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Original Article

Long-term adherence to continuous positive airway pressure therapy in non-sleepy sleep apnea patients

Francisco Campos-Rodriguez [a], Montserrat Martinez-Alonso [b,c], Manuel Sanchez-de-la-Torre [c,d], Ferran Barbe [c,d,*] on behalf of the Spanish Sleep Network

[a] Respiratory Department, Hospital Universitario de Valme, Seville, Spain
[b] Department of Statistics, IRB Lleida, Catalonia, Spain
[c] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain
[d] Respiratory Department, Hospital Universitari Arnau de Vilanova and Santa Maria, IRB Lleida, Catalonia, Spain

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ABSTRACT

Objective: The effectiveness of continuous positive airway pressure (CPAP) therapy greatly depends on consistent use. However, data regarding adherence in non-sleepy obstructive sleep apnea (OSA) patients are scarce. The aim of this study was to assess long-term adherence and predictors of CPAP compliance in a large sample of non-sleepy OSA patients.

Methods: We conducted a prospective, multicenter study comprising 357 non-sleepy patients (Epworth Sleepiness Scale score <11) with moderate-to-severe OSA (apnea–hypopnea index [AHI] of ≥20) who began CPAP therapy between May 2004 and May 2006; follow-up ended in May 2009. Non-compliance was scored as CPAP dropout or average cumulative CPAP use of <4 hours per night. Multivariate Cox regression analysis was performed to identify independent predictors of poor CPAP adherence.

Results: Patients were followed up for a median of four years (interquartile range [IQR] = 3.0–4.4). At the end of the study period, 230 patients (64.4%) fulfilled the criteria for good CPAP compliance, whereas 127 patients (35.6%) were considered non-compliant. The median CPAP use was five hours per night (interquartile range = 2.18–6.25). Multivariate analysis showed that interactions between the AHI and the percentage of nighttime spent with an O_2 saturation of <90% (TC90) ($p = 0.010$) and between the AHI and hypertension at baseline ($p = 0.029$) predicted long-term compliance with CPAP.

Conclusion: This study demonstrates that CPAP treatment is feasible in non-sleepy, moderate-to-severe OSA patients. Good CPAP adherence was predicted by greater OSA severity as measured by both the AHI and TC90 and by the presence of hypertension at baseline in patients with higher AHI levels.

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder characterized by repetitive episodes of upper airway obstruction during sleep that lead to intermittent hypoxia and sleep fragmentation. The most typical symptom of this sleep disorder is the presence of excessive daytime sleepiness (EDS). However, several population-based and clinical cohort studies have reported that this complaint is absent in approximately 40%–50% of all OSA patients [1–3]. There is growing evidence suggesting that non-sleepy OSA patients may have risks of cardiovascular consequences similar to those of patients with EDS, and that treatment with continuous positive airway pressure (CPAP) may reduce these adverse outcomes [4–8]. Accordingly, the American Academy of Sleep Medicine recommends CPAP treatment for symptomatic patients with an apnea–hypopnea index (AHI) of ≥5 and for patients with an AHI of ≥15, irrespective of symptoms [9].

The effectiveness of CPAP therapy in reversing the clinical complaints, impaired quality of life, and potential cardiovascular

The Spanish Sleep Network is composed of the following individuals: Joaquin Duran-Cantolla (Hospital Universitario de Alava, Vitoria, Spain), Carmen Carmona (Hospital Universitario Virgen del Rocıo, Sevilla, Spain), Antonia Barcelo (Hospital Universitario Son Espasses, Palma de Mallorca, Spain), Eusebi Chiner (Hospital Sant Joan, Alacant, Spain), Juan F. Masa (Hospital San Pedro de Alcantara, Caceres, Spain), Monica Gonzalez (Hospital Marques de Valdecilla, Santander, Spain), Jose M. Marin (Hospital Miguel Servet, Zaragoza, Spain), Francisco Garcia-Rio (Hospital Universitario La Paz-IdiPAZ, Madrid, Spain), Josefa Diaz de Atauri (Hospital 12 de Octubre, Madrid, Spain), Joaquın Teran (Hospital Universitario de Burgos, Burgos, Spain), Mercedes Mayos (Hospital Sant Pau, Barcelona, Spain), Carmen Monasterio (Hospital de Bellvitge, Barcelona, Spain), Felix del Campo (Hospital Rio Hortega, Valladolid, Spain), Josep M. Montserrat (Hospital Clinic, Barcelona, Spain), and Silvia Gómez (Hospital Arnau de Vilanova, Lleida, Spain).

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* Corresponding author. Respiratory Department, Hospital Universitari Arnau de Vilanova and Santa Maria, IRBLleida, 25198 Lleida, Catalonia, Spain. Tel.: +34 973705372.
E-mail address: febarbe.lleida.ics@gencat.cat (F. Barbe).

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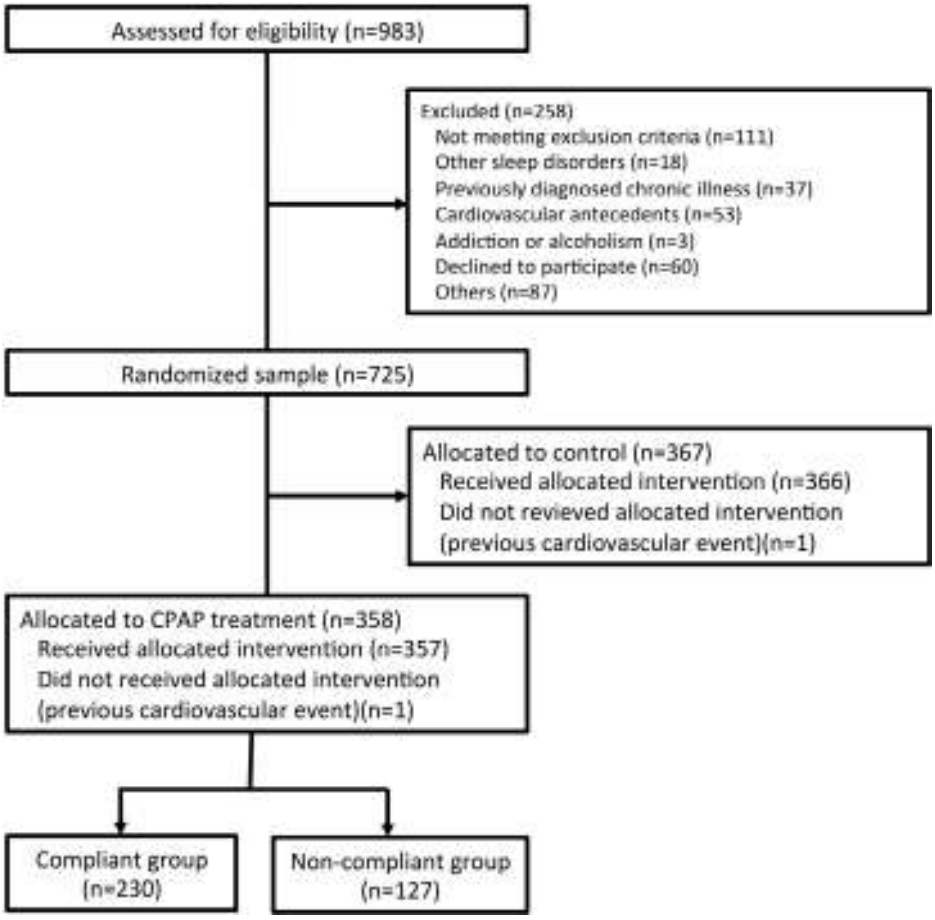

Fig. 1. Flowchart for study participants.

consequences associated with OSA are closely related to the profile of adherence to this therapy [5,6,10–12]. Although CPAP compliance has been extensively addressed, relevant studies have yielded conflicting results, and specific predictors of adherence have not been identified [13–19]. Subjective sleepiness has been proposed as a factor influencing adherence with the argument that patients with EDS may be more motivated to use CPAP because they achieve greater benefits in terms of EDS relief [16–18,20]. If this is true, patients without EDS should be less likely to accept CPAP treatment and should have higher non-compliance rates. However, very few studies have evaluated CPAP adherence in non-sleepy OSA patients. The aims of this study were to analyze long-term compliance and to identify independent predictors of CPAP adherence in non-sleepy patients with moderate-to-severe OSA.

2. Methods

2.1. Patients

The sample population in this study is part of a larger multicenter, randomized, controlled trial conducted in 14 Spanish teaching hospitals to evaluate the effect of CPAP treatment on the incidence of hypertension and cardiovascular events in non-sleepy OSA patients; patient characteristics have been described in detail elsewhere [5]. Patients were excluded from the initial study if they had any previous cardiovascular events, physical or psychological incapacity, chronic disease, or drug or alcohol dependency. Briefly, between May 2004 and May 2006, a total of 725 consecutive patients aged 18–70 years who were diagnosed with moderate-to-severe OSA (AHI ≥20) and who were without EDS (Epworth Sleepiness Scale [ESS] score of <11) were enrolled. For the present compliance study, 357 patients randomized to receive CPAP treatment were analyzed (Fig. 1). The study was approved by the ethics committee (345/04PI), and all participants provided signed informed consent.

2.2. Procedures

Baseline variables were systematically recorded prospectively using a standardized protocol that included clinical and anthropometric data, subjective sleepiness based on ESS score, smoking habit, alcohol intake, cardiovascular medication use, blood pressure, and fasting blood analyses. The data were collected before the sleep study, with the participants in a stable condition.

Every patient underwent a diagnostic sleep study, either full standard polysomnography or validated cardio-respiratory polygraphy. Both types of sleep studies have previously been described in detail [5]. All sleep studies were manually scored by trained personnel at each participating center according to standard criteria. Apnea was defined as the absence of airflow for at least ten seconds, and was classified either as obstructive or central based on the presence or absence of respiratory efforts. Hypopnea was defined as airflow reduction of >50% for at least ten seconds, followed by a drop in oxygen saturation of at least 4% or arousal. The AHI was calculated according to the average number of apnea and hypopnea episodes per hour of sleep or recording time.

Patients allocated to CPAP underwent a titration study on a second night. The CPAP titration was performed using either conventional

polysomnography at the sleep laboratory or an automatic CPAP (autoCPAP) device, used either in the sleep laboratory or at home, following a validated protocol [21].

2.3. Follow-up

After CPAP prescription, patients attended a workshop conducted by skilled staff, where they were taught how to use the device and were thoroughly informed of the need for daily CPAP use during sleeping hours. The subjects were evaluated at 3, 6, and 12 months and annually thereafter. At each follow-up visit, CPAP use was reinforced, and any side effects or concerns with the device were addressed. The CPAP machines were provided to the patients free of charge. Information regarding CPAP use was objectively assessed by reading the time-counter of the device at each follow-up appointment. The compliance data were analyzed until the date of the last visit, date of death, CPAP dropout, or loss to follow-up, whichever occurred first. The follow-up ended in May 2009.

2.4. Endpoints

The endpoints of this study were adherence to CPAP treatment and the variables associated with CPAP compliance. For the purpose of this study, non-compliance was defined as dropout or an average cumulative CPAP use of <4 hours per night. Patients who continued to use the CPAP machine with an average cumulative use of ≥4 hours per night were considered to have good adherence. A CPAP dropout was registered whenever a patient abandoned the treatment or whenever the device was reclaimed for non-compliance. In patients who died, were lost to follow-up, or dropped out, the follow-up was censored at the date of the last visit, and the information generated up to that point was used to analyze adherence.

The estimated average cumulative treatment compliance during the follow-up period was computed individually for each patient as the area under the curve obtained from the measurements reported during the follow-up visits, taking into account the time between the visits and the last available information. Therefore, because compliance was registered during each follow-up visit (months 3, 6, 12, 24, 36, and 48), the estimated average cumulative treatment adherence for the whole follow-up period was the pooled average, weighting each compliance by the time elapsed since the last available individual compliance information was collected.

2.5. Statistical analyses

The statistical software package R was used for data processing and analysis. Continuous variables are expressed as median and interquartile range (IQR, expressed as the interval between the first and third quartiles), and categorical variables as absolute frequencies and percentages.

The association between CPAP adherence and different baseline variables of clinical interest (gender, type of diagnostic study and CPAP titration, smoking habit, alcohol intake, prior history of hypertension, cardiovascular drug use, age, body mass index [BMI], CPAP pressure, AHI, percentage of nighttime spent with an O_2 saturation of <90% [TC90], and systolic and diastolic blood pressure [BP]) was evaluated by univariate Cox regression analysis. To identify the independent predictors of CPAP adherence, multivariate logistic regression analysis was performed using a model with all variables with a p value of <0.20 associated with their coefficients in the univariate analysis. The variable selection included in the final model was based on the likelihood ratio (LR) test used to assess the significance of the contribution of each added variable to the model. Only variables with a statistically significant contribution according to this test were included in the model. The variables that were not included in the final model were individually subjected to an LR test to confirm the nonsignificant contribution to the final model and the confusion effect on the rest of the variables in the model. The confusion effect of a non-significant variable was defined as any change greater than 20% in the coefficients of the remainder of the significant variables as a consequence of including or excluding the nonsignificant variable. The interactions were confirmed among the variables in the final model.

A p value of <0.05 was considered statistically significant.

3. Results

The baseline characteristics of the 357 patients analyzed in this study are listed in Table 1. The majority (87.7%) were male and had severe OSA (median AHI = 42.0, IQR = 29.0–59.0). The median age was 53.5 years (IQR = 44.6–59.6). The median follow-up of the sample was four years (IQR = 3.0–4.4). During the study period, 70 patients were lost to follow-up, eight died, and 26 CPAP dropouts occurred. Thus, 253 patients completed the study. No differences ($p > 0.1$) were found between the 70 patients lost to follow-up and the 253 patients who completed the study regarding age, sex, obesity, sleep test, titration method, OSA severity, BP, fasting blood analysis results, and smoking or alcohol intake; thus, these patients did not have any special baseline characteristics that could explain the loss. At the end of the study period, 230 patients (64.4%) fulfilled the criteria for good CPAP compliance, whereas 127 (35.6%) were considered non-compliant. The non-compliant patients included 101 patients who remained on therapy but had a cumulative CPAP use of <4 hours per night, and 26 patients with CPAP dropped out. The proportion of patients with good CPAP adherence barely changed throughout the follow-up, ranging from 61.6% to 64.7%. The median CPAP use for the entire cohort was five hours per night (IQR = 2.18–6.25) and differed significantly between the groups with good and poor adherence (median = 5.96; IQR = 5.05–6.70 vs. 1.00, IQR = 0.00–2.75, respectively).

In the univariate analysis (Table 2), BMI at baseline, CPAP pressure, AHI, TC90, systolic BP at baseline, and prior history of hypertension predicted poor adherence at the end of follow-up. Significant interactions were identified between the AHI and TC90 (likelihood ratio test [LRT], $p = 0.009$) and between the presence of hypertension at baseline and the AHI (LRT, $p = 0.034$). Both interactions were included in the final multivariate regression model as predictors of long-term adherence (Table 3). The effect of the AHI and TC90 on adherence was non-additive. Thus, the negative

Table 1
Baseline characteristics of the 357 patients in the study.

Variables	
Categorical	
Female gender	44 (12.3%)
Polygraphy	159 (44.5%)
AutoCPAP titration	269 (75.3%)
Active smoke	113 (31.6%)
Alcohol intake	112 (31.3%)
Cardiovascular drug use	142 (39.7%)
History of hypertension	190 (53.2%)
Continuous	
Age (years)	53.5 (44.6–59.6)
BMI (kg/m^2)	30.8 (28.0–34.2)
ESS score	7.0 (5.0–8.0)
CPAP pressure (cmH_2O)	8.0 (7.0–10.0)
AHI	42.0 (29.0–59.0)
% of nighttime spent with oxygen saturation <90%	8.00 (2.0–22.8)
SBP (mmHg)	130 (120–140)
DBP (mmHg)	80 (70–90)

BMI = body mass index, ESS = Epworth Sleepiness Scale, CPAP = continuous positive airway pressure, AHI = apnea–hypopnea index, SBP/DBP = systolic/diastolic blood pressure.
Data are presented as the n (%) or median (IQR).

Table 2
Association between baseline variables and poor continuous positive airway pressure (CPAP) adherence according to univariate Cox analysis.

Variables	Compliant (n = 230)	Non-compliant (n = 127)	OR (95% CI)	*p*-value
Categorical				
Female gender	29 (12.6%)	15 (11.8)	0.98 (0.84–1.14)	0.826
Polygraphy	106 (46.0%)	53 (41.7%)	0.96 (0.86–1.06)	0.429
AutoCPAP titration	173 (75.2%)	96 (75.5%)	1.08 (0.96–1.21)	0.181
Active smoke	71 (30.8%)	42 (33.0%)	1.02 (0.92–1.13)	0.669
Alcohol intake	74 (32.1%)	38 (29.9%)	1.01 (0.90–1.13)	0.834
Cardiovascular drug use	99 (43.0%)	43 (33.8%)	0.91 (0.82–1.01)	0.090
History of hypertension	132 (57.3%)	58 (45.6%)	0.89 (0.81–0.99)	0.033
Continuous				
Age	53.8 (44.6–60.2)	53.3 (44.8–58.2)	1.00 (0.99–1.00)	0.856
BMI	31.2 (28.3–34.6)	30.1 (27.1–33.3)	0.98 (0.97–0.99)	0.009
CPAP pressure	9.0 (7.0–10.0)	8.0 (7.0–9.0)	0.97 (0.94–0.99)	0.037
AHI	46.5 (33.0–63.0)	33.0 (26.5–52.5)	0.99 (0.98–0.99)	<0.001
% of time spent with oxygen saturation <90%	10.0 (2.2–27.0)	5.0 (1.1–15.0)	0.99 (0.98–0.99)	0.013
SBP	130 (120–140)	130 (120–140)	0.99 (0.99–1.00)	0.050
DBP	80 (70–90)	80 (70–85)	0.99 (0.99–1.00)	0.103

BMI = body mass index, CPAP = continuous positive airway pressure, AHI = apnea–hypopnea index, SBP/DBP = systolic/diastolic blood pressure.
Descriptive data are presented as n (%) or median (IQR). The estimated odds-ratios (OR) are presented together with their 95% confidence interval and the p-value obtained from each logistic regression model.

coefficients associated with each 10-unit increase in both variables tended to be compensated for by the positive coefficient associated with the interaction term, especially in the presence of high values for both variables. Hypertension showed a significant protective effect on CPAP adherence in the presence of high AHI values; specifically, the OR associated with hypertension was increasingly significant with AHI values of ≥47. The interaction between the AHI and hypertension is further assessed in Table 4.

Table 3
Variables associated with poor long-term adherence to continuous positive airway pressure: final multivariate logistic regression model.

	Estimate	Standard error	*p*-value
AHI (per 10-unit increase)	–0.23	0.09	0.012
Percent of the nighttime spent with an oxygen saturation <90% (per 10-unit increase)	–0.27	0.12	0.021
Hypertension	0.24	0.38	0.52
Interaction between AHI and percent of the nighttime spent with an oxygen saturation <90%	0.07	0.03	0.009
Interaction between AHI and hypertension at baseline	–0.28	0.13	0.034

AHI = apnea–hypopnea index.

Table 4
Odds ratio of the presence vs. absence of baseline hypertension, depending on different AHI values.

AHI values	OR (hypertension)	95% CI	*p*-value
20	1.27	0.61–2.68	0.5252
29 (percentile 25)	0.99	0.55–1.79	0.9812
42 (percentile 50)	0.69	0.43–1.12	0.1343
59 (percentile 75)	0.44	0.22–0.81	0.0107

AHI = apnea–hypopnea index, OR = odds ratio, 95% CI = 95% confidence interval.
The estimated odds ratios (ORs) for hypertension vs. no hypertension are presented together with their 95% confidence interval and with the p-value obtained from the final multivariate logistic regression model, depending on certain specific AHI values (minimum and quartiles in our sample). The increasingly protective effect of hypertension against poor adherence significantly increases with AHI values of 47 or higher.

4. Discussion

This study shows that CPAP treatment is feasible in non-sleepy, moderate-to-severe OSA patients; approximately two-thirds of our cohort showed good adherence to the therapy after a long-term follow-up of four years. Predictors of CPAP compliance at baseline were greater OSA severity, as assessed by the AHI and the TC90, and hypertension combined with high AHI levels.

Compliance is paramount to achieve the beneficial effects of CPAP on quality of life and cardiovascular outcomes, but the predictors of adherence to this therapy are far to be known. OSA severity, clinical complaints, age, gender, BMI, CPAP pressure, and other variables have been identified as potentially associated with adherence [13–20,22–24]. EDS has been suggested as one of the most important determinants of adherence to CPAP because the relief of hypersomnolence encourages these patients to use the therapy. However, other studies do not concur with this finding [13–18,25]. One-half of patients with OSA do not complain of EDS, and the feasibility of long-term CPAP treatment in this population is controversial. Unfortunately, most studies of compliance have been conducted on patients with EDS, and the few studies that have focused on non-sleepy OSA patients have yielded conflicting findings [10,26,27].

In our study, the median CPAP use was five hours per night, and 64.4% of patients were considered to have good CPAP compliance at the end of the 4-year follow-up. These findings suggest that CPAP therapy is feasible and highly acceptable, even in non-sleepy OSA patients. Our results are consistent with those of Gagnadoux et al. [27], who reported a mean CPAP use of 5.0 ± 2.5 hours per night, with 67.1% using CPAP for at least four hours per night, in an observational study that included 589 non-sleepy OSA patients treated with CPAP for a mean of 1.7 years. These figures clearly surpass those of the SAVE and MOSAIC studies, two randomized controlled trials that also included non-sleepy or minimally symptomatic OSA patients [10,26]. The SAVE study reported compliance data for 275 patients (average ESS = 7.7 ± 3.6) with OSA and established cardiovascular diseases who were allocated to CPAP treatment [26]. At 12 months, only 39% of the patients used the device ≥4 hours per night, and the mean CPAP use was 3.3 ± 2.4 hours per night. In the MOSAIC study [10], 391 minimally symptomatic OSA patients (mean ESS = 7.9 ± 4.4) were randomized to standard care or CPAP for six months. In the group randomized to CPAP, the median CPAP use at

six months was 2.39 hours per night (IQR = 0.36–4.59), and 43 of the 195 patients (22%) in this group stopped treatment during follow-up. Some of these differences in CPAP adherence, however, may be attributable to different study methodologies. Patients in the SAVE trial did not present to a sleep clinic but were recruited predominantly from cardiology and neurology clinics and thus had different clinical and cardiovascular profiles, whereas patients in the MOSAIC study had milder OSA severity compared with those in the present study. As we found OSA severity to be a predictor of adherence, the patients in the current study are likely more motivated to comply with CPAP.

The figures in our study are also similar or only slightly lower than those reported in other studies that were not focused on non-sleepy OSA patients. The median CPAP use of five hours per night falls within the range of 5.0–6.2 hours per night reported in other long-term studies [14–17] and the 64.4% of patients with good adherence observed in this study is similar to the 67%–68% reported by McArdle et al. [16] and Pelletier-Fleury et al. [17] but clearly lower than the 80%–85% reported in other studies [14,15].

CPAP adherence was predicted by OSA severity as measured by both the AHI and TC90 levels, and by the presence of hypertension in patients with high AHI in the multivariate analysis. Other studies of non-sleepy [27] and sleepy OSA patients [14–17] have reported that the severity of OSA, measured using either the AHI or oxygen desaturation index, was a determinant of long-term adherence to CPAP. Greater OSA severity is likely associated with greater disease burden, more symptomatic disease, and poorer perceived health status, regardless of the level of EDS, which may motivate patient compliance with the therapy. In our study, greater OSA severity, as assessed by higher AHI levels, and a greater percentage of nighttime spent with an O_2 saturation of <90% were associated with better CPAP compliance; these findings are in agreement with the aforementioned findings. However, the interaction between these two variables showed that their effect was not additive, and that their increasingly protective effect against poor adherence for only one of the variables did not lower the odds of poor adherence if both variables were high, possibly due to a ceiling effect.

The combination of baseline hypertension with elevated AHI levels is a novel finding as a predictor of adherence to CPAP. In our study, the presence of hypertension was significantly associated with increasingly better CPAP adherence from an AHI cutoff point of 47 events per hour. Thus, the presence of both hypertension and greater OSA severity may encourage greater patient adherence to CPAP compared with that in patients without hypertension or with hypertension and milder OSA severity, as they may be aware of the increased cardiovascular risk.

Notably, no significant differences in adherence were found between patients who underwent home sleep testing and titration and those who underwent conventional in-laboratory management. These results are in agreement with previous data suggesting that home OSA management is cost-effective and does not compromise adherence [28,29].

Our study does have some limitations. First, this study was not originally designed to analyze adherence, so some potentially interesting variables such as the type of interface, humidification, number and type of side effects, social factors, psychoactive medications, and psychiatric disorders were not considered. Second, our patients were non-sleepy but not necessarily asymptomatic. Other non-EDS, OSA-related complaints such as snoring, breathing pauses, fatigue, and choking were not considered, but these may be important variables associated with adherence. Third, EDS was assessed in our study using the ESS, which is a widely used subjective measure of sleepiness. This tool, however, has several limitations. The cutoff point that is generally used to define EDS is arbitrary; thus, some patients with daytime sleepiness symptoms might not reach the threshold to be classified as sleepy. Moreover, the ESS does not correlate with objective measures of sleepiness and has not been validated in populations such as women or elderly persons. Thus, some patients included in this study might have been found to have EDS if we had used other tools to assess sleepiness [30–32]. Finally, 32 of the 70 patients who were lost to follow-up had been using CPAP for >4 hours per night based on data available up to their last visit, and they were considered to have good adherence. Although some of them may have dropped out and declined further contact, most of them likely have not changed their compliance profile.

5. Conclusion

In conclusion, we have demonstrated that long-term CPAP treatment is feasible in non-sleepy, moderate-to-severe OSA. OSA severity, as measured by both the AHI and TC90, and the presence of baseline hypertension in patients with high AHI levels were both predictors of adherence in this cohort.

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Conflict of interest

The authors declare that they have no conflict of interest in regard to this work.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.07.038.

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