# **ORIGINAL ARTICLE**

# Obstructive Sleep Apnea with Insomnia Overlap: An Under-recognized Entity

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## **A**BSTRACT

**Introduction:** The association between obstructive sleep apnea (OSA) and insomnia is relatively common but is underrecognized. There are important diagnostic and therapeutic implications of comorbid OSA–insomnia overlap but there is no data available from India.

**Objectives:** (1) To find out the prevalence of insomnia among patients with OSA; (2) To compare the demographic characteristics, Epworth sleepiness scale (ESS) scores and the presence of comorbidities among patients of OSA with insomnia vs OSA without insomnia.

Materials and methods: It was a prospective observational study involving 250 patients with suspected OSA. A total of 189 patients had OSA based on type I polysomnography and were further analyzed. Insomnia was diagnosed based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) criteria.

Results: The prevalence of insomnia among OSA was 15.34% (29/189). Overlap was seen in 22.45 and 12.86% of women and men respectively among patients with OSA. The prevalence of overlap increased with decreasing severity of obesity and OSA. Those with OSA–insomnia overlap had significantly lower ESS scores as compared to OSA without insomnia (12.31 vs 15.24; p = 0.019). A total of 10.34% (3/29) of patients of overlap had depression whereas none from OSA alone had depression.

**Conclusion:** There is a high prevalence of insomnia among patients with OSA (15.34%), similar to findings worldwide. Insomnia is more common among women with OSA. Overlap patients have lower ESS scores and are likely to be depressed.

Keywords: Comorbid insomnia, Obstructive sleep apnea, Obstructive sleep apnea–insomnia overlap.

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# ABBREVIATIONS USED IN THIS ARTICLE

OSA = Obstructive sleep apnea; ESS = Epworth sleepiness scale; DSM-V = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICSD-3 = International Classification of Sleep Disorders, Third Edition; CPAP = Continuous positive airway pressure; AASM = American Academy of Sleep Medicine; AHI = Apnea-hypopnea index; BMI = Body mass index; OAD = Obstructive airway disease; IHD = Ischemic heart disease.

### Introduction

Obstructive sleep apnea and insomnia are among the commonest disorders presenting to sleep clinics with an increasing burden on health care resources.<sup>1,2</sup> Obstructive sleep apnea is characterized by a repetitive pattern of upper airway collapsibility and airflow obstruction resulting in recurrent arousals. It is recognized as a major risk factor for cardiovascular morbidity and mortality.<sup>3</sup> Obstructive sleep apnea has a varied prevalence in the general population ranging from 2% to 38%.<sup>3,4</sup> Insomnia presents with symptoms of difficulty in sleep initiation or sleep maintenance or early-morning awakening. When the nocturnal symptoms are associated with significant distress or daytime dysfunction and last for a minimum of 3 months, the condition is known as chronic insomnia disorder. 5,6 Insomnia was earlier categorized into primary and secondary based on the etiology. However, as per the recent *International Classification of Sleep Disorders, Third Edition (ICSD-3)* definition, if the patient has the above-mentioned criteria, he/she should be categorized into chronic insomnia disorder irrespective of cause or comorbidities. Insomnia results in reduced quality of life,

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productivity, increased risk of accidents, and absenteeism. It is a risk factor for various psychiatric and cardiovascular consequences.<sup>7,8</sup> The prevalence rates of insomnia varies from 6% to 48%.<sup>9</sup>

Recently, there is increasing evidence of the association between OSA and insomnia. The comorbid OSA-insomnia overlap is also known as "sleep-insomnia apnea syndrome" and "sleep apnea plus." The association was first reported in 1973. This seemed like a paradox as OSA and insomnia have opposing spectrums. Patients with OSA commonly present with excessive daytime sleepiness rather than insomnia. The OSA-insomnia overlap relationship is bidirectional with one contributing to the exacerbation of the other. Repeated nocturnal apneas and awakenings in OSA may lead to insomnia. Similarly, insomnia may lead to nocturnal arousals and superficial sleep increasing upper airway instability. The company of the other is increasing upper airway instability.

The prevalence of insomnia among OSA varies from 6.4 to  $84\%.^{14-17}$  The variation is wide due to differing definitions of

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insomnia and varied regional prevalence. Most of the studies are from the Western population especially the USA and Europe. The consequences of this dual threat are serious. The patients with OSA–insomnia overlap have a greater daytime impairment and poorer quality of life as compared to either disease alone. It also constitutes a cumulative risk factor for psychiatric and cardiovascular diseases. Such patients have poor compliance to continuous positive airway pressure (CPAP), the first line of treatment for OSA. <sup>14,18</sup> Owing to the higher association of adverse health consequences with OSA–insomnia overlap, this dual threat needs to be recognized. Since the awareness regarding OSA–insomnia overlap is low, we conducted this study, the first of its kind from India for the prevalence and clinical consequences of insomnia among patients with OSA.

## AIMS AND OBJECTIVES

- To find out the prevalence of insomnia among patients with OSA.
- To compare the demographic characteristics, ESS scores and presence of comorbidities among patients of OSA with insomnia vs OSA without insomnia.

#### MATERIALS AND METHODS

It was a prospective observational study conducted in a tertiary care center from January 2018 to August 2019. The study was approved by the institutional ethics committee. The patients referred to our pulmonary and sleep medicine department for polysomnography were included. Our sleep center is the only center that is catering to sleep disorders of employee state insurance corporation patients from North India. So, the patients at our center represent the North Indian population. The exclusion criteria were those with active and unstable cardiovascular disease and those who had received treatment for OSA.

## **Study Method**

Written and informed consent was taken from those individuals fulfilling the inclusion and exclusion criteria. Patients were asked for a detailed history and subjected to thorough clinical examination and routine laboratory evaluation. The clinical evaluation included demographics, symptoms of OSA, symptoms of insomnia, vital parameters, and anthropometric measurements. Excessive daytime sleepiness was assessed utilizing ESS. All patients were specifically asked about insomnia symptoms as per the diagnostic protocol.

Insomnia was diagnosed as per the DSM-V criteria, which is similar to the ICSD-3 criteria. <sup>5,6</sup> It defines insomnia as dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms for at least 3 times per week in the last 3 months: Difficulty in initiating sleep, difficulty in maintaining sleep, or early-morning awakening with inability to return to sleep. This should be associated with daytime dysfunction. The reported sleep/ wake complaints cannot be explained purely by an inadequate opportunity for sleep. <sup>5,6</sup>

All the patients were subjected to diagnostic type I polysomnography. The full night attended polysomnography was performed on a Philips Alice S5 polysomnograph. It included a recording of electroencephalogram, electro-oculogram, electromyogram (submental and pretibial), oronasal flow (thermistor and nasal pressure transducer), thoracoabdominal movements, and oxygen saturation. Sleep stages and respiratory events were scored as per the American Academy of Sleep Medicine

(AASM) guidelines.<sup>19</sup> The diagnosis of OSA was based on an apneahypopnea index (AHI) of  $\geq$ 5 events/hour. The severity of OSA was classified based on the following AHI values: AHI  $\geq$ 5 and <15/hour as mild OSA, AHI  $\geq$ 15 and <30/hour as moderate OSA, and  $\geq$ 30/hour as severe OSA.

# **Statistical Analysis**

The sample size was calculated using the standard formula:  $n = Z^2_{1-a/2} \times P(1-P)/d^2$ , where n is the number of patients required, Z is the confidence interval of 95%, P is the anticipated population proportion, and d is the precision required. Oconsidering P = 50% and a precision of 8%, a minimum sample size of 150 was required. We have included a total of 189 patients for our data to have statistical importance. The statistical analysis was performed using SPSS software, version 17 (IBM, Chicago, IL, USA). The data were presented as mean  $\pm$  standard deviation. The prevalence of OSA and insomnia was determined by establishing the proportion of patients meeting the criteria for the diagnosis of OSA and insomnia, respectively. The data were compared among patients of OSA with insomnia and OSA without insomnia using Student's t-test or Chi-squared test wherever applicable. The p <0.05 was considered statistical significance.

# RESULTS

A total of 250 patients presented with clinical suspicion of OSA. All of them were subjected to polysomnography. OSA was found in 189 (75.6%) patients. So, 189 patients with OSA were included in our final analysis. Their age varied from 19 to 70 years with a mean  $\pm$  SD of 51.19 1 0.38 years. Body mass index (BMI) was  $32.27\pm6.15\,\mathrm{kg/m^2}$ . A total of 140 (74.07%) were men and 49 (25.93%) were women. The mean AHI was  $33.24\pm23.68\,\mathrm{events/hour}$ . A total of 87 patients (46.03%) had severe OSA whereas 51 patients (26.98%) had moderate OSA, and 51 patients (26.98%) had mild OSA.

The prevalence of insomnia among patients with OSA was 15.34% (29/189). Table 1 demonstrates the prevalence of comorbid

**Table 1:** Prevalence of OSA–insomnia overlap among patients with OSA as per various parameters

	Total number of	Number of patients with OSA-insomnia
Parameter	patients	overlap (prevalence in %)
OSA	189	29 (15.34)
Sex		
Male	140	18 (12.86)
Female	49	11 (22.45)
Severity of obesity		
BMI 25-29.9 kg/m <sup>2</sup>	53	11 (20.75)
BMI ≥30 kg/m <sup>2</sup>	116	16 (13.79)
BMI ≥40 kg/m <sup>2</sup>	22	1 (4.54)
BMI ≥50 kg/m <sup>2</sup>	2	0 (0)
Severity of OSA		
Mild	51	14 (27.45)
Moderate	51	6 (11.76)
Severe	87	9 (10.34)

BMI, body mass index; OSA, obstructive sleep apnea



OSA-insomnia as per various demographic characteristics and OSA severity. The prevalence was higher among women (22.45%) as compared to men (12.86%). With the increasing severity of obesity, the prevalence of comorbid insomnia decreased. The prevalence of comorbid insomnia was 20.75% among overweight patients (BMI 25–29.9 kg/m²) as compared to nil among those with BMI ≥50 kg/m². We observed a similar decrease in the prevalence of insomnia with increasing severity of OSA. Those with mild OSA had the highest prevalence of comorbid insomnia (27.45%).

The occurrence of any symptom of insomnia was seen in 78.31% (148/189) of patients, however, only 15.34% met the criteria for diagnosis of insomnia. We have also analyzed the prevalence of insomnia among patients with non-OSA ailments. These were suspected of OSA based on the symptoms but had no polysomnographic evidence of OSA. The prevalence was 13.11% among patients with non-OSA ailments (8/61). The difference in the prevalence of insomnia among patients with OSA and non-OSA ailments was statistically insignificant (p = 0.669).

On comparison of various demographic parameters such as age, sex, and BMI among patients of OSA–insomnia overlap with those of OSA alone, we found comparable characteristics in both groups (Table 2). The mean  $\pm$  SD ESS score in OSA with insomnia was 12.31  $\pm$  7.13 as compared to 15.24  $\pm$  5.96 in OSA without insomnia (p = 0.019). Thus, overlap patients had significantly lower ESS scores.

The patients of OSA with insomnia had lower AHI (23.84  $\pm$  19.91 events/hour) as compared to OSA without insomnia (34.95  $\pm$  23.97 events/hour). The difference in AHI was also statistically significant (p = 0.019) (Table 2).

The prevalence of various comorbidities was compared among patients of OSA with insomnia and those of OSA without insomnia as shown in Table 3. The prevalence of cardiovascular comorbidities, gastroesophageal reflux disorder, hypothyroidism, and obstructive airway disease (OAD) in both groups was similar without any significant difference. The difference was significant for depression in that those with insomnia had a higher prevalence of depression. A total of 10.34% patients among OSA with insomnia (3/29) were diagnosed with depression whereas none of the OSA without insomnia had depression. One patient from those OSA without insomnia had bipolar disorder. He was symptomatically stable under regular psychiatric treatment and did not have any insomnia symptoms.

# Discussion

The OSA-insomnia overlap is a prevalent but under-recognized disorder. Multiple mechanisms are involved in the pathogenesis of OSA-insomnia overlap. Also, OSA is associated with repeated arousals leading to difficulty in maintaining sleep. The sympathetic

Table 2: Various characteristics of patients of OSA with insomnia compared to those of OSA without insomnia

Parameter	OSA with insomnia $(n = 29)$	OSA without insomnia ( $n = 160$ )	p-value
Demographic parameters			
Age	52.10 ± 10.20	51.03 ± 10.43	0.61
Sex (male:female)	18:11 (62.07:37.93%)	122:38 (76.25:23.75%)	0.108
BMI (kg/m²)	31.33 ± 4.85	$32.44 \pm 6.36$	0.37
Smoking status (Yes:No)	10:19	62:98	0.662
Sleep-related parameters			
ESS score (mean score)	12.31 ± 7.13	15.24 ± 5.96	0.019
AHI (events/hour)	23.84 ± 19.91	34.95 ± 23.97	0.019

p < 0.05, significant; p > 0.05, non-significant; AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth sleepiness score; OSA, obstructive sleep

Table 3: Prevalence of various comorbidities among patients of OSA with insomnia compared to those of OSA without insomnia

- Parameter	Number of patie		
	OSA with insomnia (n = 29)	OSA without insomnia (n = 160)	p-value
Obesity	16 (55.17)	100 (62.5)	0.456
Hypertension	15 (51.72)	90 (56.25)	0.651
Diabetes	8 (27.59)	51 (31.87)	0.646
Gastroesophageal reflux disorder	16 (55.17)	91 (56.87)	0.864
COPD	7 (24.14)	26 (16.25)	0.303
Other OAD	6 (20.69)	24 (15)	0.440
Hypothyroidism	4 (13.79)	15 (9.37)	0.466
Cardiac disease IHD	0 (0)	11 (6.87)	0.145
Depression	3 (10.34)	0 (0)	<0.001
Bipolar disorder	0 (0)	1 (0.625)	0.669

p < 0.05, significant; p > 0.05, non-significant; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; OAD, obstructive airway disease; OSA, obstructive sleep apnea

activation caused by respiratory events can also cause hyperarousal and insomnia. Nocturia also contributes to frequent nocturnal awakenings. There are reports of precipitation of insomnia following treatment of OSA. Older age, menopause, and other systemic diseases may contribute to the development of insomnia in these patients. Contrarily, insomnia also has a role in the pathogenesis of OSA. Sleep deprivation and sleep fragmentation in insomnia adversely affect the tone of the pharyngeal muscles, genioglossus in particular. This leads to higher collapsibility of the upper airways and worsening of OSA. <sup>10,21</sup> We have attempted to find out the frequency of this deadly duo among North Indian patients with OSA. To the best of our knowledge, this study is the first of its kind from India. The prevalence of OSA–insomnia overlap in our study was 15.34%. The prevalence of insomnia among OSA in the Western population varies from 6.4% to 84%.<sup>14–17</sup>

Our prevalence was on the lower side of the observed range. This might be due to the stringent criteria used in our study or actual lower regional prevalence. Also, as per the recent change in the diagnostic criteria for insomnia, in the DSM-V, non-restorative sleep or poor sleep quality is no longer a part of the insomnia diagnosis. Patients with OSA more commonly present with non-restorative sleep than sleep initiation and maintenance difficulties. So, according to the new criteria, there is a high likelihood that the prevalence of insomnia among OSA would decrease. Hence, prior studies that had included the older criteria had possibly recorded a higher prevalence. 5,22,23

A recent systematic review and meta-analysis by Zhang Y et al., has analyzed the prevalence rates of insomnia or insomnia symptoms among OSA as per six regions classified by the World Health Organization.<sup>14</sup> It included only one study from the South East Asia region. The study from India by Hasan et al. had evaluated only one of the insomnia symptoms, that is, difficulty in maintaining sleep in OSA. However, they did not find the prevalence of insomnia as a disorder. They recorded 92% of patients with OSA had difficulty maintaining sleep.<sup>24</sup> In our study also, the occurrence of any symptom of insomnia was seen in 78.31% of patients, however, only 15.34% satisfied the diagnostic criteria for insomnia. This might be because most patients usually have one or more symptoms related to insomnia but do not actually have insomnia.

We also found a high prevalence of insomnia among patients without OSA (13.11%). The comparatively similar prevalence among the patients with non-OSA ailments might be because of similar clinical presentation of OSA and insomnia. Both the disorders present with night-time sleep difficulty associated with daytime consequences. Insomnia is often considered in the differential diagnosis of OSA. Earlier studies have also shown a high prevalence of insomnia (57.6% by Bjorvatn et al.) among patients presenting with symptoms of OSA.<sup>22</sup>

Our study showed a higher prevalence of insomnia among women (22.45%) compared to men (12.86%) similar to earlier studies by Cho et al. and Vozoris NT.<sup>18,25</sup> Also, we found that obese patients with OSA were unlikely to have insomnia. This might be attributed to the higher daytime sleepiness and ESS scores observed in obese patients.<sup>26</sup> We also observed that insomnia prevalence decreased with the increasing severity of OSA. Smith et al. and Hagen et al. found no association between the prevalence of insomnia symptoms and the severity of OSA, whereas Bjorvatn et al. and Krell et al. have shown findings similar to ours.<sup>12,23,27,28</sup> On comparison of the polysomnographic findings among the patients of OSA with insomnia and OSA without insomnia, we

found those with OSA–insomnia overlap had significantly lower AHI compared to OSA alone (23.84  $\pm$  19.91 vs 34.95  $\pm$  23.97 events/hour, p = 0.019). An earlier study by Cho et al. showed no significant difference.<sup>18</sup>

We did not find any significant difference in the prevalence of cardiovascular and other comorbidities except for depression. Similar to our study, earlier studies have also reported a higher frequency of psychiatric disorders among OSA-insomnia overlap patients compared to OSA alone, but not cardiovascular symptoms. <sup>16,25</sup> In contrast, Gupta and Knapp from a nationally representative sample from the USA found that OSA with insomnia was significantly more frequently associated with cardiovascular diseases but not psychiatric disorders. This might be attributed to the stringent diagnostic criteria used in their study for the diagnosis of psychiatric disorders. <sup>15</sup> Recently, Cho et al. also found a higher rate of heart disease in OSA with insomnia in the Korean population, but there was no difference for hypertension and diabetes. <sup>18</sup> Possibly a study with a larger sample size will be exactly able to confirm or refute the findings in the Indian population.

The OSA-insomnia overlap has significant diagnostic and therapeutic implications. The history pertaining to insomnia should be taken prior to polysomnography as it will help in deciding which type of study the patient should undergo. As per the AASM guidelines, for patients with a high pretest probability of moderateto-severe uncomplicated OSA, type III study is recommended. However, in patients with comorbidities and other sleep disorders including severe insomnia, type I study is indicated.<sup>29,30</sup> This is because total recording time and total sleep duration are not the same in patients with OSA-insomnia overlap and may result in falsely low AHI. The treatment of OSA-insomnia overlap differs from OSA alone as the overlap patients may require a hypnotic drug as add-on therapy to improve compliance with CPAP. Benzodiazepines are the preferred drugs for insomnia; however, should be avoided for overlap patients because they might exacerbate OSA. The nonbenzodiazepine hypnotics such as zolpidem and eszopiclone are the ideal choice.<sup>21</sup>

Our study is limited by the fact that the study population consisted predominantly of North India. So, the prevalence cannot be generalized to all over India because there might be some regional variation.

To conclude, since there are diagnostic and therapeutic implications in patients with OSA–insomnia overlap and the prevalence is high, all patients of OSA especially women with lower ESS, AHI, and BMI should be evaluated for insomnia.

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