditions are associated. Both insomnia and OSA contribute to a higher risk of depression. Complaints of depression are worse in individuals with both conditions when compared to those individuals with insomnia alone [48].

1.3. Treatment

The therapeutic options are well validated for each sleep disorder separately, but due to the absence of medical evidence, there is currently no formal recommendation or guideline for the treatment of comorbid insomnia and OSA. As the most common comorbid sleep condition, COMISA may present with many challenges to clinicians [32]. Decreased adherence to CPAP is often observed, with worsening of insomnia complaints [34,44,49]. Wickwire et al. showed that the symptom of insomnia is associated with low adherence to PAP [50]. It is also important to remember that treatment of insomnia with benzodiazepines, often indicated in patients who did not undergo a sleep examination, may worsen respiratory sleep disorders [51]. This may be less of a problem with non-benzodiazepines [52]. CPAP is the most effective treatment for sleep-related breathing disorders; however, there is a low adherence rate often limiting the benefits of such intervention. The use of hypnotics to improve CPAP compliance can be an effective option; however, there are no controlled randomized studies to establish safety, effectiveness, and long-term effects of this treatment.

Currently, clinical judgment should indicate whether treatment begins with CPAP (or other treatment for OSA), or CBT (cognitive behavioral therapy) for insomnia, or both. CBT can effectively treat patients with comorbid OSA [33,53]. The benefits of CBT were similar in patients with or without OSA, indicating that the effectiveness of CBT is not impaired by the presence of OSA. It has also been demonstrated that starting CBT before CPAP treatment can improve adherence to treatment and insomnia complaints. After improvement of the insomnia disorder, the treatment of OSA can be better accepted and tolerated [53].

Studies have shown that regardless of the association of OSA with insomnia, individuals with CPAP indication have better adherence when associated with cognitive behavioral therapy (CBTi). For example, in a randomized trial, Richards et al. examined whether an educational intervention based on components of social cognitive theory and executed using CBTi improved acceptance and adherence to CPAP in participants with OSA. the authors reported that 30% of the cohort refused CPAP either before or after the CPAP titration study, compared with 8% in the CBTi group. At 28 days, only 31% of the COMISA group was using CPAP for 4 h or more per night, and approximately 15% for more than 6 h. In contrast, in the CBTi group, 77% were using CPAP for at least 4 h, with 50% using CPAP for at least 6 h. In conclusion, a brief CBTi intervention resulted in marked improvements in CPAP acceptance, adherence, and usage, compared with standard care [54]. These data need to be confirmed in other populations and clinical settings; however, they encourage the development of CBTi-related interventions aimed at improving acceptance and adherence to CPAP. We should also point out that when OSA is associated with insomnia, favorable results have been observed with CBTi. Sweetman et al. conducted a randomized clinical trial in OSA patients who underwent CBTi for 6 weeks, with weekly sessions lasting 45 min, either individually or in small groups. The components of CBTi included bedtime restriction therapy, basic sleep information, sleep hygiene information, cognitive therapy, and relapse prevention. The CBTi protocol did not include any information about OSA or CPAP therapy. CPAP use was calculated in two ways: mean use from CPAP set up to 6 months after randomization (primary outcome), and mean use between each review visit (secondary outcome to assess temporal changes in use). Participants with OSA and concomitant insomnia who received a four-session CBTi program before starting CPAP therapy showed 87% lower rates of immediate CPAP rejection and a 1-h increase in nightly CPAP use than participants who did not receive CBTi. Thus, the authors suggest that 4-week CBTi in OSA patients with coexisting insomnia provides immediate benefit in perceived sleep quality that helps ensure greater acceptance of CPAP therapy [55]. Notwithstanding the favorable findings, no differences emerged between standard and CBTi groups regarding daytime sleepiness, fatigue, depression, anxiety, or stress over 6 months. It is possible that the daytime symptoms were predominantly a manifestation of OSA and were not affected by CBTi. However, one should be vigilant about excessive daytime sleepiness when individuals with OSA undergo CBTi as a treatment for insomnia. There is concern that the bedtime restriction component of CBTi may exacerbate the daytime sleepiness in such patients. Sweetman et al., examined data from randomized controlled trials to investigate the effect of OSA severity and pre-treatment daytime sleepiness on weekly changes in daytime sleepiness and sleep parameters during CBTi as well as in controls. Among patients in the CBTi-treated group, a main effect of time indicated that subjects experienced a significant increase in daytime sleepiness between the first and second week of CBTi (ie immediately after starting bedtime restriction therapy [55]; before returning to pretreatment levels for each subsequent week. Since COMISA patients may experience a circadian misalignment, it was suggested that CBTi-

associated improvements in those patients could be related to a circadian realignment, and therefore, sleep-wake schedule readjustments should be always considered [56].

2. Conclusions and future directions

COMISA is common and has important clinical consequences. The sleep specialist must assess for signs and symptoms of both insomnia and the sleep breathing disorder to best manage the patient. Maintenance insomnia is the type of insomnia most frequently associated with a sleep breathing disorder. It is almost always necessary to assess the patient with polysomnography to confirm sleep breathing disorders. The management of COMISA involves measures for both conditions and it is important for sleep specialists to understand the specific needs of patients with both sleep disorders. The increasing recognition of phenotypic descriptions can improve proper characterization and direct management of specific patient characteristics, favoring personalized treatment. This trend is increasingly strong and aims to improve the response to treatment, leading to a better quality of sleep and quality of life. However, there are many unresolved issues, such as: Should insomnia and OSA when present together even be considered a unique clinical entity? Should other entities frequently comorbid with OSA (eg depression, hypertension) be considered unique clinical entities? How do the co-morbidities interact, and how do they impact the natural history of each comorbidity? A great deal of research is needed to resolve therapeutic approaches when insomnia and OSA co-exist.

Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.05.043.

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