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Predictors of Sleepiness in Obstructive Sleep Apnea at Baseline and After 6 months of Continuous Positive Airway Pressure therapy

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Abbreviations:

OSA: Obstructive sleep apnea

CPAP: Continuous positive airway pressure

EDS: Excessive daytime sleepiness

BMI: Body Mass Index

AHI: Apnea-Hypopnea Index

CVD: Cardiovascular Disease

GERD: Gastroesophageal Reflux Disease

DM: Diabetes Mellitus

HAMD: Hamilton Rating Scale for Depression

ESS: Epworth Sleepiness Scale

MWT: Maintenance of Wakefulness Test

MSL: Mean sleep latency

MSL-B: Mean sleep latency on the Maintenance of Wakefulness Test at baseline

MSL-6m: Mean sleep latency on the Maintenance of Wakefulness Test at 6-months after CPAP

initiation

We evaluated factors associated with subjective and objective sleepiness at baseline and after 6 months of continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnea (OSA).

We analyzed data from the Apnea Positive Pressure Long-term Efficacy Study (APPLES), a prospective 6-month multicenter randomized controlled trial with 1105 subjects with OSA, 558 of who were randomized to active CPAP. Epworth sleepiness scores (ESS) and the mean sleep latency (MSL) on the maintenance of wakefulness test at baseline and after 6 months of CPAP therapy were recorded.

Excessive sleepiness (ESS > 10) was present in 543 (49.1%) participants. Younger age, presence of depression and higher apnea-hypopnea index (AHI) were associated with higher ESS scores and lower MSL. Randomization to the CPAP group was associated with lower odds of sleepiness at 6-months. The prevalence of sleepiness was significantly lower in those using CPAP >4hours /night versus using CPAP ≤4 hours a night. Among those with good CPAP adherence, those with ESS >10 at baseline had significantly higher odds (OR 8.2, P<0.001) of persistent subjective sleepiness.

Lower average nightly CPAP use and presence of sleepiness at baseline were independently associated with excessive subjective and objective sleepiness after 6 months of CPAP therapy.

Excessive daytime sleepiness (EDS) is frequently reported in patients with obstructive sleep apnea (OSA). Conversely, OSA has been suggested to be the most common medical disorder that causes EDS. [1] A variety of factors may be associated with EDS in OSA patients. Several studies have assessed the association between the apnea-hypopnea index (AHI) and sleepiness, but while some studies found an association between AHI and EDS, [2-5] others did not.[6-8] Obesity, oxygen desaturation index and depressive symptoms have also been associated with EDS in OSA patients. [9-11] However, many of these studies had small sample sizes or did not have objective means of assessment such as the multiple sleep latency test (MSLT) or maintenance of wakefulness test (MWT). Furthermore, while several medical and psychiatric disorders have been associated with poor sleep quality and insomnia,[12-14] there are few investigations assessing the impact of comorbid disorders on sleepiness in OSA. Finally, there are few large studies assessing the factors associated with residual sleepiness in patients on CPAP therapy.

The Apnea Positive Pressure Long-term Efficacy Study (APPLES) was a prospective multicenter randomized controlled trial designed to assess the impact of CPAP on several domains of neurocognitive outcomes in adults with OSA. Participants with OSA were randomized to either active CPAP or sham CPAP for 6 months. The subjects completed a number of questionnaires including the Epworth sleepiness scale (ESS) and underwent several tests including the MWT at baseline and 6 months after initiation of CPAP therapy.

In this report, we evaluated the prevalence of subjective and objective sleepiness as well as demographic and polysomnographic variables and medical and psychiatric conditions associated with sleepiness in participants with OSA. We also assessed the factors associated with sleepiness after 6-months of CPAP therapy. Specifically, we aimed to evaluate the impact of different levels of CPAP adherence on prevalence of sleepiness.

METHODS:

Study Design

The APPLES protocol has been described in detail elsewhere.[15] In brief, participants were recruited from sleep clinics and through public advertisements at 5 sites: Stanford University, Stanford, CA; University of Arizona, Tucson, AZ; Providence St. Mary Medical Center, Walla Walla, WA; St. Luke's Hospital, Chesterfield, MO; and Brigham and Women's Hospital, Boston, MA. Those who did not have exclusion criteria during the initial interview and consented to participate in the study underwent a diagnostic polysomnogram (PSG). Those who had an AHI ≥ 10/h without severe oxygen desaturation (*i.e.,* oxygen saturation < 75% for > 10% of the diagnostic sleep study) were randomized to either active or sham CPAP (REMStar Pro, Phillips Respironics, Murrysville, PA) for 6 months. The participants randomized to active CPAP then underwent a titration in the sleep laboratory to determine the optimal therapeutic pressure. A sham titration was performed for those randomized to sham CPAP. Although participants' adherence was monitored continuously during the study, for this report we calculated adherence at the 6-month time point after initiation of CPAP.

Participants

Of the 1516 participants screened, 1105 were ultimately randomized [268 participants removed from study pre-randomization due to exclusion criteria (e.g., taking exclusionary medication); 143 participants withdrew study "pre-randomization" for any reason (e.g., too busy)],[15] with 558 assigned to active CPAP and 547 assigned to sham CPAP. Heated humidification was used in all participants. Staff (*e.g.,* respiratory therapists, sleep technologists, physicians) worked in a systematic manner to troubleshoot nasal congestion and other problems that may have been reported by a participant. Subjects using hypnotics, anxiolytics, sedating antidepressants, anticonvulsants, sedating antihistamines, stimulants, or other medications likely

to affect neurocognitive function and/or alertness were excluded from the study. Some subjects were on antidepressants and some on opioids, including that in antitussive medications.

Pre-existing Medical Conditions:

At their baseline visit, all participants underwent a clinical evaluation including a physical examination to obtain a medical history and information pertaining to symptoms of sleep disorders, and presence of other medical and psychiatric conditions such as cardiovascular disease (CVD), gastroesophageal reflux disease (GERD), chronic pain, nasal congestion and depression. A condition was considered present when the participant answered that they currently had it. Furthermore, the Hamilton Rating Scale for Depression (HAMD)[16] was administered at baseline and at the 6-month post-CPAP follow-up visit. We considered a score ≥ 8 as indicative of depression being present.

Epworth Sleepiness Scale (ESS)[17,18]

The ESS is one of the most widely used assessments of subjective daytime sleepiness. It is a self-administered questionnaire where individuals rate their usual chances of dozing off or falling asleep in 8 common situations or activities on a 4-point scale (0 – 3). Hence, the minimum possible score on the scale is 0 (not sleepy at all) and the maximum is 24 (extremely sleepy). The ESS was administered at baseline and at 6 months after starting active CPAP or sham CPAP. Sleepiness was considered clinically significant if the ESS total score was > 10.

Maintenance of Wakefulness Test (MWT)[18,19]

The MWT test is used to assess objective daytime sleepiness. With the participant sitting in bed with eyes open, it measures sleepiness when the intent is to stay awake. Hence, it provides an objective estimate of the propensity to fall asleep when people would want to stay awake during their normal day. The MWT was performed at baseline and at the 2- and 6-month follow-up

visits. For this study, we used the tests performed at the baseline and 6-month follow-up visits. Briefly, after overnight PSG (diagnostic at baseline and with patient's own CPAP at 6 months), four 20-min trials were conducted at 10:00 AM, 12:00 noon, 2:00 PM, and 4:00 PM. A trial was ended after 20 minutes or after 3 consecutive 30-second epochs of any stage of sleep, whichever occurred first. Once a trial was terminated, the room lights were turned on and the subject was asked to open his or her eyes, stay seated in bed, and remain awake until the 20 min of the trial had elapsed. The mean sleep latency (MSL) of all 4 trials was used for these analyses. Interrater reliability assessments were conducted for PSGs and MWTs blindly scored by the Data Coordinating Center PSG Technologists, and the Data Coordinating Center was responsible for further quality assurance/quality control procedures for these data.[15]

CPAP Adherence

Adherence to active CPAP or sham CPAP was measured objectively using Encore Pro SmartCards (Phillips Respironics, Inc., Murrysville, PA) that were exchanged at the clinic twice monthly. For this report, at the 6-month period after start of CPAP, the mean hours of daily use were analyzed for the preceding 2-month period to assess adherence during that time interval. The Smart Card is a memory card that records data regarding the duration of each CPAP therapy use and provides reliable objective evidence of CPAP use.

Statistical Analyses

To assess the factors associated with sleepiness at baseline, we included all 1105 participants. For the 6-month analyses, we focused only on those randomized to active CPAP therapy with relevant data available. For assessment of residual sleepiness in those with good adherence, analyses were limited to those participants who were using CPAP >4 hours a night. For continuous variables, unadjusted comparisons between groups were made using Student's unpaired t-test. Data were expressed as mean ± SD. Differences in proportions were assessed

using the χ^2 test. Logistic regression was used to assess odds ratios (with 95% confidence intervals) for sleepiness (ESS >10) at baseline and at 6 months after CPAP initiation, with predictors of interest including demographic and polysomnographic characteristics and comorbid conditions. A multiple regression model was used to examine the association between the ESS scores and MSL values as dependent variables, with demographic and polysomnographic characteristics and comorbid conditions at baseline and at 6 months. The statistical significance level was set at $P<0.05$ (2-tailed) for all tests. Statistical analyses were conducted using SPSS v 20.0 for Windows (SSPS Inc, Chicago, IL).

RESULTS

Sleepiness at baseline

A total of 1105 participants were assessed, including 382 women and 723 men, of whom 611 (55%) had severe OSA defined as AHI >30. The baseline demographics for all participants and subsequently randomized participants stratified by gender are provided in an earlier publication.[20] Briefly, the mean age of the participants was 51.5 (12.2), mean BMI was 32.2 (7.1) mean AHI was 38.2 (26.7) and the mean Oxygen Desaturation Index was 25.5 (25.1). The mean baseline ESS of the participants was 10.4±4.4 (minimum 0, maximum 22). In bivariate analyses, women were significantly sleepier (ESS 10.9±4.5 vs. 10.2±4.3, P=0.006) than men. There was a trend for severe sleep apnea to be sleepier than those without severe sleep apnea (ESS 10.7±4.5 vs. 10.2±4.3, P=0.07). The ESS scores correlated directly with BMI, several polysomnographic variables including AHI, and HAMD score, and inversely with age (Table 1). Of the 1105 participants, 543 (49.1%) had excessive sleepiness (ESS > 10). As shown in Table 2, the ESS total scores as well as proportion of participants who were sleepy (ESS > 10) were higher in those with depression and chronic pain. Except for a trend towards greater sleepiness in those with GERD, no differences were observed in a variety of other medical and psychiatric conditions. Of all subjects, 196 were on antidepressants and 73 were on opiates. The use of antidepressants (P=0.31) or opiates (P=0.15) was not significantly associated with greater sleepiness.

A linear regression model revealed younger age, higher AHI and elevated HAMD scores to be independently associated with higher ESS total scores (Table 3a). Logistic regression showed higher odds of sleepiness in those with depression (HAMD scores ≥8, OR=1.4, P=0.03) and lower odds with increasing age (Table 3b).

The MWT MSL at baseline (MSL-B, n=1086) was 17.0 minutes (minimum 1.9 minutes, maximum 20 minutes). An MSL-B equal to 20 minutes was seen in 521 participants (48%) and an MSL-B <20 minutes in 565 participants (52%). For these analyses, a MSL <20 minutes was considered abnormal. Notably, we repeated analyses using MSL ≤17 minutes as abnormal, which was seen in 37.5% (n=407) of all participants at baseline. The results obtained using this cutoff to define sleepiness were generally similar to those obtained using MSL <20 minutes as abnormal.

As expected, MSL-B was significantly lower in those with ESS >10 than those with ESS ≤10 (16.3±4.3 minutes vs. 17.7±3.5 minutes, P<0.001). Of those with ESS >10, 61.2% had a MSL-B <20 minutes compared to only 43.2% in those with ESS ≤10 (P<0.001). Logistic regression showed that younger age, presence of depression and AHI >30 were associated with higher odds of sleepiness (MSL-B <20 minutes) (Table 3c).

<u>Sleepiness at 6 months after CPAP initiation</u>

The mean age of the participants randomized to CPAP was 52.2 ± 12.1 years, mean BMI was 32.3 ± 7.4, mean AHI was 39.5 ± 24.9 and the mean Oxygen Desaturation Index was 26.3 ± 24.1. At 6-month period, the mean AHI in this group was 6.1 ± 8.3 and the mean Oxygen Desaturation Index was 4.8 ±7.3. In contrast, the mean AHI in the sham group at 6 months was 29.8 ± 25.1 and the mean Oxygen Desaturation Index was 24.8 ±24.9. The ESS was significantly lower in the CPAP group compared to the sham group at 2-month (7.9 vs. 8.8, P=0.003), 4- month (7.0 vs. 8.2, P<0.001) and 6- month (7.3 vs. 8.4, P=0.003) periods after initiation of therapy despite similar ESS at baseline (10.5 vs. 10.5, P=0.99).

At 6 months, 88 (22.3%) of the 394 participants initiated on CPAP had excessive sleepiness defined as ESS >10. The mean nightly adherence at 6 months in those randomized to active CPAP was 4.70 ± 2.04 hours and 67.3% of the participants were using CPAP > 4 h per night. Further details of adherence in the study participants are provided in an earlier publication.[21] The prevalence of sleepiness generally declined progressively with increasing CPAP use (Figure 1). The prevalence of sleepiness was higher in those using CPAP ≤4 hours/night versus those using CPAP >4hours a night (31% vs. 18%, P=0.003). Fewer hours of CPAP use and higher ESS total scores at baseline were independently associated with higher 6-month ESS total scores in a linear regression model (Table 4a). A logistic regression model (Table 4b) showed lower odds of sleepiness in those using CPAP >4 hours a night (OR=0.42, P=0.001), and higher odds in those who were sleepy at baseline (OR=5.1, P<0.001). Women had lower odds of sleepiness than men, the presence of chronic pain was associated with higher odds and the presence of depression was associated with a trend towards higher odds of sleepiness (Table 4b). The use of antidepressants (n=100, P=0.4) or opiates (n=38, P=0.08) was not significantly associated with ESS >10.

The MWT and CPAP adherence data were available for 380 participants randomized to CPAP, 6-months after initiation of therapy. The mean sleep latency on MWT at 6–months (MSL-6m) was 18 minutes. MSL-6m was significantly higher in those using CPAP >4hours a night compared to those using CPAP 4 hours or less (18.5±2.8 vs. 17.5±3.8 minutes, P=0.01). MSL-6m was <20 minutes in 147 participants (38.7%) and ≤17 minutes in 90 participants (23.7%). Logistic regression revealed significantly lower odds of excessive sleepiness, defined as MSL-6m <20 minutes (MSL-6m <20), in those using CPAP >4 hours a night (OR=0.55, P=0.008).

Those with MSL-B <20 minutes also had significantly higher odds of MSL-6m <20 (OR=6.7, P<0.001) (Table 4c). Using a cutoff of 17 minutes for MSL-6m to define sleepiness yielded similar results.

Sleepiness at 6 months in participants with good adherence to CPAP

The prevalence of ESS >10 was 18.1% (48/265) among those using CPAP >4 hours a night.

The presence of excessive sleepiness at 6 months in these patients with good CPAP adherence was higher in those with baseline excessive sleepiness, whether assessed by ESS >10 (OR 8.2, P<0.001) or MSL-B <20 minutes (OR=9.6, P<0.001). No other variables assessed, including age, BMI, AHI on the sleep study done at 6-months, presence of depression, chronic pain or GERD, were significantly associated with odds of sleepiness at 6 months in this group of patients.

Discussion

The current study found that excessive sleepiness, as measured by ESS total score >10 or a MSL <20 minutes on MWT, was present in half the patients with sleep apnea, and was associated with presence of depression, more severe sleep apnea and younger age. The prevalence of excessive sleepiness 6 months after initiating CPAP was greatly reduced to 22.3%, and was inversely associated with mean hours of CPAP use. Presence of excessive sleepiness at baseline was a strong determinant of excessive sleepiness after 6 months of therapy, even in those who had good adherence to CPAP.

We found that younger age, higher AHI and presence of depression are associated with increased sleepiness in patients with sleep apnea. The past literature assessing association between AHI and EDS has shown conflicting results, with some studies [2-5] but not others[6-8] showing an association. The studies that have not shown this association probably reflect a referral bias, since sleepy patients are more likely to be referred for sleep evaluation, thereby obscuring the relation of AHI to sleepiness that is seen in population-based studies.

The association between depression and increased sleepiness confirms findings of prior reports [10,22,23]. Depression is a common finding in patients with OSA. We found an 18.6% prevalence of depression, defined as HAMD score ≥8. This is similar to a 20.8% prevalence of depression found in patients with untreated OSA in a recent study. [22] Similar to that study, we found an association between depression and ESS. This strongly argues for making appropriate inquiries for the presence of depression in those with SDB, especially in presence of sleepiness.

The ESS scores and prevalence of sleepiness decreased with increasing age, as has been reported in some prior studies. [23,24] This may be related to less potent sleep homeostasis mechanisms with increasing age, including morphological and neurological changes in suprachiasmatic nucleus and a reduction in melatonin concentration with aging.[25] These

findings suggest that complaints of sleepiness in the elderly would represent a less common response, and should not be considered a normal part of the physiologic aging process.

Lower average nightly CPAP use and presence of sleepiness at baseline were the primary determinants of residual sleepiness identified in this study. The effect of good adherence on reducing sleepiness confirms the benefit of this therapy demonstrated in the past studies.[26-28] We found, however, that after 6 months of CPAP therapy, 22.3% of the participants on CPAP (18.1% of those using CPAP >4 hours a night) still had sleepiness. This prevalence is close to that noted in recent studies,[27,28] and is similar to the prevalence of excessive sleepiness in the general population among those without sleep apnea.[4] Thus, while increasing CPAP adherence beyond 4 hours per night might yield some further reduction in daytime sleepiness, much of the residual sleepiness in these patents may be caused by factors other than OSA, indicating the importance of evaluating patients with residual sleepiness on CPAP for alternative causes of sleepiness. Oxidative injury to sleep-wake brain regions from long-term intermittent hypoxia has been suggested as a reason for residual sleepiness following treatment of OSA.[29] However, reasons for sleepiness, such as chronic pain or other conditions contributing to repeated wakefulness at night, sedative medications, depression, poor sleep hygiene or insufficient habitual sleep duration should be sought and modified before attributing residual sleepiness to a failure of CPAP therapy. In view of the finding that those who were sleepy at baseline had significantly higher odds (OR 8.2, P<0.001) of sleepiness despite good CPAP adherence, it is imperative that these patients be closely followed to ensure improvement in sleepiness.

The study has several limitations. First, we used the ESS for assessment of sleepiness in patients with OSA. The ESS, while a commonly used measure of sleepiness, has only a limited correlation with objective sleepiness measurements.[30] However, we also used the MWT, an objective measurement of ability to resist sleep onset, and the results were similar to those obtained using subjective measurements from the ESS. Second, while we used MWT-SL to

objectively assess ability to maintain wakefulness, the optimal MWT cutoff values in those with OSA have not been defined. To overcome this limitation, we used different cutoff values to decide whether the patients had decreased wakefulness. Notably, we obtained similar predictors of sleepiness while using these different cutoffs, and the results were consistent with those obtained using ESS. Third, the information about medical and psychiatric conditions was self-reported in most cases and obtained only at baseline. Hence, whether the conditions were present at the 6-month evaluation period, and may have influenced sleepiness, is not clear. Furthermore, apart from depression, for which we had HAMD scale values, the severity of other conditions was not assessed. Fourth, residual confounding by several factors including habitual sleep duration, disorders not documented in the study, medications, and genetic and socioeconomic factors cannot be excluded.[31] Finally, the standard MWT administration consists of 40-minute nap opportunities, while the naps in this trial were only 20 minutes. However, the resultant ceiling effect is expected to reduce power to detect effects of treatment and makes the differences with therapy even more compelling.

In conclusion, this study shows that depression, younger age and higher AHI, are associated with sleepiness in people with OSA. CPAP use is associated with reduced odds of sleepiness at 6 months. Lower average nightly CPAP use and presence of sleepiness at baseline are the primary determinants of persistent sleepiness in those using CPAP therapy, even among CPAP-adherent patients. Specific strategies targeting these patients, including stressing the role of CPAP in decreasing sleepiness, frequent follow-up clinic visits to evaluate residual sleepiness and promote adherence,[21,32] as well as thorough evaluation for other etiologies of sleepiness should be strongly considered. An appreciable number of OSA patients will continue to have sleepiness despite using CPAP. Other causes of sleepiness and other measures including addition of wake-promoting medications should be considered in these patients.

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Table 1: Bivariate correlation between clinical and PSG variables and the ESS total score at baseline.

Variable	Pearson Correlation	P
Age	-0.07	0.02
BMI	0.10	0.001
AHI	0.08	0.01
Desaturation Index	0.08	0.01
Sleep Efficiency	0.09	0.02
HAMD total score	0.13	<0.001

PSG: Polysomnographic
ESS: Epworth Sleepiness Scale
BMI: Body Mass Index
AHI: Apnea-Hypopnea Index
HAMD: Hamilton Rating Scale for Depression

Table 2: The mean ESS total score and proportion of sleepy participants in various medical and psychiatric disorders.

Condition (n with condition/ n without condition)	Mean ESS			% of participants with ESS> 10		
	Condition present	Condition absent	P value	Condition present	Condition absent	P value
CVD (399/706)	10.2 ± 4.4	10.6 ± 4.4	0.26	47.1	50.3	0.32
Asthma (76/1022)	10.6 ± 4.7	10.4 ± 4.4	0.81	51.3	48.9	0.39
GERD (316/782)	10.8 ± 4.3	10.3 ± 4.4	0.06	52.2	47.8	0.20
Nocturia (322/776)	10.7 ± 4.4	10.3 ± 4.4	0.16	52.8	47.6	0.13
Chronic Pain (173/925)	11.1 ± 4.5	10.3 ± 4.4	0.03*	53.2	48.3	0.14
DM (74/1024)	10.6 ± 4.7	10.4 ± 4.4	0.41	76.9	68.5	0.51
Self-reported Depression (163/935)	11.0 ± 4.2	10.3 ± 4.4	0.08*	52.8	48.4	0.35
Depression (HAMD Total Score ≥8, 204/894)	11.4 ± 4.7	10.2 ± 4.3	<0.001*	57.8	47.0	0.005*
Anxiety (76/1021)	11.0 ± 4.0	10.4 ± 4.4	0.23	52.6	48.8	0.48
Claustrophobia (88/1008)	10.9 ± 4.7	10.4 ± 4.4	0.24	51.1	48.8	0.32

ESS: Epworth Sleepiness Scale

CVD: Cardiovascular Disease
GERD: Gastroesophageal Reflux Disease
DM: Diabetes Mellitus
HAMD: Hamilton Rating Scale for Depression

Table 3a: Linear regression analysis with ESS total score as the dependent variable

Variable	Beta	Std. Error	Standardized Coefficient (Beta)	t	P
Age	-0.025	0.011	-0.068	-2.211	0.027*
Gender (Female)	0.530	0.292	0.057	1.812	0.070
BMI	0.021	0.021	0.033	0.984	0.325
AHI	0.012	0.006	0.066	2.009	0.045*
HAMD Total Score ≥8	0.118	0.033	0.109	3.556	<0.001*
Chronic Pain	0.609	0.373	0.050	1.631	0.103
GERD	0.364	0.297	0.037	1.227	0.220

ESS: Epworth Sleepiness Scale
BMI: Body Mass Index
AHI: Apnea-Hypopnea Index
HAMD: Hamilton Rating Scale for Depression
GERD: Gastroesophageal Reflux Disease

Table 3b: Odds of ESS > 10 at baseline

Variable	ESS>10 (n=543)	ESS<10 (n=562)	Wald	Odds Ratio	P
Age (years)	50.4 ± 11.9	52.7 ± 12.4	9.318	0.984	0.002*
Gender (Female) , n (%)	206 (37.9%)	176 (31.3%)	3.493	1.290	0.062
BMI (kg/m2)	32.7 ± 6.9	31.7 ± 7.3	0.108	1.003	0.742
Baseline AHI >30, n (%)	312 (57.5%)	299 (53.2%)	2.974	1.005	0.085
HAMD Total Score ≥8, n (%)	118 (21.9%)	86 (15.4%)	4.732	1.423	0.030*
Chronic Pain, n (%)	92 (17.1%)	81 (14.5%)	0.624	1.148	0.429
GERD, n (%)	165 (30.6%)	151 (27.0%)	1.010	1.149	0.315

ESS: Epworth Sleepiness Scale
BMI: Body Mass Index
AHI: Apnea-Hypopnea Index
HAMD: Hamilton Rating Scale for Depression
GERD: Gastroesophageal Reflux Disease

Table 3c: Odds of objective sleepiness (MWT < 20 minutes) at baseline

Variable	MWT < 20 (n=521)	MWT = 20 (n=565)	Odds Ratio	P
Age (years)	49.6 ± 12.6	53.8 ± 11.3	0.972	0.000*
Gender (Female) , n (%)	196 (34.7%)	178 (34.2%)	0.977	0.868
BMI (kg/m2)	33.1 ± 7.4	31.2 ± 6.6	1.018	0.064
Baseline AHI >30, n (%)	354 (62.7%)	249 (47.8%)	1.858	<0.001*
HAMD Total Score ≥8, n (%)	123 (21.9%)	79 (15.2%)	1.500	0.016*
Chronic Pain, n (%)	91 (16.1%)	81 (15.5%)	1.081	0.664
GERD, n (%)	161 (28.5%)	149 (28.6%)	0.921	0.563

MWT: Maintenance of Wakefulness Test
BMI: Body Mass Index
AHI: Apnea-Hypopnea Index
HAMD: Hamilton Rating Scale for Depression
GERD: Gastroesophageal Reflux Disease

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Table 4a: Linear regression analysis with ESS total score at 6 months as the dependent variable

Variable	Beta	Std. Error	Standardized Coefficient (Beta)	t	P
Age	0.020	0.015	0.058	1.328	0.185
Gender (Female)	-0.548	0.374	-0.062	-1.466	0.143
BMI	-0.031	0.025	-0.055	-1.210	0.227
HAMD Total Score	0.023	0.040	0.023	0.566	0.571
Chronic Pain	0.766	0.462	0.069	1.660	0.098
GERD	0.045	0.380	0.005	0.119	0.906
Baseline ESS	0.495	0.039	0.528	12.679	<0.001*
AHI Baseline	-0.007	0.008	-0.038	-0.841	0.401
AHI at 6 Months	-0.025	0.022	-0.049	-1.144	0.253
Mean Hours of CPAP Adherence	-0.240	0.067	-0.151	-3.579	<0.001*

ESS: Epworth Sleepiness Scale
BMI: Body Mass Index
HAMD: Hamilton Rating Scale for Depression
GERD: Gastroesophageal Reflux Disease
AHI: Apnea-Hypopnea Index
CPAP: Continuous Positive Airway Pressure

Table 4b: Odds of ESS >10 at 6 months

Variable	ESS>10 (n=88)	ESS<10 (n=306)	Odds Ratio	P
Age (years)	51.2 ± 12.5	53.0 ± 12.0	1.001	0.920
Gender (Female) , n (%)	29 (33.0%)	106 (34.6%)	0.582	0.049*
BMI (kg/m2)	31.6 ± 6.8	32.2 ± 7.3	0.982	0.356
HAMD Total Score ≥8, n (%)	19 (21.6%)	51 (16.7%)	1.766	0.059
Chronic Pain, n (%)	23 (26.1%)	45 (14.7%)	2.289	0.008*
GERD, n (%)	29 (33.0%)	86 (28.1%)	0.979	0.939
Baseline ESS >10, n (%)	65 (73.9%)	127 (41.5%)	5.143	<0.001*
Baseline AHI >30, n (%)	48 (54.5%)	171 (55.9%)	1.106	0.715
AHI >5 at 6 Months, n (%)	27 (30.7%)	111 (36.3%)	0.754	0.291
CPAP Use >4 Hours/Night, n (%)	48 (54.5%)	217 (70.9%)	0.425	0.001*

ESS: Epworth Sleepiness Scale
BMI: Body Mass Index
HAMD: Hamilton Rating Scale for Depression
GERD: Gastroesophageal Reflux Disease
AHI: Apnea-Hypopnea Index
CPAP: Continuous Positive Airway Pressure

Table 4c: Odds of objective sleepiness (MSL-6m <20 minutes) at 6 months

Variable	MSL-6m < 20 (n=147)	MSL-6m = 20 (n=233)	Odds Ratio	P
Age (years)	53.8 ± 12.4	53.8 ± 11.4	.994	.521
Gender (Female) , n (%)	46 (31.3%)	84 (36.1%)	.678	.109
BMI (kg/m2)	32.2 ± 6.7	31.9 ± 7.2	1.004	.794
HAMD Total Score ≥8, n (%)	30 (20.4%)	39 (16.7%)	1.168	.587
Chronic Pain, n (%)	24 (16.3%)	43 (18.5%)	.827	.524
GERD, n (%)	49 (33.3%)	65 (27.9%)	1.249	.364
Baseline MWT<20, n (%)	156 (67.0%)	33 (22.4%)	6.711	.000*
Baseline AHI >30, n (%)	80 (54.4%)	128 (54.9%)	.811	.398
AHI >5 at 6 Months, n (%)	51 (34.7%)	84 (36.1%)	1.020	.933
CPAP Use >4 Hours/Night, n (%)	85 (57.8%)	169 (72.5%)	.547	.008*

MSL-6M: Mean Sleep Latency- 6 Months
BMI: Body Mass Index
HAMD: Hamilton Rating Scale for Depression
GERD: Gastroesophageal Reflux Disease
MWT: Maintenance of Wakefulness Test
AHI: Apnea-Hypopnea Index
CPAP: Continuous Positive Airway Pressure

Figure 1: The prevalence of sleepiness in all participants with different mean daily CPAP use.
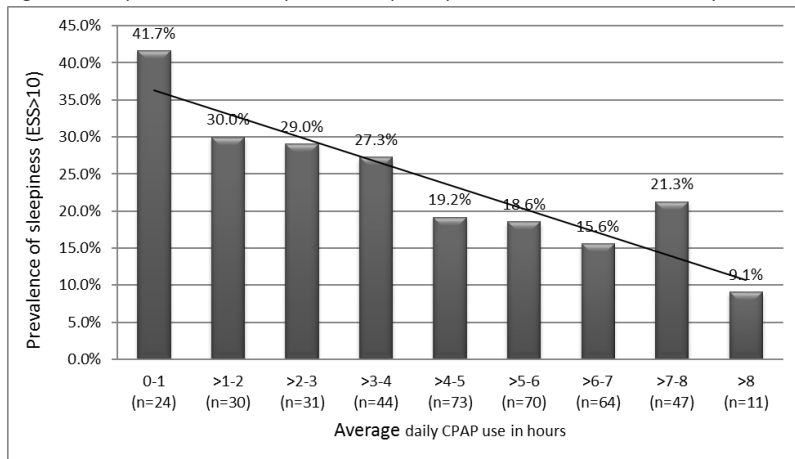
CPAP: Continuous Positive Airway Pressure
ESS: Epworth Sleepiness Scale