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Symptoms of Insomnia among Patients with Obstructive Sleep Apnea Before and After Two Years of Positive Airway Pressure Treatment

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Study Objectives: To assess the changes of insomnia symptoms among patients with obstructive sleep apnea (OSA) from starting treatment with positive airway pressure (PAP) to a 2-y follow-up.
Design: Longitudinal cohort study.
Setting: Landspitali—The National University Hospital of Iceland.
Participants: There were 705 adults with OSA who were assessed prior to and 2 y after starting PAP treatment.
Intervention: PAP treatment for OSA.
Measurements and Results: All patients underwent a medical examination along with a type 3 sleep study and answered questionnaires on health and sleep before and 2 y after starting PAP treatment. The change in prevalence of insomnia symptoms by subtype was assessed by questionnaire and compared between individuals who were using or not using PAP at follow-up. Symptoms of middle insomnia were most common at baseline and improved significantly among patients using PAP (from 59.4% to 30.7%, $P < 0.001$). Symptoms of initial insomnia tended to persist regardless of PAP treatment, and symptoms of late insomnia were more likely to improve among patients not using PAP. Patients with symptoms of initial and late insomnia at baseline were less likely to adhere to PAP (odds ratio [OR] 0.56, $P = 0.007$, and OR 0.53, $P < 0.001$, respectively).
Conclusion: Positive airway pressure treatment significantly reduced symptoms of middle insomnia. Symptoms of initial and late insomnia, however, tended to persist regardless of positive airway pressure treatment and had a negative effect on adherence. Targeted treatment for insomnia may be beneficial for patients with obstructive sleep apnea comorbid with insomnia and has the potential to positively affect adherence to positive airway pressure.
Keywords: Adherence, CPAP, insomnia, obstructive sleep apnea
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INTRODUCTION

Chronic insomnia and obstructive sleep apnea (OSA) are two of the most common sleep disorders. Several studies have documented extensive comorbidity with these disorders, with the prevalence of insomnia symptoms in patients with OSA (40-60%) far exceeding that in the general population.[1-6] When these disorders coexist, not only is there an increase in cumulative morbidity, but it is likely that these two diseases interact to promote overall greater illness severity and influence each other in negative ways.[3] Further, the co-occurrence of OSA and insomnia symptoms may complicate OSA treatment and reduce PAP adherence. Recent reviews have called for more research on the comorbidity between insomnia and OSA.[7-10]

Insomnia is not, however, a homogenous disorder. There are a variety of types and subtypes. The subtypes of insomnia are typically characterized as difficulties initiating sleep (initial insomnia), difficulties maintaining sleep (middle insomnia), and early morning awakenings (late insomnia).[1] OSA may serve as a predisposing and/or a precipitating factor for each of the subtypes of insomnia. It also may be the case that one or more of the insomnia subtypes respond differently to OSA treatment and/or are associated with different levels of OSA treatment adherence.

Treatment with positive airway pressure (PAP) is the first-line treatment for OSA, but it can be difficult for patients to tolerate PAP and studies have shown that as few as 50% of patients adhere to the treatment over time.[11,12] Currently, few studies have (1) assessed the relative prevalence of insomnia subtypes in patients with OSA, (2) explored how PAP affects insomnia that is comorbid with OSA (both overall and by subtype), and (3) evaluated how insomnia affects PAP adherence. Of the studies that exist, the findings are mixed.[13-15] Nguyen et al.[13] showed that even though insomnia symptoms were highly prevalent among patients with OSA, they had no effect on PAP adherence. In contrast, Wickwire et al.[14] showed that symptoms of middle insomnia were related to poor PAP adherence; in addition, a recent study by Pieh et al.[15] found a negative effect of psychological factors related to insomnia symptoms on PAP adherence.

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In our previous study,[2] we found that most patients with untreated OSA had symptoms of middle insomnia but the prevalence of initial insomnia was the same as in the general population. Another study found symptoms of middle insomnia to be the most common subtype among patients with OSA.[16] Theoretically, it is surprising that patients with OSA might find it difficult to fall asleep at night because excessive daytime sleepiness (EDS) is a common symptom of untreated OSA. However, it seems likely that repeated breathing disturbances could result in sleep fragmentation and hence middle or late insomnia. Therefore, patients who wake up frequently because of apneic episodes may experience more refreshing sleep when using PAP and as a result adjust favorably to the treatment. Initial insomnia may be expected to diminish adherence to PAP because patients are awake longer and thus more likely to experience the adverse aspects of this treatment (e.g., mask or airflow discomfort) for longer periods of time.[12]

The purpose of the current study was to compare the prevalence of symptoms of initial, middle, and late insomnia in patients with OSA prior to and following the start of PAP treatment, as well as to explore the changes in insomnia symptoms by subtype in individuals who were or were not using PAP at follow-up. It was hypothesized that symptoms of middle insomnia would have the strongest association with untreated OSA and would therefore improve significantly among patients on PAP treatment. However, we expected that symptoms of initial and late insomnia would be more resistant to change despite successful treatment of OSA and that patients with these symptoms would more likely not be using PAP at follow-up.

PATIENTS AND METHODS

Patients in whom OSA had been diagnosed in Iceland and who were referred for PAP treatment to Landspitali—The National University Hospital of Iceland in Reykjavik (the only site in Iceland providing PAP treatment) from September 2005 through December 2009 were invited to participate in the study. They are part of the Icelandic Sleep Apnea Cohort (ISAC).[3] OSA had been recently diagnosed in all enrolled participants (minimum apnea-hypopnea index [AHI] of 15 events/h) and these patients were about to begin PAP treatment. Two y after treatment initiation, participants were invited for a follow-up visit where treatment adherence was examined and baseline assessments were repeated.

Questionnaire and Procedures

All participants were invited to the outpatient clinic at Landspitali—The National University Hospital of Iceland in Reykjavik. The study was approved by Iceland´s National Bioethics Committee, the Data Protection Authority of Iceland, and the Institutional Review Board of the University of Pennsylvania. After a written informed consent was obtained from the research participants, they answered standardized questionnaires about their health and sleep. Additional details are provided in the study by Bjornsdottir et al.[2]

Insomnia Definition

Insomnia symptoms were defined using answers to three questions from the Basic Nordic Sleep Questionnaire. "I have difficulties falling asleep at night" (initial insomnia), "I wake up often during the night" (middle insomnia), and "I wake up early in the morning and can't fall back asleep" (late insomnia).[17] Patients were not asked to refer to a specific time period when answering these questions. Answers were rated on a five-point scale: never/almost never (1); less than once a week (2); once or twice a week (3); three to five times a week (4); every day or almost every day of the week (5). Those who scored ≥ 4 on one or more of these items were defined as having insomnia of that subtype. A patient with insomnia could be classified as having one or more subtype.

Quality of Life

Participants completed the 12-Item Short Form Health Survey (SF-12) questionnaire to assess quality of life. Two summary component scores were derived from the SF-12: physical and mental health summary scores.[18] These scores range from 0-100, where a score of zero indicates the lowest life quality and 100 indicates the highest life quality.

Excessive Daytime Sleepiness

Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS), a brief questionnaire that measures daytime sleepiness.[19] Participants with ESS score ≥ 10 were considered to have excessive daytime sleepiness.

Sleep Apnea Assessment

All participants had a sleep study while untreated with a type 3 portable sleep monitor (Natus Medical Inc, San Carlos, CA, USA or NoxMedical, Reykjavik, Iceland). The same signals were recorded by each monitor. To test for systematic differences in the measurement of OSA severity by the Embla (available from Natus Medical) versus NoxMedical monitors, simultaneous overnight recordings were obtained in 12 patients. No significant differences were found in the AHI or oxygen desaturation index (ODI) measured with the different devices. A two-way random effect model for Intraclass Correlation Coefficient (ICC) for consistency showed that the ICC for AHI was 0.99 ($P < 0.001$) and the ICC for ODI was 0.97 ($P < 0.001$).

The sleep recordings were rescored in a uniform manner by a centralized scoring laboratory using the Somnologica Studio (Natus) software. Scoring of a hypopnea required a ≥ 30% decrease in airflow with ≥ 4% oxygen desaturation or a ≥ 50% decrease in airflow for ≥ 10 sec with a sudden increase in flow at the end of the event. Scoring of an apnea required a ≥ 80% decrease in flow for ≥ 10 sec. The ODI was calculated as the number of falls in oxygen saturation of ≥ 4% per h of recording. Additional details are provided in the study by Arnardottir et al.[20]

PAP Use

All patients prescribed PAP were taken care of at the Department of Respiratory Medicine and Sleep, Landspitali University Hospital. Patients on PAP had direct access to the outpatient clinic where trained staff helped them to find the type of device and settings they needed. Various mask types and heated humidifiers were available. PAP users were all in a constantly updated register and they paid a monthly service fee.

PAP adherence at follow-up was estimated based on downloads of usage in the previous 4 w from memory cards (objective data), if available, from ResMed S8 machines (ResMed

Corp. San Diego, CA, USA). Some patients had older PAP devices that did not allow for this type of download. Self-reported data from all patients (subjective data) was also collected at the follow-up visit, based on three multiple choice questions about average PAP use: (1) Do you use PAP for your sleep apnea? (Response alternatives: yes, no, or don't know) (2) How many nights/w do you use PAP? (Response alternatives: 1, 2, 3, 4, 5, 6, or 7 nights/w) and 3) How much of the sleeping time each night do you use PAP? (Response alternatives: all the sleeping time [100%]; almost all the sleeping time [80-99%]; most of the sleeping time [60-79%]; about half of the sleeping time [40-59%], about one third of the sleeping time [20-39%]; almost none of the sleeping time [1-19%]; none of the sleeping time [0%]; don´t know).

Statistical Analyses

All statistics were calculated with STATA 11.0 for Windows (Stata Corporation, College Station, TX, USA). Change in the prevalence of insomnia symptoms with PAP treatment was estimated using population-averaged generalized estimating equations for binomial outcome. The Wald test was used to examine differences in change of prevalence by level of PAP use. Logistic regression was used to analyze risk factors for PAP nonusers at follow up. A P value ≤ 0.05 was deemed statistically significant.

RESULTS

Population Characteristics

At baseline, 822 patients with untreated OSA were enrolled in the study and 90% (n = 741) came to the 2-y follow-up (average ± standard deviation [SD] time between baseline and follow-up visit was 774 ± 135 days). Of these patients, three did not answer the insomnia questions and were therefore excluded from the analyses. In addition, 33 were excluded because they were using a mandibular device instead of PAP at the follow-up. The final study cohort was therefore n = 705 (568 males [80.6%] and 137 females [19.4%]). Additional details are presented in Figure 1.

There was no baseline difference in the distribution of insomnia symptoms, OSA severity, or other main characteristics between the 117 patients who were excluded or did not finish the follow-up and the final study cohort.

Table 1 provides the baseline characteristics of the study population while untreated. The women were on average 4 y older and were more likely to report symptoms of initial insomnia.

Prevalence of Insomnia at Baseline

The prevalence of the three different insomnia subtypes was assessed prior to and 2 y after starting PAP treatment. At baseline, 15.5% of patients exhibited symptoms of initial insomnia, 59.3% had symptoms of middle insomnia, and 27.7% exhibited symptoms of late insomnia. The prevalence of having some type of insomnia symptoms at baseline was 68.3%, but there was considerable overlap between the three different insomnia subtypes, with most patients having more than one symptom of insomnia (Figure 2). Almost half of those who had symptoms of initial insomnia at baseline also had symptoms of middle and late insomnia. Most of those with symptoms of late insomnia at baseline also had symptoms of middle insomnia. Interestingly, most of those with symptoms of middle insomnia did not present with one or the other subtypes. As a result, 33% of the sample had symptoms of isolated middle insomnia at baseline

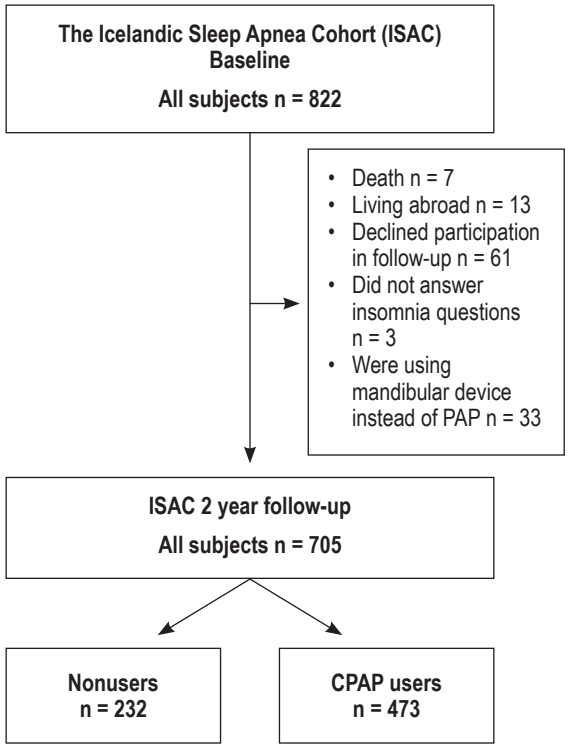

Figure 1—Flow chart of participants.

Table 1—Baseline characteristics of the study population

	All patients (n = 705)	Men (n = 568)	Women (n = 137)	P value for sex difference
Age	54.9 ± 10.2	54.1 ± 10.3	58.4 ± 8.9	**< 0.001**
Body mass index	33.7 ± 5.6	33.6 ± 5.5	32.3 ± 6.0	0.18
AHI	45.5 ± 20.5	46.0 ± 20.5	43.1 ± 20.4	0.15
ODI	36.3 ± 20.0	36.9 ± 19.8	33.9 ± 20.8	0.12
ESS	11.9 ± 5.0	11.9 ± 5.0	11.7 ± 5.3	0.60
Smoking history				
Never smoker	27.3%	26.0%	30.7%	0.27
Ex-smoker	53.0%	53.3%	51.8%	0.76
Current smoker	20.1%	20.7%	17.5%	0.40
Hypertension	46.5%	45.5%	50.4%	0.30
Diabetes	8.5%	8.6%	8.1%	0.84
Initial insomnia	15.5%	12.5%	27.9%	**< 0.001**
Middle insomnia	59.3%	57.8%	65.7%	0.09
Late insomnia	27.7%	26.6%	32.1%	0.20

AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale score; ODI, oxygen desaturation index. Significance is indicated in bold.

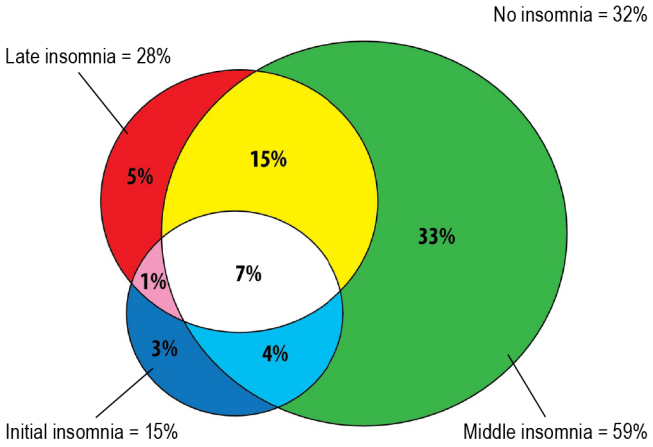

Figure 2—Baseline prevalence of insomnia symptoms among all patients.

Table 2—Baseline differences between those with isolated middle insomnia and those with other symptoms of insomnia (initial, late or mixed)

	Isolated middle insomnia (n = 244)	Other type of insomnia (n = 258)	P value
Age	55.2 ± 10.7	55.5 ± 9.6	0.77
BMI	34.2 ± 6.1	33.1 ± 5.5	**0.04**
AHI	48.4 ± 21.1	41.6 ± 20.0	**< 0.001**
ODI	39.1 ± 21.2	32.5 ± 18.2	**< 0.001**
ESS	12.5 ± 5.0	11.8 ± 5.0	0.11
SF-12 PS	39.3 ± 11.1	39.0 ± 11.0	0.77
SF-12 MS	49.1 ± 10.0	45.7 ± 11.2	**< 0.001**

AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale score; ODI, oxygen desaturation index; SF-12 MS, mental quality of life; SF-12 PS, physical quality of life. Significance is indicated in bold.

and these patients were more obese, had more severe OSA (i.e., a higher AHI) and better mental quality of life compared with patients with other symptoms of insomnia (initial, late, or mixed insomnia) (Table 2).

PAP Use and Estimate of Adherence

Among the 705 patients who completed the follow-up, 473 reported current PAP use and 232 reported being nonusers. Objective data were available for 77.6% of PAP users (367 of 473), and based on these data the average (± SD) use per night was 6.2 (± 2.0) h for the last 4 w. Only 46 of those individuals used the device less than 4 h per night on average. At baseline all patients were prescribed automatic positive airway pressure (autoPAP) and treatment was changed to continuous positive airway pressure (CPAP) if the pressure requirements over the night were stable. Of the PAP users, 53% were on autoPAP and 43% were on fixed CPAP, 3% on bilevel pressure (BiPAP), and 1% on adaptive servoventilation. Treatment was only changed to BiPAP or adaptive servoventilation if treatment efficacy was inadequate. The average (± SD) PAP pressure was 10.9 (± 1.5) cm H_2O and the pressure below which participants on autoPAP spent 95% of the time over the last 7 days was 11.1 (± 1.9) cm H_2O.

Full Versus Partial Users

Patients using PAP for ≥ 5 days/w and ≥ 4 h/night on average for the past 4 w were considered full users (n = 287 of 367 with objective data). On average, full users were using their device for 26.7 ± 2.0 nights for the last 4 w and 6.8 ± 1.2 h per night based on objective data.

Among the 367 with both objective (memory cards) and self-reported data on frequency of CPAP use, we compared those reporting PAP usage ≥ 5 nights/w and ≥ 60% of the night with those fulfilling criteria for full PAP use based on memory cards (≥ 5 days/w and ≥ 4 h/night). Self-reported data had 98.6% sensitivity and 45.1% specificity in distinguishing full versus partial users. Consequently, objective data were used when available, but for the remaining patients, the self-reported data were used to define patients as full, partial, and non-PAP users. Therefore, a total of n = 372 were classified as full users and n = 101 as partial users (367 and 106 were classified based on objective and subjective data, respectively).

On average, partial users were using their device for 14.3 ± 7.2 nights for the last 4 w and 3.5 ± 2.2 h per night (for all 28 nights) based on objective data.

Among the 232 nonusers, n = 60 (26.0%) returned their devices within 3 mo from starting PAP. Most of the nonusers (n = 133) had a repeat sleep study at the 2-y follow-up. On average, AHI in these individuals increased from baseline to follow-up (mean increase ± SD = 10.7 ± 22.2 events per hour). There were 98% of the 133 patients who still had an AHI > 15 at the 2-y follow-up. A few of the nonusers (n = 11) had lost more than 10 kg from baseline to follow-up but they were not different in insomnia status or OSA severity at follow-up compared with that at baseline. Of these 11 patients, seven had a repeat sleep study at follow-up and they were all still affected with OSA (AHI ≥ 15) despite their weight loss. In total, the nonusers (n = 133) lost on average 0.2 ± 8.2 kg from baseline to follow-up.

The primary analyses of this paper were conducted by comparing all PAP users (full and partial) with nonusers. Additional sensitivity analysis was performed by assessing the three use designations for group differences (full users, partial users, and nonusers). Using three groups of PAP users did not affect the significance of the results. Partial users were not significantly different from full users and therefore we used only two groups for analysis, all PAP users and nonusers. Furthermore, all analysis were repeated using only PAP users with objective data (n = 367), which did not affect the significance of any of the results.

Changes in Insomnia Symptoms from Baseline to Follow-up among PAP Users and Nonusers

Symptoms of Initial Insomnia

The baseline prevalence of symptoms of initial insomnia was 12.9% among those who were PAP users at follow-up, compared with 20.8% among nonusers (P = 0.007). At follow-up, 9.3%

of PAP users had symptoms of initial insomnia compared with 17.7% of nonusers (P = 0.001). Improvement in these symptoms from baseline to follow-up was of the same magnitude for PAP users and nonusers (Table 3 and Figure 3).

In total, 45.9% of those who had symptoms of initial insomnia at baseline also had these symptoms at follow-up. However, there was no baseline difference in regard to age, body mass index (BMI), or OSA severity between those whose initial insomnia improved and those with persistent symptoms of initial insomnia. There was, however, more improvement in daytime sleepiness among those without symptoms of initial insomnia at follow-up (Table 4).

Patients who reported symptoms of initial insomnia at baseline were more likely to be PAP nonusers at follow-up and this effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 5).

Table 3—The difference in changes of insomnia symptoms from baseline to follow-up between positive airway pressure users and nonusers

	Baseline (%)	Follow-up (%)	P_{change}	P*
Initial insomnia				
Nonusers	20.8	17.7	0.25	
PAP users	12.9	9.3	0.03	0.75
Middle insomnia				
Nonusers	59.1	43.5	< 0.001	
PAP users	59.4	30.7	< 0.001	**0.001**
Late insomnia				
Nonusers	36.6	26.0	0.001	
PAP users	23.3	21.2	0.34	**0.05**

*P for difference in change between PAP users and nonusers. PAP, positive airway pressure. Significance is indicated in bold.

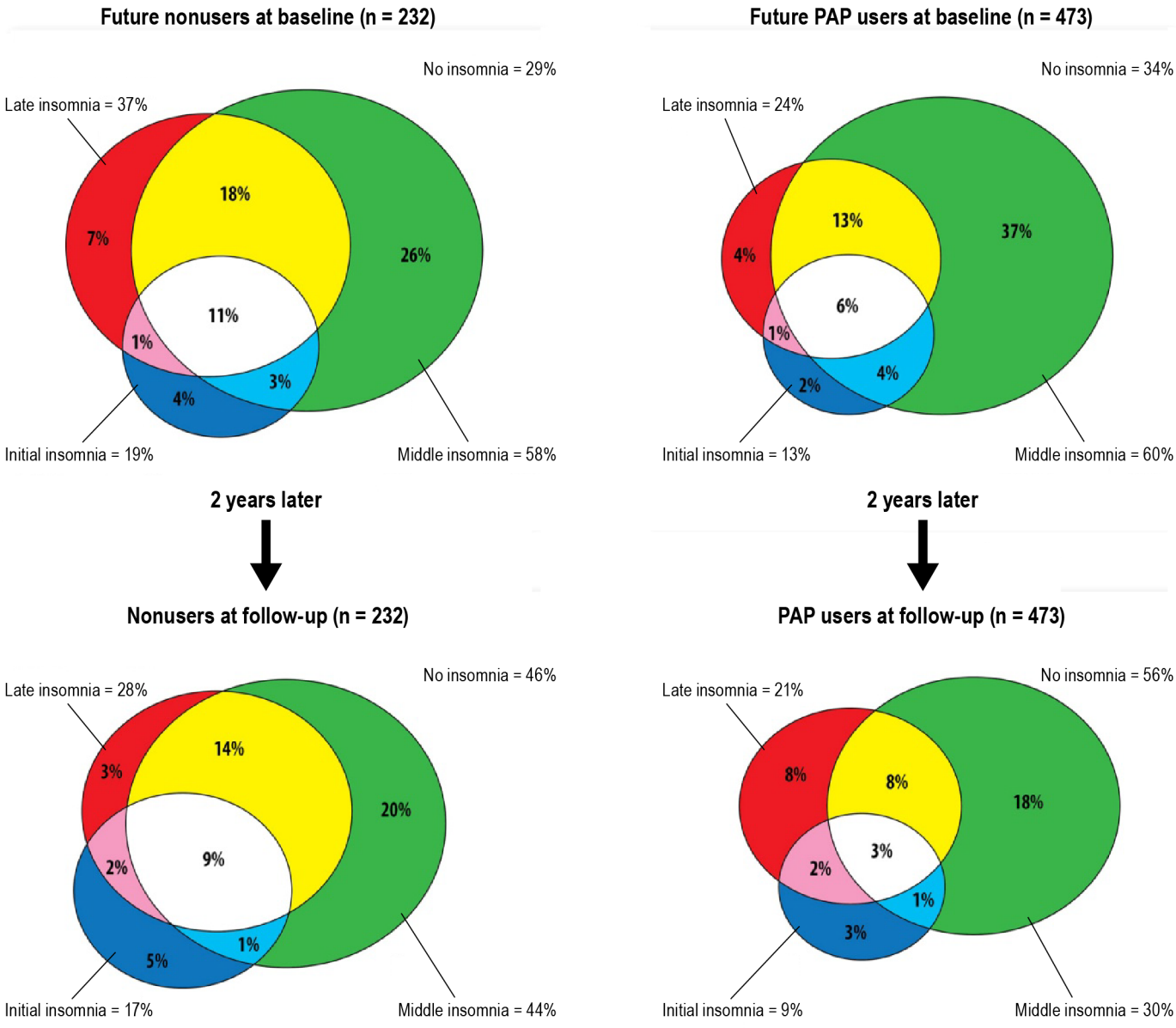

Figure 3—The changes and overlap of insomnia subtypes for both positive airway pressure (PAP) users and nonusers.

Table 4—Change in daytime sleepiness and quality of life among those whose insomnia improved and persisted

	Initial insomnia			Middle insomnia			Late insomnia		
	persisted (n = 50)	improved (n = 59)	P	persisted (n = 199)	improved (n = 219)	P	persisted (n = 91)	improved (n = 103)	P
ESS change	-1.0 ± 4.3	-3.5 ± 4.8	**0.006**	-2.6 ± 4.5	-4.6 ± 5.0	**< 0.001**	-1.8 ± 4.8	-3.9 ± 4.5	**0.002**
SF-12 MS change	-0.5 ± 10.2	1.5 ± 9.9	0.34	1.3 ± 10.0	3.5 ± 9.4	**0.02**	1.4 ± 10.6	2.9 ± 10.0	0.29
SF-12 PS change	3.0 ± 14.3	2.2 ± 13.9	0.78	2.5 ± 11.8	3.3 ± 11.8	0.48	0.3 ± 12.3	4.2 ± 11.7	**0.03**

ESS, Epworth Sleepiness Scale; SF-12 MS, mental quality of life; SF-12 PS, physical quality of life. Significance is indicated in bold.

Table 5—Unadjusted and adjusted effects of insomnia symptoms on PAP nonuse

	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)[a]	P value[a]
Initial insomnia (n = 109)	0.56 (0.37-0.86)	**0.007**	0.59 (0.38-0.91)	**0.01**
Middle insomnia (n = 418)	1.01 (0.73-1.40)	0.93	0.98 (0.70-1.37)	0.89
Late insomnia (n = 194)	0.53 (0.37-0.74)	**< 0.001**	0.55 (0.39-0.79)	**< 0.001**
Isolated middle insomnia (n = 244)	1.61 (1.14-2.27)	**0.007**	1.48 (1.04-2.12)	**0.03**

[a]Adjusted for sex, age, body mass index, and obstructive sleep apnea severity (apnea-hypopnea index and oxygen desaturation index). Significance is indicated in bold. CI, confidence interval; PAP, positive airway pressure.

Table 6—Baseline characteristics among those whose middle insomnia symptoms improved and persisted

	Middle insomnia persisted (n = 199)	Middle insomnia improved (n = 219)	P value
Male (%)	81.0	76.3	0.23
Age	57.3 ± 9.4	54.8 ± 10.2	**0.01**
BMI	32.8 ± 5.1	35.1 ± 6.4	**< 0.001**
AHI	43.4 ± 20.1	47.3 ± 20.9	**0.05**
ODI	33.3 ± 18.5	39.9 ± 20.5	**< 0.001**

AHI, apnea-hypopnea index; BMI, body mass index; ODI, oxygen desaturation index. Significance is indicated in bold.

Symptoms of Middle Insomnia

The baseline prevalence of middle insomnia symptoms was 59.1% among those who were PAP users at follow-up compared with 59.4% among nonusers (P = 0.93). Compared with baseline, there was a significant improvement in symptoms of middle insomnia for both PAP users and nonusers at follow-up (follow-up prevalence was 30.7% among PAP users compared with 43.5% among nonusers; P ≤ 0.001). However, improvement in these symptoms was much more likely to occur among patients who were adherent with PAP treatment (P = 0.001 for difference in change between PAP users and nonusers). See Table 3 and Figure 3 for details.

Patients whose middle insomnia improved (as compared with those with persistent symptoms of middle insomnia) were younger, more obese, and had more severe OSA at baseline (Table 6). There was also greater improvement in physical quality of life and daytime sleepiness among those patients (Table 4).

Having symptoms of middle insomnia overall did not affect PAP adherence, but individuals with symptoms of isolated middle insomnia were more likely to be PAP users at follow-up and the effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 5).

Symptoms of Late Insomnia

The baseline prevalence of having symptoms of late insomnia was 23.3% among those who were PAP users at follow-up compared with 36.6% among nonusers (P < 0.001). Nonusers were more likely to experience improvement in late insomnia compared with PAP users (P = 0.05), improving to levels comparable to those of PAP users (PAP users: 21.2%, nonusers: 26%) (Table 3 and Figure 3).

In total, 46.7% of those who had symptoms of late insomnia at baseline also had these symptoms at follow-up, but there was no baseline difference in regard to age, BMI, or OSA severity between those whose late insomnia improved compared with those with persistent symptoms of late insomnia. Patients whose late insomnia improved did, however, show a greater improvement in mental quality of life and daytime sleepiness (Table 4).

Patients who reported symptoms of late insomnia at baseline were more likely to be PAP nonusers at follow-up and this effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 5).

When looking at how long the mask is worn based on objective PAP data, PAP users with symptoms of late insomnia at follow-up had on average 36 min shorter mask-on time than those without late insomnia (P = 0.02). This difference in mask-on time was not seen for patients with other types of insomnia.

No Insomnia Symptoms

Having no symptoms of insomnia at baseline was equally prevalent among those who were PAP users and nonusers at follow-up (PAP users: 33.3%, nonusers: 28.5%, P = 0.20). At follow-up, 55.7% of PAP users had no insomnia compared with 47.4% of nonusers (P = 0.04). Most patients who reported no symptoms of insomnia at baseline were also without insomnia symptoms at follow-up. However, 22.4% of them reported some insomnia symptoms at follow-up. Developing symptoms of middle and late insomnia were much more prevalent

than developing symptoms of initial insomnia among these patients (12.6%, 13.1%, and 2.7%, respectively). Among those who reported symptoms of insomnia at follow-up, PAP users were most likely to report symptoms of late insomnia whereas nonusers were more likely to report symptoms of middle insomnia ($P < 0.05$) (Figure 4).

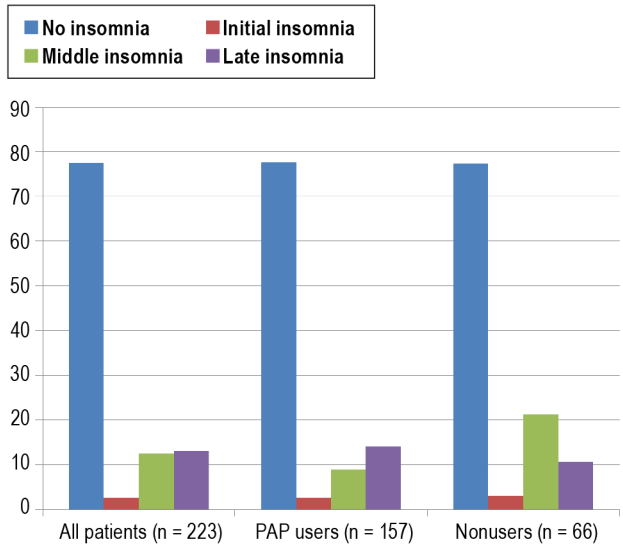

Figure 4—Insomnia status (%) at follow-up among those who had no insomnia symptoms at baseline.

DISCUSSION

The current study shows that insomnia symptoms are common among patients with OSA, especially symptoms of middle insomnia, and these types of symptoms generally improve with PAP treatment. Symptoms of initial insomnia, however, tend to persist even though patients adhere to PAP and can also negatively affect adherence to PAP treatment. Symptoms of late insomnia are (surprisingly) more likely to improve among patients with OSA who are PAP nonusers. Furthermore, some patients with OSA develop insomnia symptoms over the course of treatment. PAP users were more likely to develop symptoms of late insomnia whereas the new onset of middle insomnia symptoms was more common among nonusers.

The high prevalence of middle insomnia among patients with OSA and the indication that these symptoms improve significantly with successful PAP treatment suggests that symptoms of middle insomnia are a consequence of sleep disordered breathing. Our results show that untreated patients with OSA with symptoms of isolated middle insomnia are more obese and have more severe OSA, which supports this theory. This difference in BMI and OSA severity was not present for patients with other types of insomnia symptoms. Another study examining the relationship between insomnia subtypes and daytime sleepiness among patients with OSA also found that those with symptoms of middle insomnia had more severe OSA as well as increased daytime sleepiness compared with patients with symptoms of initial insomnia.[5] The increase in OSA severity among nonusers could therefore possibly cause symptoms of middle insomnia in some patients. The fact that nonusers who had no insomnia at baseline were most likely to develop symptoms of middle insomnia over the study period supports this idea.

In the current study, we saw that patients with symptoms of isolated middle insomnia were more likely to adhere to PAP treatment. A possible explanation is that patients who are waking up frequently during the night while untreated may experience relief both from OSA and insomnia symptoms while being treated with PAP and therefore adjust favorably to the treatment. Conversely, it seems that other mechanisms contribute to symptoms of initial and late insomnia in these patients. Given the negative effects of these subtypes of insomnia on PAP adherence and the indication that these patients do not experience relief from their insomnia despite PAP treatment suggests that some additional intervention is necessary.

We are aware of only one previous study that evaluated the association between insomnia subtypes and PAP adherence. Wickwire et al.[14] conducted a retrospective medical record review of 232 patients with OSA and found that only symptoms of middle insomnia predicted poor adherence to PAP,[14] which contradicts our findings. This discrepancy could partly be explained by the different methods performed, in our study the insomnia assessment was performed at both baseline and follow-up.

Interestingly, symptoms of late insomnia were more likely to improve among nonusers in comparison with PAP users. In general, sleep is not as sound early in the morning as in the beginning of the night when delta sleep is dominant.[21,22] Because of this, patients may be more likely to wake up because of environmental noises, light, or the need to use the bathroom early in the morning. Patients who are using PAP may therefore become more aware of their device when their sleep gets lighter in the morning and for some patients this may disrupt their sleep and cause persistence of late insomnia symptoms. This could also explain why PAP users who had no insomnia at baseline were most likely to develop symptoms of late insomnia. The fact that 13.1% of them had new onset of late insomnia symptoms is noteworthy, especially because the overall prevalence of these symptoms among patients with OSA in this study is not nearly as high as symptoms of middle insomnia, for example.

This study had a number of strengths including the large sample size, the length of the follow-up period, the high response rate at follow-up (> 90%), the use of standardized and validated procedures and instruments, and most importantly being by far the largest study that has looked prospectively at insomnia symptoms among patients with OSA before and following PAP treatment. In addition, this is a clinical sample with various comorbidities, representing the entire spectrum of patients with OSA. Our results have important clinical implications and highlight the need for more studies on additional treatment interventions for patients with OSA and comorbid insomnia.

This study is not, however, without limitations. First, the insomnia definition was based on three questions from the Basic Nordic Sleep Questionnaire describing symptoms; having more detailed questions on insomnia would have been beneficial. However, the definitions we used proved to be very instructive in the context of OSA and we have a previous publication using the same definitions of insomnia.[2] Although the 2-y follow-up is a strength of the study, evaluating the long-term effects of PAP treatment, it can also be considered a limitation. We did not have short-term follow-up results to evaluate the acute effects of

PAP treatment. However, in terms of comparative effectiveness research, what matters to patients is not what happens to them in 1 mo but over the long term. Because this is a cohort study there are many factors that can change in the 2-y study period that may affect insomnia other than the use of PAP treatment. Second, it would have been beneficial to have more detailed information on those patients with initial and late insomnia who stopped using PAP. Did they stop using their device purely because of their insomnia or were there some other underlying reasons? We did not have objective PAP data for all patients but we are confident with the way we estimated PAP use. The lack of objective PAP data on all participants prevented our inclusion of the AHI on the PAP download, a measure of treatment efficacy, as a covariate in our analyses.[23] It is possible that the ability of PAP treatment to reduce AHI to clinically acceptable levels may affect adherence to treatment. Patient-reported nonusage at follow-up was consistent with the patient PAP register, and the results did not change if those without objective PAP data were excluded from the analyses. Finally, this is an observational study, not a randomized controlled trial (RCT), which may be considered a limitation. However, a RCT with such long-term follow-up of severely affected patients with OSA would be difficult to perform for ethical reasons. The importance of observational studies was highlighted in a recent publication of a National Institutes of Health workshop on comparative effectiveness research.[24]

To summarize, our results show approximately 50% reduction in middle insomnia following 2 y of PAP treatment, which suggests that frequent awakenings are a symptom of untreated OSA. Initial and late insomnia, however, did not improve on PAP treatment and these symptoms may negatively affect PAP adherence. These results suggest that initial and late insomnia in patients with OSA are comorbid but unrelated disorders and highlight the importance of including assessment of insomnia subtypes in the management of OSA. Future studies should focus on exploring the benefits of additional interventions prior to or during PAP for patients with OSA and insomnia. For example, it may be useful to undertake a trial of cognitive behavioral treatment for insomnia (CBT-I) prior to or during treatment with PAP to assess whether this intervention not only improves the insomnia in the context of OSA, but whether such treatment increases compliance with PAP, especially in cases of initial and late insomnia. This said, symptoms of initial and/or late insomnia may be undiagnosed advanced sleep phase syndrome or delayed sleep phase syndrome. In these instances, CBT-I may be less helpful and chronotherapeutic strategies may be more useful.

ABBREVIATIONS

AHI, apnea hypopnea index
BMI, body mass index
BPAP, bilevel pressure
CPAP, continuous positive airway pressure
EDS, excessive daytime sleepiness
ESS, Epworth sleepiness scale
ICC, intraclass correlation coefficient
ISAC, Icelandic sleep apnea cohort
ODI, oxygen desaturation index
OR, odds ratio
OSA, obstructive sleep apnea
PAP, positive airway pressure
SF-12, short form 12
SF-12 MS, short form 12 mental score
SF-12 PS, short form 12 physical score

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