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Insomnia and Obstructive Sleep Apnea

Jason C. Ong, PhD* and **Megan R. Crawford, PhD**
Department of Behavioral Science, Rush University Medical Center, 710 South Paulina Street, Suite 600, Chicago, IL 60612, USA

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Introduction

With more than 80 distinct sleep disorders classified in the International Classification of Sleep Disorders (ICSD-2[1]), comorbidity of sleep disorders has emerged as an important topic with clinical and research significance. In particular, obstructive sleep apnea (OSA) and insomnia are 2 sleep disorders that co-occur frequently, involve clinical features and associations that are distinct from the separate conditions, and are treatable. OSA, which affects about 10% to 20% of middle to older aged adults,[2] is characterized by the repeated obstruction of the upper airway during sleep that leads to complete cessation (apnea) or reduction (hyperpnea) of airflow, occurring irrespective of continued ventilatory effort. Before termination, these events lead to a decrease in blood oxygen saturation and an associated increase in carbon dioxide levels during longer events. The termination of the apnea is often preceded by an arousal, which leads to sleep fragmentation and activation of the sympathetic nervous system. The former is hypothesized to be involved in the neurocognitive sequelae, whereas the latter leads to cardiovascular dysregulation. This process is identified as the possible cause for the daytime sleepiness and cardiovascular health and functioning problems witnessed in these individuals.[3–7] Severe OSA has been linked to a 4- to 6-fold increased risk of mortality, irrespective of factors such as age, diabetes, or high cholesterol.[8,9]

Symptoms of insomnia include difficulty initiating and/or maintaining sleep, waking too early, and/or nonrestorative sleep. When the nocturnal symptoms are associated with significant distress or daytime dysfunction and last for at least 3 months, the condition is considered an insomnia disorder.[10] As a result of evolving diagnostic criteria for insomnia, there are large variations in the cited prevalence rates of these types of sleep difficulties, ranging from around 6% to 30%.[11–13] The pathophysiology of insomnia is thought to involve hyper-arousal in the form of cognitive arousal (eg, increased cognitive activity or negative tone of cognitions) and physiologic arousal (eg, elevations in core body temperature, muscle tension, and sympathetic activation).[14] The most frequently cited consequences of insomnia are the reduction in quality of life and productivity, and increased risk of accidents, and absenteeism.[13,15] Insomnia may also be a risk factor for various psychiatric conditions[16,17] and health problems suchashyper-tension,[18] type 2 diabetes,[19] and even mortality after controlling for hypertension and diabetes.[20]

The co-occurrence of both conditions was first described in 1973 by Guilleminault and colleagues,[21] who reported on 3 individual cases who presented to the sleep laboratory for

*Corresponding author. jason_ong@rush.edu.

evaluation of insomnia and were subsequently investigated for sleep-disordered breathing. More recently, the comorbidity between sleep apnea and insomnia has garnered increased research and clinical interest, likely resulting from a paradigm shift in how insomnia is conceptualized. Whereas insomnia was previously considered secondary to a primary condition, a consensus statement released by the US National Institutes of Health[22] regards insomnia as a distinct disorder that can also be comorbid to another condition. This conceptualization challenges the traditional assumption that insomnia is merely a symptom of another condition, and allows for a separate diagnosis of "comorbid insomnia" even in the context of another sleep disorder such as sleep apnea.

Diagnosing comorbid insomnia in the context of another sleep disorder can be challenging, as there can be overlap in the complaint of sleep disturbance (eg, difficulty maintaining sleep) and daytime dysfunction (eg, daytime fatigue). Moreover, our understanding of the mechanisms involved in the comorbid relationship remains very limited. Even well-trained clinicians cannot make reliable distinctions with regard to the attribution of insomnia symptoms.[23] As a response, recent recommenda-tions[10,24] enable a diagnosis of an insomnia disorder without attributing the causal relationship between the symptoms and the co-occurring disorder. In the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-V), specifiers are used with an insomnia disorder to note the comorbid condition rather than attempting to assign causal attributions, as was the case in previous classification systems such as DSM-IV (ie, primary vs secondary insomnia). With these shifts in conceptualization and nosology, several research studies focusing on the insomnia/OSA co-morbidity have emerged. This growing body of literature is shaping our understanding of the relationship, consequences, and treatment implications of comorbid insomnia and sleep apnea.

This review of the literature is organized on the basis of the progression of research on the comorbidity between insomnia and sleep apnea. First, clinical features and associations with this comorbidity are discussed, much of which has been informed by cross-sectional studies. Second, the authors discuss models of pathogenesis that have been proposed in the literature. Here, emerging data from longitudinal studies and relevant retrospective studies that are capable of examining the time course of the two disorders are highlighted. Finally, the clinical implications of this review are discussed, and suggestions are made regarding future research.

Clinical Features and Associations

Given that most patients are not aware of the classification of sleep disorders or possible comorbidity, the rates of comorbidity can depend on the chief complaint (Table 1). Among individuals with a presenting complaint related to sleep apnea (eg, snoring, excessive daytime sleepiness, nocturnal breathing issues), the co-occurrence of insomnia varies between 6% and 84%.[25–30,33,35,36,40,42,43] By contrast, in those seeking evaluation for insomnia, rates of co-occurring sleep apnea ranged from 7% to 69%.[31,32,34,37–39,41] Of note, these reports may underestimate the true rates of comorbidity. These prevalence rates have emerged largely from samples that were excluded from the primary study because of the comorbid sleep apnea as determined through polysomnography. These rates often do not include those who present with clinical symptoms of sleep apnea who are excluded during previous screenings. For example, in one such study 17% of the recruited sample were excluded because of witness apneas and snoring or sleepiness during telephone/hospital interviews.[37] The variability in rates is likely affected by several other factors. First, the criteria for insomnia vary across studies. When insomnia is defined as the presence of at least 1 nocturnal symptom (onset, maintenance difficulties, or early morning awakening), rates are higher (6%– 84%)[25–27,29,33,35,42,43] than if insomnia is classified as nighttime

symptoms with concomitant daytime dysfunction that would justify a diagnosis of insomnia disorder (21%–39%).[28,40] The discrepancy might also vary according to insomnia subtypes (ie, difficulty falling asleep vs difficulty maintaining sleep). In a group of 157 individuals referred to a sleep clinic for suspected OSA, more individuals reported problems with sleep maintenance or waking too early (26% and 19%, respectively) relative to difficulties falling asleep (6%).[29] Subsequent studies (eg, Refs.[26,27,33]) have found similar differences across subtypes, suggesting different etiologic pathways. Finally, rates of insomnia vary as a function of OSA severity. However, results are in conflict with some that have shown a strong positive relationship between severity and prevalence of insomnia,[33] whereas others have not.[27,36]

Several cross-sectional studies also shed light on some of the clinical features of these comorbid conditions. As with the prevalence rates, the features differ as a function of the "primary" condition. Individuals with a primary complaint of OSA were more likely female,[26,36,42–45] had more dysfunctional beliefs about sleep,[40,46] were more likely to present with restless legs syndrome,[26,35,36] and reported less alcohol use[36] compared with OSA-only individuals. In individuals with a primary complaint of insomnia, patients were more likely than those without OSA to be male,[37,39] have a higher body mass index,[31,32,34,37,39] be older,[31,39] and have more daytime and nighttime nocturnal symptoms consistent with OSA.[32,34] These findings suggest that the patient's chief complaint (OSA or insomnia) might yield different clinical considerations, and that secondary complaints should be fully explored.

In addition to clinical features, comorbidity of insomnia and sleep apnea is associated with increased morbidity and impairment. In this regard the literature suggests that concurrent insomnia and OSA increase risks for depression or other comorbid psychiatric conditions,[35,36,40,43] medical conditions such as chronic pain,[36] cardiovascular disease (hypertension and congestive heart failure),[43] reduced quality of life,[26] functional impairment,[32] sleepiness (only found in sleep maintenance insomnia),[26,29] and absenteeism from work.[47] Because the majority of these findings are from cross-sectional data, it is unclear as to whether the increased morbidity is a cause or a consequence of the comorbidity of insomnia and OSA.

The presence of both OSA and insomnia can also have a negative impact on the treatment process and outcomes. Specifically, the presence of insomnia can negatively affect treatment outcomes of OSA. In 20 OSA patients who were unsuccessfully treated with a mandibular advancement device, Machado and colleagues[48] reported 'that the presence of insomnia was the only significant predictor of nonimprovement. Other studies have examined the impact of insomnia on adherence to continuous positive airway pressure (CPAP). Wick-wire and colleagues[49] conducted a retrospective chart review of 232 OSA patients who had been prescribed CPAP and had provided information on possible insomnia symptoms. After controlling for age and gender, sleep maintenance symptoms were associated with worse objective CPAP adherence at clinical follow-up, assessed 4 months after titration. Similarly, a recent longitudinal study of 705 OSA individuals treated with positive airway pressure (PAP) revealed that insomnia symptoms (both initial and maintenance) at baseline were predictive of reduced PAP use at the 2-year follow-up.[27] Other studies have found similar evidence for the negative impact of insomnia before initiating CPAP, on CPAP use during the first 7 days of use as well as the first 6 months of use.[50,51] However, one study did not find a relationship between insomnia (as measured by the Insomnia Severity Index) and CPAP adherence at 6 months.[52]

In contrast to the impact of insomnia on OSA, much less is known about the potential impact of OSA on insomnia treatment outcome. One preliminary report found that the

presence of OSA did not negatively affect the outcomes of cognitive-behavioral therapy (CBT) for insomnia.[53] In another study, Nguyen and colleagues[54] reported the improvement of insomnia symptoms after 24 months of auto-PAP treatment in 80 individuals with sleep apnea. Of the 39 subjects who had insomnia, baseline sleepiness and disease severity were associated with insomnia improvement after 24 months. Taken together, the available literature suggests that the coexistence of insomnia and OSA is likely to have a negative impact on OSA treatment, but if or how it might affect insomnia treatment is unclear. Indeed, further research is needed to clarify the potential impact of comorbidity on treatment, as this has very important implications for patient management.

Models of Pathogenesis

The pathophysiology and developmental course of comorbid OSA and insomnia is not clearly understood. A few theoretical models outlining possible pathways have been proposed and discussed in the literature.[55,56] One pathway is that OSA is a precursor and putative risk factor for an insomnia disorder. This notion has intuitive appeal, given that respiratory events could lead to nocturnal awakenings and repeated awakenings could lead to chronic insomnia.[55,57] Krakow and colleagues[58] found that nocturnal awakenings reported by patients with insomnia were frequently due to respiratory events. This conceptualization would also fit the diathesis stress-response model of insomnia proposed by Spielman and colleagues[59] whereby the onset of OSA is a precipitating factor for insomnia. Another hypothesis supporting this pathway is that respiratory events can also lead to sympathetic activation thereby increasing hyperarousal, which is a key feature of insomnia.[29,58] A third hypothesis is that treatment of OSA can precipitate insomnia. One study examining retrospective data of patients treated at a sleep clinic reported that 21.4% (12 of 56) of patients who did not report insomnia at baseline developed insomnia after 3 months or more of receiving PAP (primarily auto-PAP).[28] The investigators speculated that this type of pressure delivery, with changing pressure levels, can actually lead to more sleep fragmentation, and could be a possible contributor to the development of insomnia resulting from PAP treatment. Thus, insomnia might emerge from poor tolerance to OSA therapy. However, another viable explanation of these data is that the auto-PAP effectively treated the OSA, and insomnia emerged once the sleep debt was resolved and the homeostatic sleep drive was regulated. In other words, effective treatment of OSA could unmask an underlying insomnia disorder.

Despite the intuitive appeal of this pathway, recent longitudinal data dispute this temporal relationship. In one report OSA at baseline, defined as an apnea-hypopnea index score of 5 or greater, was not a significant predictor of patients' responses to the question, “Do you feel you have insomnia?” posed at a 7.5-year follow-up.[60] Another report from the same dataset found that moderate to severe sleep apnea, defined as an AHI of 15 or greater, is a risk factor for the development of poor sleep (moderate to severe ratings on nocturnal symptoms of insomnia) but not chronic insomnia as defined earlier.[61] The investigators propose that respiratory events in the context of OSA can lead to acute sleep disruption but do not evolve into an insomnia disorder over time, as earlier hypotheses have posited.

A second pathway is suggested whereby the insomnia disorder develops first and is a precursor to OSA. This pathway has less intuitive appeal in that prolonged awakenings or hyperarousal from insomnia do not have obvious causal connections with respiratory mechanisms. It has been hypothesized that the sleep deprivation resulting from chronic insomnia might compromise the upper airway (eg, pharyngeal) muscle tone.[35,57] Unfortunately, no empirical studies have been found to support or dispute this pathway.

A third potential pathway involves an underlying mechanism that links the two sleep disorders. Theoretical models have focused on the potential role of the hypothalamic-pituitary-adrenal axis (HPA) pathway and metabolic factors.[55,62] It is hypothesized that stress increases HPA activity, leading to sleep fragmentation associated with insomnia. In addition, repeated respiratory events in the context of OSA can lead to autonomic activation, triggering HPA activation.[62] Furthermore, the increased HPA activity might disrupt metabolic activity associated with metabolic syndrome (eg, glucose imbalance). To the authors' knowledge, there is no published evidence directly testing these theoretical models or the possibility that a third variable, such as depression, is a mediator between the onset of sleep apnea and the development of insomnia.

Clinical Implications for Sleep Medicine

Assessment

Given the literature showing that insomnia symptoms can predict OSA and can also have a negative impact on treatment, effective assessment of both OSA and insomnia is advised to provide comprehensive care. First, the chief complaint (insomnia or sleep-related breathing issues) should give rise to more specific considerations regarding the comorbid (or "secondary") condition. For example, women might appear to fit a profile for an insomnia disorder (eg, complain of sleep disturbance, hold dysfunctional sleep-related cognitions), but a comprehensive assessment for sleep-related breathing disorder should still be considered. Appropriate assessment can give rise to considerations regarding the timing of treatment sequences (see later discussion) or whether the patient might be aided by use of a hypnotic during the overnight polysomnography. Indeed, there is evidence that higher sleep efficiency on the night of the CPAP titration predicts future compliance with CPAP.[63] Lettieri and colleagues[64,65] have found that administration of eszopiclone (3 mg) on the titration night improved the quality of the titration study and improved CPAP adherence when compared with placebo. This finding can serve as an example of how comprehensive baseline assessment can improve patient management of these comorbid sleep disorders.

Treatment Strategies

Effective treatments are available when insomnia and sleep apnea occur separately. Pharmacologic therapy using hypnotic medication is the most common treatment option for insomnia. However, some hypnotics, such as benzodiazepines, can have adverse effects on nocturnal respiration, thus exacerbating the OSA.[66,67] Therefore, these should be used with caution for the patient with both OSA and insomnia. The newer nonbenzodiazepine agents, such as zolpidem and eszopiclone, seem to have less effect on the airway.[68,69] CBT has become the first-line nonpharmacologic treatment for insomnia. Although CBT is generally regarded as safe and effective across a variety of comorbid conditions, it remains unclear as to whether there are specific counterindications when insomnia and OSA are comorbid. For example, sleep restriction could exacerbate daytime sleepiness because of the OSA. As noted earlier, only one study has documented that the presence of OSA did not negatively affect the outcomes of CBT for insomnia.[53] This finding would suggest that CBT is a potential treatment for those with comorbid insomnia and OSA. Components such as sleep restriction and stimulus control, aimed at eliminating the extended periods of wakefulness spent in bed, might also potentially improve poor sleeping habits in individuals with comorbid insomnia and OSA (eg, napping and extended time in bed).

The first-line treatment for moderate to severe OSA is CPAP.[70–72] Although treatment of OSA using CPAP provides many health benefits, it is currently unclear whether this will also improve insomnia for patients with both OSA and insomnia. Bjornsdottir and colleagues[27] showed that effective use was associated with a 50% reduction in the

prevalence of sleep maintenance insomnia, but symptoms of initial insomnia were largely still present at follow-up. Other treatments for OSA include a dental oral appliance, positional training, and surgery. These treatments are typically recommended based on specific features related to the OSA (eg, mild OSA, position-dependent OSA, enlarged tonsils). However, to the authors' knowledge no studies have examined the impact of these procedures on comorbid insomnia.

While there are effective treatments available for insomnia and OSA separately, there are currently no known monotherapies that effectively treat insomnia and sleep apnea simultaneously. Therefore, management of patients with both OSA and insomnia entails the combining of treatments for insomnia with treatments for OSA. One study by Krakow and colleagues[73] examined a sequence of CBT for insomnia followed by treatment for OSA (CPAP, oral appliance, turbinectomy). Of the 17 patients treated, 8 reported clinically significant improvements from insomnia after CBT, with an additional 7 (for a total of 15 of 17) reporting clinically significant improvements in insomnia after receiving both treatments. Guilleminault and colleagues[74] tested sequences of CBT before or after ear/nose/throat surgery for 30 patients with mild OSA and insomnia. Optimal outcomes were achieved for patients who received both treatments, with some evidence that treating OSA first led to resolution of insomnia in some patients before CBT. The retrospective study by Caetano Mota and colleagues[28] found that 45.8% (11 of 24) of patients who reported insomnia and were diagnosed with sleep apnea no longer reported insomnia following PAP treatment. However, 21.4% of patients (12 of 56) who did not have insomnia at baseline developed insomnia during the course of PAP treatment. Thus, insomnia symptoms might be present at baseline or could appear during treatment, suggesting that insomnia symptoms should be monitored over time and that appropriate treatment should be delivered should it arise during OSA treatment. For patients who initially present with OSA but develop treatment-emergent insomnia after starting OSA therapy, a course of CBT or hypnotic medications should be considered as an adjunct to the OSA therapy. For other patients who initially present with insomnia (particularly sleep maintenance insomnia) but are treatment resistant to CBT or hypnotics, evaluation for OSA should be considered because the insomnia could be masking the symptoms of OSA. Finally, some patients might initially present with both insomnia and OSA symptoms. For these patients it is advisable to treat both disorders, but there currently is no clear guidance as to the order or sequence of treatment. Until a uniform treatment is developed, considerations should be given to combination approaches in treating the patient with OSA and insomnia.

Future Research Agenda

As the comorbidity between sleep apnea and insomnia gains more research attention, future studies should be hypothesis driven with an eye toward improving patient care. First, research should examine methods for diagnosing the co-occurrence of insomnia and OSA. Studies examining the reliability and validity of various diagnostic questionnaires, interviews, or objective measures could improve the precision of the prevalence and incidence of this comorbid condition. Second, research should seek to clarify the pathophysiology and time course of these disorders. Prospective studies using longitudinal designs would be particularly useful to examine temporal precedence and the natural course of the co-occurrence of the two disorders. Studies examining the clinical course of treatment-emergent or treatment-resistant insomnia as it relates to OSA could inform clinicians regarding treatment implementation. At the mechanistic level, studies examining the relationship between repeated respiratory events and their associated sequelae with insomnia mechanisms such as hyperarousal or changes in sleep-related thoughts and behaviors could provide further insight into the etiology of the comorbid condition. Finally, treatment studies examining various combinations or sequences of treatment could provide

evidence to optimize the care of this population. A more ambitious aim would be to investigate a unified treatment for both sleep apnea and insomnia. For example, preliminary evidence has indicated that cannabimimetic drugs have promise as a drug treatment for OSA.[75] Such treatment could serve as a tool to reduce AHI and improve sleep continuity, thus targeting symptoms of OSA and sleep maintenance insomnia. It could also be a potential tool for the treatment of OSA while preventing treatment-emergent insomnia. Another approach would be to combine behavioral treatments into one treatment package for subtypes of comorbid OSA and insomnia. For example, positional training could be integrated into CBT for patients with positional sleep apnea and comorbid insomnia. Such studies could also provide insights into the causes and consequences of the two disorders. Achieving these research goals would significantly improve our understanding and treatment of these common sleep disorders.

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Key Points

- The comorbidity between insomnia and obstructive sleep apnea (OSA) is highly prevalent in patients presenting to sleep clinics and is associated with significant morbidity.
- Sleep clinicians should conduct comprehensive evaluations for both OSA and insomnia regardless of the presenting complaint.
- Patient management should include considerations to both OSA and insomnia treatments.

Table 1

Prevalence rates of comorbid sleep apnea and insomnia

Authors,[Ref.] Year	Sample Size	Criteria for Sleep Apnea	Criteria for Insomnia	Prevalence of Comorbid Insomnia	Prevalence of Comorbid Sleep Apnea
Billings et al,[25] 2013	191	OSA (AHI ≥ 15)	DIS frequent or always	24%	
Bjornsdottir et al,[26] 2012	826[a]	Untreated OSA patients referred for CPAP	DIS, DMS nearly every day	DIS: 12.6% men and 27.3% women; DMS: 51.6% men and 62.4% women	
Bjornsdottir et al,[27] in press	705	OSA (AHI ≥ 15)	DIS, DMS or EMA ≥3 nights/wk	DIS = 15.5%, DMS = 59.3%, EMA = 27.7%	
Caetano Mota et al,[28] 2012	80	OSA (AHI ≥5)	Self-reported present and new onset (self-report questionnaires)	30% present, 21.4% new onset	
Chung,[29] 2005	157	OSA meeting ICSD criteria and AHI ≥5	Insomnia symptoms (DIS, EMA and DMS [difficulty returning back to sleep and multiple wakenings])	42% at least 1 symptom; DIS = 6%, DMS = 26% (multiple wakenings) and 12% (difficulty returning to sleep), and EMA = 19%	
Chung,[30] 2003	119[a]	OSA (AHI ≥5)	Insomnia symptoms (DIS, EMA and DMS [difficulty returning back to sleep and multiple wakenings])	DMS = 33% (multiple wakenings) and 16% (difficulty returning to sleep), EMA = 21%, and DIS = 9%	
Cronlein et al,[31] 2012	93	SAS (AHI ≥ 10)	Meet ICSD-2 criteria for psychophysiological insomnia		23%
Gooneratne et al,[32] 2006	99[a]	SRBD (AHI ≥15)	Insomnia symptoms ≥3 nights/wk for ≥3 wk		29.3%
Johansson et al,[33] 2009	183[a]	OSA (AHI ≥5)	Some or more problems with DIS, DMS, EMA reported	DIS = 44%, DMS = 63%, EMA = 37%	
Kinugawa et al,[34] 2012	64	SAS (AHI ≥ 15)	ICSD-2 criteria for insomnia		68.7%
Krakow et al,[35] 2001	231	SDB (UARS or OSA: clinical criteria and AHI ≥5)	Clinically apparent insomnia symptoms (2 or more insomnia symptoms)	50%	
Krell and Kapur,[36] 2005	228[a]	SDB (AHI ≥10)	At least DIS, DMS, or EMA often/almost	54.9% (DIS = 33.4%, DMS = 38.8%, always EMA = 531.4%)	
Lichstein et al,[37] 1999	80	AHI >15	ICSD criteria for insomnia		29% (43% with AHI >5)
McCall et al,[38] 2009	73	AHI ≥15	SOL >30 min and SE <85% *or* RDC for >4 nights/wk		7%
Ong et al,[39] 2009	51	ICSD-2 criteria and AHI ≥15	DSM-IV-TR criteria for insomnia		39%
Smith et al,[40] 2004	105	OSAHS (unclear)	Presenting with insomnia disorder	39%	
Stone et al,[41] 1994	45	OSA (RDI >10)	TST <6 h, SOL/WASO >30 min for minimum 6 mo		40%

Authors,[Ref.] Year	Sample Size	Criteria for Sleep Apnea	Criteria for Insomnia	Prevalence of Comorbid Insomnia	Prevalence of Comorbid Sleep Apnea
Subramanian et al,[42] 2001	300	OSA (AHI >10)	Insomnia (unclear), DIS, DMS, EMA, PPI	Insomnia 5 84%, DIS = 57%, DMS 5 68%, EMA = 48%, PPI = 49%	
Vozoris,[43] 2012	546[a]	Self-reported health professional diagnosis of sleep apnea	DIS, DMS, EMA often or almost always	Any symptom 43.3% DIS = 25.9%, DMS = 28.8%, EMA = 20.8%	

Abbreviations: AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure; DIS, difficulty initiating sleep; DMS, difficulty maintaining sleep; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revised; EMA, early morning awakenings; ICSD, International Classification of Sleep Disorders; OSA, obstructive sleep apnea; OSAHS, obstructive sleep apnea and hypopnea syndrome; PPI, psychophysiologic insomnia; RDC, research diagnostic criteria; RDI, respiratory disturbance index; SDB, sleep-disordered breathing; SOL, sleep-onset latency; TST, total sleep time; UARS, upper airway resistance syndrome; WASO, wake after sleep onset.

[a]Sample size is not identical to the overall sample size recruited.