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More than sleepiness: prevalence and relevance of nonclassical symptoms of obstructive sleep apnea

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Purpose of review
The purpose of this review is to describe the nonclassical symptoms and manifestations occurring in patients with obstructive sleep apnea (OSA), both from a standpoint of prevalence and in terms of clinical relevance. Particular emphasis will be given to nightmares, comorbid insomnia, restless legs syndrome and periodic limb movement disorder, bruxism, morning headache, nocturia, acid reflux, chronic cough and dysphagia.

Recent findings
A review of the recent literature suggests that nonclassical symptoms have a high prevalence, are underestimated, and can interact with quality of life. Although these disturbances may occur together by mere coincidence, they may interact reciprocally. However, the degree of symptoms is not always correlated with OSA severity.

Summary
OSA is a heterogeneous disease with variable clinical manifestations. This review highlights the need for detailed evaluation of patients with OSA to diagnose other important sleep disorders and clinical manifestations, given their frequent association.

Keywords
acid reflux, bruxism, dysphagia, headache, insomnia, nightmares, nocturia, periodic limb movement disorder, restless legs

INTRODUCTION

Obstructive sleep apnea (OSA) is a common sleep disorder and affects nearly one billion people worldwide, with substantial morbidity, mortality and financial and societal costs [1]. It is characterized by the presence of repetitive episodes of partial or complete collapse of the upper airway during sleep [2,3]. The two major pathophysiological consequences of OSA are arterial oxygen desaturation and sleep fragmentation [4]. The typical OSA syndrome is represented by an overweigh male patient with reported heavy snoring and witnessed apneas, nocturnal gasping, excessive daytime sleepiness and cardiovascular and metabolic comorbidities. This picture is contrasted by a subgroup of individuals who do not report discomfort at night, do not complain about sleepiness at all or have unusual symtoms such as bruxism, morning headache, nocturia, acid reflux, chronic cough and dysphagia, which are not directly linked with the nocturnal breathing problem [5]. Because of these nonspecific symptoms, OSA remains often undiagnosed. Moreover, intrinsic sleep disorders can coincide or may be provoked by OSA, including nightmares, chronic insomnia disorder, periodic limb movement disorder (PLMD) and restless legs syndrome (RLS), amongst others [6]. When these entities occur together, implications for therapeutic management may arise. This review will present actual data with respect to the prevalence of these atypical symptoms and concommittant sleep disorders, and clinical relevance.

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KEY POINTS

- Nightmares, comorbid insomnia, RLS/PLMD and bruxism are common in OSA.
- Morning headache, nocturia, acid reflux, chronic cough and dysphagia are underestimated manifestations of OSA.
- Concommittant sleep disorders and somatic symptoms may impact outcomes of OSA patients receiving treatment.

NIGHTMARES

The International Classification of Sleep Disorders (ICSD-3) defined nightmares as 'dreams with strong negative emotions that result in awakening from the dreams. The dream plot can be recalled very vividly upon awakening' [6]. Several lines of evidence suggest that OSA may be potentially associated with a higher incidence of nightmares [7].

Sleep disturbance associated with OSA may interfere with normal rapid eye movement (REM) functioning and might thus provoke nightmares. The most recent registry-based cross-sectional study in 2800 patients with OSA revealed that the prevalence of nightmares was 41% [8], which was inversely related to OSA severity. However, the prevalence of nightmares in the controls (50%) was much higher than that reported in the general population, which is close to 19% [9]. The majority of previous studies had a relatively small sample size, which affects statistical power and ability to account for confounding factors that may impact both OSA and nightmares [10]. Multiple logistic regression analysis identified the apnea-hypopnea index during REM sleep (REM AHI) and interrupted nocturnal sleep as the independent predictors of nightmares in patients with OSA [10]. On the contrary, Tamanna *et al.* [11] found no signficant correlation between REM AHI and the number of nightmares, signifying that obstructive events during REM sleep may not be the only trigger for nightmares. It appeared that in patients with good adherence to continuous positive airway pressure (CPAP) therapy, nightmares disappeared in 91%, compared with 36% of patients who did not adhere to CPAP [10]. It is necessary to distinguish nightmares due to OSA from posttraumatic nightmares that are part of the posttraumatic stress syndrome (PTSD) as a result of a traumatic event. However, several studies have found a clear association between posttraumatic stress disorder comorbid OSA and nightmares [12], with about 55% of PTSD patients with OSA having a low arousal threshold endotype [13▪]. Also, a reduction in the frequency of nightmares during CPAP treatment has been shown [12], with a dose-dependent response to the duration of CPAP usage [14]. On the contrary, CPAP also presents challenges to tolerance in the PTSD population. However, low arousal threshold endotype was not correlated with CPAP utilization, and insomnia was the only factor associated with decreased CPAP use in patients with PTSD [13▪]. For complex cases, alternative treatments have to be considered [15]. Both CPAP and mandibular advancement device (MAD) have been shown to be efficacious in improving OSA, leading to an increased quality of life and alleviation of PTSD symptoms [16]. Interestingly, one study showed that PTSD veterans with OSA with CPAP treatment profited more from psychotherapy than PTSD veterans with OSA without CPAP treatment [17]. Moreover, notwithstanding adherence to CPAP, residual sleepiness is highly prevalent in patients with PTSD and OSA and is independently associated with percentage time spent in REM, duration of CPAP utilization and symptoms of depression [18]. Also, in the case of nightmares, we should not forget to use psychotherapy as a first choice, particularly in patients with poor compliance to CPAP and poor sleep and overall life quality [19]. At the same time, we should emphasize sleep hygiene and a healthy lifestyle.

COMORBID INSOMNIA

The essential feature of chronic insomnia disorder is a frequently and persistent difficulty initiating or maintaining sleep (DIMS) or waking up earlier than desired. According to the ICD-3, symptoms last at least 3 months and occur at least 3 nights/week [6].

In 1973, the first report was provided describing the coexistence of OSA and insomnia [20]. Later, in 2017, the term comorbid insomnia and OSA, or COMISA, was introduced [21]. The prevalence of COMISA has varied between 6.7 and 84% in previous studies [22▪]. Differences in diagnostic criteria, study design and patient selection (depending on whether insomnia is viewed as a specific disorder or a symptom) might explain this wide range. Furthermore, a few studies have attempted to estimate the prevalence of COMISA in the general population. Hence, these data differ depending on which specific population is assessed [21]. Chung [23] studied the prevalence of various insomnia subtypes in 157 OSA patients, and found that 28% had one insomnia symptom, 10% had two insomnia symptoms and 4% had three of four insomnia symptoms. In a recent meta-anaysis that looked at global and regional prevalence data, the overall prevalence rates of any insomnia complaints, difficulty falling asleep, difficulty maintaining sleep and early morning awakening found in OSA patients

were 36, 18, 42 and 21% [24]. In a Brazilian cohort, almost one-third of adult OSA patients fulfilled diagnostic criteria for COMISA. COMISA was more prevalent in older participants, and was associated with a more complicated clinical picture [25]. In a population-based online survey data from 2044 Australian adults, insomnia occurred more frequently among participants with doctor-diagnosed OSA (22%), compared with those without (14%) [26]. DIMS also occurred more frequently among participants with OSA symptoms (67%), compared with those without (47%). Of 269 patients newly diagnosed with OSA (aged 21–70 years; 73% men), 54% were categorized as having insomnia [27]. In another series of 155 OSA patients, 49% had an Athens Insomnia Scale score of at least 6 [28]. In a series of 296 OSA patients, 80% reported at least one major symptom of insomnia: 57% reported sleep onset insomnia, 68% sleep maintenance insomnia and 48% had early morning awakenings. COMISA (OSA and two or more major symptoms of insomnia) was seen in 63% of patients [29]. In 707 patients with OSA, underestimation and overestimation of sleep state perception were noted in 22.5 and 10.6% of individuals, respectively [30▪]. Finally, in a large sample of consecutive outpatients, there was an inverse relationship between the number of nocturnal symptoms of insomnia and OSA diagnosis [31]. In a sleep surgery clinic, the prevalence of COMISA was 42% [32]. Clinically significant insomnia was associated with a history of CPAP device use. In a cross-sectional study containing 1737 bariatric surgery candidates, 40% presented with insomnia, and OSA prevalence was similar among participants with or without insomnia [33]. Participants with symptom-level COMISA reported increased comorbid conditions, and worse general health compared with participants with symptoms of insomnia-alone, OSA-alone or neither insomnia/OSA [26]. Using data from the Sleep Heart Health Study (SHHS), those with comorbid OSA reported the greatest sleep discrepancy and the lowest quality of life [34]. Also, comorbid insomnia may contribute to greater diabetes-related distress in persons with type 2 diabetes mellitus and OSA [35▪]. To answer the question whether people with COMISA are at a heightened risk of incident cardiovascular events, longitudinal data were used from the SHHS ($N = 5803$) over nearly 11 years of follow-up. COMISA was associated with a 75% increase in likelihood of having cardiovascular disease (CVD) at baseline (after adjusting for prespecified confounders). However, after adjusting for prespecified covariates, COMISA was not significantly associated with incident cardiovascular events (hazard ratio 1.38) [36]. In another study looking at the risk of CVD associated with COMISA in type 2 diabetes, Hein *et al.* [37] found that only COMISA was associated with a higher risk of CVD in this population. In a sleep clinic population, insomnia did not increase the risk of chronic kidney disease (CKD) progression, nor did it further increase the risk of CKD progression associated with moderate-to-severe OSA [38]. Lechat *et al.* [39▪] also looked at data from the SHHS ($n = 5236$) to assess associations between COMISA and all-cause mortality risk. Three percent had insomnia-alone, 42% had OSA-alone and 3% had COMISA. Compared with controls, COMISA was associated with a 47% increased risk of mortality [39▪].

Interaction with treatment acceptance and outcome

Many patients with COMISA have adequate acceptance and use of CPAP therapy and show improvements in both OSA and insomnia symptoms [22▪]. Lundetræ *et al.* [40] assessed the effect of CPAP on symptoms and prevalence of insomnia in patients with OSA. The proportion of patients with chronic insomnia was significantly reduced from 51% at baseline to 33% at follow-up. Drakou *et al.* [41] studied the co-occurrence of depression and insomnia in OSA patients and its impact on treatment acceptance in a real-life controlled trial. They found no differences in CPAP trial acceptance between subgroups except in patients from the mild depression/severe OSA/insomnia subgroup, who denied CPAP therapy more frequently [41]. Improvement of insomnia symptoms has also been reported following non-CPAP therapies for OSA [22▪]. On the contrary, comorbid insomnia may also impact outcomes of patients with OSA receiving hypoglossal nerve stimulation (HNS), with worse patient-reported outcomes of daytime sleepiness and sleep-related quality of life [42]. Although the implanted device offsets the mask or pressure-related side effects often associated with CPAP therapy, some HNS recipients do not use the therapy consistently [43]. Recent evidence from the ADHERE registry in over 2000 patients with an implanted HNS system demonstrated that comorbid insomnia (2% of the registry) was associated with significantly less HNS usage over 12 months (-1.47 h/night) compared with patients without comorbid insomnia [44▪▪]. On the contrary, in a retrospective case series of 53 veterans receiving HNS at a Veterans Affairs hospital in the USA, HNS usage (adherence) did not differ between patients with COMISA (57% of all patients) and those with OSA alone (5.6 vs. 6.4 h/night, NS), while 57% of the patients with COMISA reported an improvement in their insomnia [45]. Also, in a cohort study with 85 OSA patients, sustained improvements in PROs were observed 1 year after HNS and were comparable to those for PAP at 3 months [46].

RESTLESS LEGS SYNDROME, PERIODIC LIMB MOVEMENTS AND OSA

Restless legs syndrome is a common chronic sensory-motor neurological disorder, which can coincide with OSA. The prevalence of RLS in patients with OSA varies between 7 and 36% [47,48], which is higher than in the normal population [49]. Recent data have shown that 21% of patients with OSA have RLS, with the proportion of women (60%) with OSA-RLS higher than for men (40%) [50]. OSA-RLS complained more insomnia-specific symptoms than OSA, such as sleep-related worries. In a study conducted among 1317 patients admitted to a sleep apnea clinic, women with OSA complained more about restless legs symptoms (43.1 vs. 17.2%) than did men [51]. PLMD is a sleep disorder characterized by involuntary periodic limb movements that occur repetitively during sleep (PLMS) [6]. PLMS are commonly seen in patients with OSA. Among 303 adult patients with OSA, 98 patients had a significant number of PLMS (32%) [52]. Lee *et al.* [53▪] studied 861 patients with OSA who underwent a full-night CPAP titration polysomnography (PSG). The proportions of the individuals with PLMS on both PSGs (persistent PLMS), those with CPAP-emergent PLMS and those with CPAP-resolved PLMS were 12.9, 9.2 and 3.9%, respectively [53▪]. Benbir Senel *et al.* [54] performed cyclic alternating pattern (CAP) analysis in these different categories. They found that PLMS related to A1 subtype of CAP were observed to decrease under CPAP titration more than PLMS related to A3 subtype of CAP. The A3 subtype of CAP was higher in patients with vanishing PLMS than those with newly emergent PLMS. The newly emergent PLMS were mostly related to A1 subtype of CAP. These differences may represent different underlying pathophysiology. The clinical significance of PLMS in OSA patients remains unclear. Nevertheless, these patients have worse sleep architecture including shorter total sleep time than those without comorbid PLMS [55,56]. Surprisingly, there is no evidence that PLMS increase daytime sleepiness in patients with OSA [57,58]. There is even evidence that PLMS may reduce daytime sleepiness in OSA [56].

BRUXISM

Sleep bruxism is a repetitive jaw-muscle activity characterized by clenching or grinding of the teeth and/or by bracing or thrusting of the mandible [6,59]. The prevalence of self-reported sleep bruxism in adults is 13% [60]. However, the prevalence of SB in adult patients with OSA ranges from 26 to 54%, which is much higher than that in the general population (13%) [60–64]. The potential negative consequences of sleep bruxism described in literature are matinal headache, temporomandibular pain complaints, severe mechanical tooth wear and tooth/dental restoration/implant fractures/failures [65]. It is noteworthy that a recent study [60] showed that PSG-confirmed bruxers had lower AHI and arousal indices than nonbruxers and that OSA decreased the risk for sleep bruxism. These results suggest an inverse association between OSA and sleep bruxism. Also, some studies [66–69] have reported that, to some extent, OSA therapies (such as CPAP and MAD) can reduce the frequency of sleep bruxism episodes as well as the signs and symptoms of sleep bruxism. Thus, for patients with concomitant OSA and sleep bruxism, OSA should be treated first. On the contrary, use of antidepressants may represent increased odds for sleep bruxism development [69].

HEADACHE

OSA is also associated with various atypical clinical symptoms, such as headache, nocturia, acid reflux and dysphagia. The importance of headache as a clinical fnding of OSA has been recognized as sleep apnea headache was included in the International Classifcation of Headache Disorders under the heading of headache attributed to disorder of homeostasis and headache attributed to hypoxia and/or hypercapnia [70]. The prevalence of headache in OSA has been reported to range between 15 and 60% [71]. A previous study reported that among 33 OSA patients using CPAP, 39% reported a greater than 50% improvement in headache severity and frequency [72].

Recent research has shown that PAP therapy may increase pain tolerance and threshold [73]. Park *et al.* [74] evaluated the change in headache prevalence in consecutive OSA patients who were treated with MAD. Eleven patients (85%) before and seven patients (54%) after treatment reported morning headache. Sixty-two percent of the patients experienced a greater than 30% reduction in headache frequency. Significantly more patients had bilateral headache in the responder group before treatment. Decrease in headache frequency itself is known to lead to a signifcant improvement in patient quality of life [75].

NOCTURNIA

Nocturia is defined by International Continence Society (ICS) as 'the complaint that the individual has to wake at night one or more times to void . . . each void is preceded and followed by sleep' [76]. Sleep disorders affect responsiveness to sensory information and can

cause nocturia [77]. Despite the bother experienced by patients, nocturia is an underreported condition, and therefore, the true extent of the problem in the population may be underestimated. Nocturia has been identified as an independent predictor for severe OSA [78,79], while a history of nocturia (≥2/night) predicts very severe OSA (AHI >60) [80]. As nocturia is underreported, the true incidence of nocturia in patients suffering from OSA is likely to be higher. Recently, Vrooman *et al.* [81] studied the prevalence of nocturia in patients with OSA who received CPAP treatment as well as the effect of CPAP treatment on nocturia. Treatment of OSA with CPAP reduced nocturia with one or more episodes per night in 42% of the patients. Clinically relevant nocturia (≥2 voids per night) was reduced from 73 to 52%. There were no statistically significant sex differences. After treatment with CPAP, almost half of the patients experienced a decrease in the nocturia frequency of one or more voids. CPAP not only reduced the number of voids during the night but also improved the associated QoL. Almost no one scored bad after treatment.

ACID REFLUX – CHRONIC COUGH – DYSPHAGIA

Several studies identified a link between acid reflux and OSA [82,83]. In this condition, acid reflux from the stomach to the oesophagus causes troublesome symptoms. Recently, Mahfouz *et al.* [84] assessed the characteristics and risk factors associated with acid reflux and OSA in a large population-based study. Out of 22 677 620 patients with the diagnosis of acid reflux, 12% had a concurrent diagnosis of OSA (compared with 5% in patients without acid reflux). Obesity was found to be the strongest association with reflux [84]. Similarly, in a study by Campanholo *et al.* [85], acid reflux was reported in 45% of the cases with OSA. The severity of OSA was not associated with the Reflux Symptom Index (RSI) score. Age, smoking, but not BMI, were associated with acid reflux [85]. Radovanovic *et al.* [86▪] found that the prevalence of acid reflux symptoms was not different in patients with OSA compared with snorers and nonsnorers, after purposely excluding key confounding factors, such as obesity and alcohol abuse. Different recent studies demonstrated that CPAP treatment in OSA potentially reduces laryngeal reflux symptoms [87–89]. Overall, significant decreases in mean RSI score were observed after CPAP treatment. It was also shown that uvulopalatopharyngoplasty (UPPP) can improve RSI score, potentially by alleviating upper airway collapse and corresponding pulse of negative intrathoracic pressure and positive abdominal pressure [90]. OSA and acid reflux may also be the contributors to chronic cough in patients with OSA and concomitant acid reflux [91]. CPAP improved the symptoms of chronic cough and acid reflux in patients with OSA and concomitant acid reflux. Patients with OSA also exhibit symptoms of dysphagia, that is an impaired bolus transit from the mouth to the oesophagus with reported prevalences between 20 and 77% [92]. Both sensory and motor changes associated with OSA impair swallowing function, but the sensory component seems to be predominant. Pizzorni *et al.* [93] reported a prevalence of 15% in a cohort of 951 patients with OSA. Symptoms of acid reflux were significantly associated with dysphagia symptoms. Its clinical relevance is in the severe complications associated with dysphagia, such as aspiration pneumonia, malnutrition and dehydratation, which impact survival, clinical management and health costs [94].

CONCLUSION

Nightmares, comorbid insomnia, RLS/PLMD and bruxism are common in OSA and can interact reciprocally with the underlying sleep apnea syndrome, leading to additional burden, and complex diagnostic decisions for clinicians, and reduced response to otherwise effective treatment approach. CPAP therapy remains the mainstay of therapy for OSA, and can occasionally improve the symptomatology of these disturbances. Somatic symptoms are also prevalent in OSA. Although a causal relationship is not always obvious, treatment usually leads to less symptoms.

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Conflicts of interest

There are no conflicts of interest.

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