



Long-term continuous positive airway pressure compliance in females with obstructive sleep apnoea

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ABSTRACT Continuous positive airway pressure (CPAP) is the treatment of choice for obstructive sleep apnoea (OSA), but compliance and variables involved in long-term CPAP adherence in females with OSA are unknown.

We performed an observational study including all consecutive females diagnosed with CPAP who started CPAP treatment in two Spanish teaching hospitals between 1999 and 2007 and were followed-up until December 2010. The Kaplan–Meier method was used to calculate the probability of continuing with CPAP treatment and a multivariate Cox regression analysis was used to identify baseline predictors of CPAP dropout.

We analysed 708 females, median (interquartile range) age 60 (52–67) years and apnoea–hypopnoea index 43.0 (27.2–66.8). Females were followed for a median of 6.2 (4.2–7.7) years. The probability of still being on CPAP at 5 and 10 years was 82.8% and 79.9%, respectively. The median CPAP use was 6 (interquartile range 4–7) h·day⁻¹. In the multivariate analysis, independent baseline predictors of CPAP dropout were psychoactive medication (hazard ratio 1.47, 95% CI 1.03–2.08), age (hazard ratio 1.01, 95% CI 1.00–1.03) and CPAP pressure (hazard ratio 0.89, 95% CI 0.81–0.96).

Long-term CPAP adherence in females with OSA is good. Psychoactive medication and increasing age were independent predictors of CPAP dropout, whereas higher CPAP was associated with continued treatment.



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Long-term CPAP adherence in females with OSA is good; psychoactive medication and increasing age predicted CPAP dropout <http://ow.ly/nzS1F>

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Introduction

Obstructive sleep apnoea (OSA) affects around 2–3% of middle-aged females in the general population [1]. This sleep disorder has an important impact on quality of life, including a wide variety of symptoms such as insomnia [2–4], headache [2, 4], depression [2, 4, 5], anxiety [5] and fatigue [2]. OSA has also recently been recognised as a risk factor for increased cardiovascular mortality in this population [6].

Continuous positive airway pressure (CPAP) is the treatment of choice for OSA patients [7]. As CPAP is a chronic treatment and, in most cases, must be used for life, good compliance is essential to achieve the beneficial effects of this therapy [8]. Although adherence to CPAP treatment has been extensively investigated in the literature [9–20], females have scarcely been represented in these series and no study to date has been specifically devoted to them. We therefore do not know how good adherence is in this population, and which variables can predict long-term compliance. Given that OSA features differ between males and females with regard to prevalence [21], clinical presentation [2–4], severity [22] and pathophysiology [23, 24], sex differences in adherence to treatment cannot be ruled out. In fact, the influence of sex on CPAP compliance has not been clarified and several studies have reported conflicting results [9, 10, 12, 15, 18]. Thus, the available evidence on this topic, mainly based on male populations, may not apply to females.

In order to try to answer these questions, we analysed long-term CPAP compliance and predictors of CPAP dropout in a large female cohort with a prolonged follow-up.

Methods

Design and patients

All consecutive females diagnosed with OSA (apnoea/hypopnoea index (AHI) ≥ 10 events·h⁻¹) who started CPAP treatment between December 1998 and December 2007 in the sleep units of the Valme (Seville, Spain) and Requena (Valencia, Spain) Hospitals were identified. This sample is part of a larger female cohort that was prospectively assessed for OSA-related cardiovascular outcomes and whose characteristics have been explained in detail elsewhere [6]. Exclusion criteria were as follows: age <18 years, central sleep apnoea syndrome (>50% of apnoeic events were central), refusal to start CPAP therapy and previous CPAP treatment. The ethics committees of both institutions approved the study.

Sleep study and CPAP treatment

We followed the Spanish Society of Pneumology and Thoracic Surgery guidelines for the diagnosis and treatment of OSA [25, 26]. The diagnosis of OSA was always based on an overnight sleep study, either by full standard polysomnography (PSG) or respiratory polygraphy (RP), using a device previously validated against PSG. Every sleep study was manually scored by skilled staff, according to standard criteria [27]. PSG included the continuous recording of neurological variables: electroencephalogram, electrooculogram and electromyogram. Breathing variables were scored on the basis of the flow tracing provided by an oro-nasal cannula and thermistor. Thoracoabdominal motion was measured with thoracic and abdominal bands. Arterial oxygen saturation (SaO₂) was recorded with a finger-pulse oximeter. An electrocardiogram was also recorded. RP included recording of the oro-nasal flow and pressure, respiratory movements, SaO₂ and ECG. Apnoea was defined as complete cessation of oro-nasal flow for >10 s and was classified as either obstructive or central, based on the presence or absence of respiratory effort. Hypopnoea was defined as a 30–90% reduction in oro-nasal flow for >10 s followed by a $\geq 4\%$ decrease in SaO₂. The AHI was defined as the number of apnoeas plus hypopnoeas per hour of sleep (PSG) or recording (RP). Severe OSA was defined as an AHI of ≥ 30 events·h⁻¹, and mild-to-moderate OSA as an AHI of 10–29.9 events·h⁻¹. CPAP treatment was offered to every female with severe OSA irrespective of symptoms, and to those with OSA and daytime hypersomnolence (Epworth Sleepiness Scale (ESS) >10) or cardiovascular risk [25, 26]. CPAP was titrated on a second night in the sleep laboratory, with either full standard PSG or an auto-titrating CPAP device, in accordance with a validated protocol [25, 26]. All the patients received education prior to the CPAP titration night.

Data collection

The following baseline variables were systematically recorded by prospectively using a standardised protocol and collected prior to the sleep study: age in years, body mass index (BMI) in kg·m⁻², excessive daytime somnolence (EDS) measured by the ESS, hospital of reference, smoking history of >20 pack-years, alcohol intake of >10 g·day⁻¹, systemic hypertension, diabetes mellitus, hyperlipidaemia, use of psychoactive medication, documented history of previous stroke or ischaemic heart disease, type of sleep study and method of CPAP titration. Patients were classified as hypertensive, diabetic or hyperlipidaemic if any of these disorders had been previously diagnosed, they were undergoing specific treatment for them, or they had systolic or diastolic blood pressure $\geq 140/90$ mmHg on two or more different ambulatory readings, fasting

glucose levels $>7.0 \text{ mmol}\cdot\text{L}^{-1}$ ($125 \text{ mg}\cdot\text{dL}^{-1}$) on two or more determinations and fasting total cholesterol or triglycerides levels $>5.17 \text{ mmol}\cdot\text{L}^{-1}$ ($200 \text{ mg}\cdot\text{dL}^{-1}$) on two or more determinations, respectively.

Follow-up

Once CPAP was started, patients were reviewed at 3–6-monthly intervals during the first year and every 12 months thereafter in the outpatient sleep clinic. During these appointments, a clinical assessment was made and patients were reminded to use the device. In the case of side-effects or questions, patients could contact the sleep unit. CPAP machines were provided to the patients free of charge. Information regarding CPAP use was provided by the home care provider in charge of the respiratory therapies and use was objectively assessed by reading the time-counter of the device. The data used in this study were the average cumulative CPAP compliance, from the start of treatment to the end of follow-up, death or censorship. The follow-up finished on December 31, 2010.

End-points

The end-points of this study were continued use of a CPAP machine and baseline variables associated with CPAP compliance. Those females who stopped CPAP and their reasons for doing so were recorded on the basis of the information provided by the home care provider, medical records and computerised databases. For the purposes of this study, CPAP dropout was registered whenever a patient abandoned the treatment, or whenever the device was reclaimed for bad compliance at the discretion of the supervising physician. Continued use of CPAP was assumed as long as a dropout did not occur. Those females who died, were lost to follow-up or had CPAP withdrawn because their OSA was resolved were considered to be still on CPAP treatment up to that point, and they were not scored as a dropout.

Statistical analysis

The SPSS 19.0 statistical package (SPSS Inc., Chicago, IL, USA) was used for data processing and analysis. Continuous variables are expressed as median (interquartile range (IQR)), and qualitative variables as absolute values and percentages. Kaplan–Meier survival analyses were used to estimate the proportion of females still on CPAP treatment. The association between CPAP dropout and clinically relevant baseline factors (sex, age, BMI, ESS, hospital of reference, smoking and alcohol use, cardiovascular comorbidities, psychoactive medication, AHI, oximetric parameters of the sleep study, type of sleep study, and type of CPAP titration) was tested using a univariate Cox regression analysis. Interactions between CPAP pressure and AHI, BMI and the titration method were also explored. To identify independent predictors of CPAP dropout, those variables found to be significant at a p -value ≤ 0.20 were entered into a multivariate Cox regression model. Variables thought to exert influence on adherence, such as age, ESS, psychoactive medication, and the type of sleep study and titration method used, were forced as covariates into the multivariate analysis irrespective of the results of the univariate analysis. The proportional hazards assumption was verified for each covariate model. A p -value < 0.05 was considered to be statistically significant.

Results

765 females with OSA were prescribed CPAP during the study period. We excluded 10 females with central sleep apnoea, two aged < 18 years, 30 who refused CPAP therapy and did not even use the device for at least one day, and 15 who had been previously treated; a total of 708 females was studied. The baseline characteristics of the sample are depicted in [table 1](#). Most females included in the study had severe OSA (496 (70.1%)), whereas mild-to-moderate OSA was present in 212 (29.9%) females.

Patients were followed up for a median of 6.2 (IQR 4.2–7.7) years. During the study period, CPAP dropout occurred in 129 (18.2%) females and CPAP was withdrawn due to OSA resolution or death in 12 (1.6%) and 45 (6.3%) cases, respectively. Only five (0.7%) females were lost to follow-up. The proportion of females still on CPAP therapy at 5 and 10 years was 82.8% and 79.9%, respectively ([fig. 1](#)). The median use of CPAP for the entire cohort was 6 (IQR 4–7) $\text{h}\cdot\text{day}^{-1}$, with differences between those females who continued on CPAP treatment (median 6 h, IQR 5–7 h) and those who dropped out (median 1, IQR 0–2 h). CPAP compliance was similar in patients with mild-to-moderate and severe OSA (median 6.0 (IQR 3–7) *versus* 6.0 (IQR 4–7) $\text{h}\cdot\text{day}^{-1}$, respectively). Most females who continued on CPAP treatment (96.3%) had an objective daily use ≥ 4 h.

In the univariate Cox analysis, age, BMI, psychoactive medication, AHI and CPAP pressure predicted long-term CPAP compliance, whereas the oximetric parameters of the sleep study, cardiovascular comorbidities, type of CPAP titration and EDS measured by the ESS were not associated with adherence ([table 2](#)). No significant interactions were found between CPAP pressure and AHI, BMI and titration method, or between AHI and BMI. The results of the multivariate Cox analysis showed that the baseline variables independently

TABLE 1 Baseline characteristics of the sample

Categorical variables	
Valme Sleep Clinic	565 (79.8)
Polysomnography	292 (41.2)
Conventional CPAP titration	453 (64.0)
Psychoactive medication	244 (34.5)
Arterial hypertension	501 (70.8)
Diabetes mellitus	246 (34.7)
Hyperlipidaemia	391 (55.2)
Previous stroke/ischaemic heart disease	108 (15.3)
Smoking habit >20 pack-years	94 (13.3)
Alcohol intake >10 g·day ⁻¹	41 (5.8)
Continuous variables	
Age years	60 (52–67)
Body mass index kg·m ⁻²	37.5 (32.4–43.0)
Epworth Sleepiness Scale	13 (9–16)
Apnoea/hypopnoea index	43 (27.2–66.8)
% of time spent with oxygen saturation below 90%	13.3 (3.0–42.9)
Minimum oxygen saturation %	74 (62–81)
CPAP pressure cmH ₂ O	9.0 (8.0–11.0)

Data are presented as n (%) or median (interquartile range). CPAP: continuous positive airway pressure.

associated with CPAP dropout were the use of psychoactive medication (hazard ratio (HR) 1.47, 95% CI 1.03–2.08), age (HR 1.01, 95% CI 1.00–1.03) and CPAP pressure (HR 0.89, 95% CI 0.81–0.96) (table 3).

Discussion

To the best of our knowledge, this is the first study to assess long-term CPAP compliance in a large cohort of females with OSA. In this large study, which included 708 consecutive females with OSA who started CPAP therapy and were followed up for >6 years, we have shown that CPAP compliance in females is good, with 82.8% still on treatment 5 years after starting the therapy. Independent baseline predictors of CPAP dropout were use of psychoactive drugs and increasing age, whereas a higher CPAP pressure level was associated with continued treatment.

Although several studies have investigated long-term adherence rates and predictors of CPAP compliance, most of these cohorts were predominantly composed of males and the number of females included was usually small, accounting for only 7–17% of the samples [12, 14–16, 20], so their findings may not be extendible to females. It is known that females manifest OSA differently from males [2–5]. They usually present a less-severe sleep disorder [22] and a distinct physiopathology of upper airway collapse [23]. Furthermore, sex itself has been identified by some researchers as a predictor of both good and bad adherence [15, 18], whereas other authors did not find sex to be independently associated with CPAP compliance [9, 10, 12, 28]. For all these reasons, adherence to CPAP therapy should be specifically assessed in females. The results of our study show that 82.8% of the females were still using CPAP 5 years after

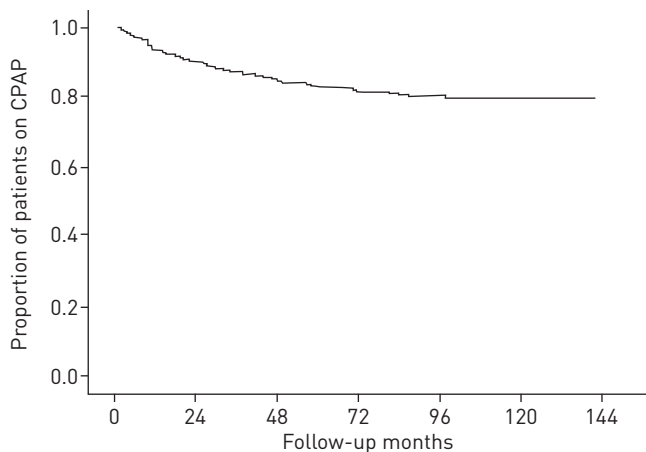


FIGURE 1 Kaplan–Meier plot showing the proportion of patients on continuous positive airway pressure (CPAP) therapy versus time. The probability of still being on CPAP therapy at 5 and 10 years was 82.8% and 79.9%, respectively.

TABLE 2 Association between baseline variables and continuous positive airway pressure (CPAP) dropout by univariate Cox analysis

Variables	CPAP dropout	Still on CPAP	Hazard ratio (95% CI)	p-value
Subjects	129	579		
Valme Sleep Clinic	98 (75.9)	467 (80.6)	0.83 (0.55–1.25)	0.38
Polysomnography study	54 (41.8)	238 (41.1)	0.87 (0.72–1.46)	0.87
Conventional CPAP titration	77 (59.6)	376 (64.9)	0.83 (0.58–1.18)	0.32
Psychoactive medication	55 (42.6)	189 (32.6)	1.46 (1.03–2.07)	0.033
Arterial hypertension	85 (65.8)	416 (71.8)	0.78 (0.54–1.12)	0.180
Diabetes mellitus	52 (40.3)	194 (33.5)	1.33 (0.94–1.90)	0.106
Hyperlipidaemia	68 (52.7)	323 (55.7)	0.89 (0.63–1.26)	0.54
Previous stroke or ischaemic heart disease	17 (13.1)	91 (15.7)	0.85 (0.51–1.42)	0.55
Smoking habit	18 (13.9)	76 (13.1)	1.07 (0.65–1.07)	0.77
Alcohol intake	9 (6.9)	32 (5.5)	1.20 (0.61–2.37)	0.58
Age	61 (53–71)	60 (52–66)	1.01 (1.00–1.03)	0.031
Body mass index kg·m ⁻²	35.8 (32.0–43.0)	37.6 (32.9–43.0)	0.97 (0.95–1.00)	0.067
Epworth Sleepiness Scale	12 (8–15)	13 (9–16)	0.97 (0.94–1.01)	0.162
CPAP pressure cmH ₂ O	8 (8–10)	9 (8–11)	0.89 (0.82–0.97)	0.009
Apnoea/hypopnoea index	38 (25–61)	45 (28–69)	0.99 (0.98–0.99)	0.019
% of time spent with oxygen saturation below 90%	11 (3–41)	15 (3–44)	0.99 (0.99–1.00)	0.58
Minimum oxygen saturation %	73 (61–82)	74 (62–81)	1.00 (0.98–1.01)	0.97

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated.

starting treatment, a figure that resembles the 81% reported by KOHLER *et al.* [12] and surpasses both the 68% of MCARDLE *et al.* [14] and the 67% reported by PELLETIER-FLEURY *et al.* [15], although it is lower than the 85% at 7 years reported by KRIEGER *et al.* [13]. The median use of CPAP in our series was 6 h·day⁻¹, which falls within the range of 5.0–6.2 h·day⁻¹ reported in other long-term studies [12–16]. We therefore consider that CPAP adherence in females with OSA is good and, although we did not compare adherence rates with those of males, they at least do not seem to be worse than those reported for mixed cohorts mainly composed of males.

The pattern of CPAP use is established early, within the first weeks of treatment, and is predictive of long-term use, but specific predictive variables of CPAP compliance have not been identified and the various studies that have assessed this topic have yielded conflicting results [9, 11–14, 16–18, 20, 28–31]. As our study is the first exclusively devoted to females, and as these predictors may vary in both sexes, it is difficult to compare our findings with those of other researchers. We have found that intake of psychoactive drugs, age and CPAP pressure level were independent predictors of long-term CPAP adherence in females.

The association between pressure level and adherence is not clear. PELLETIER-FLEURY *et al.* [15] found that a pressure of ≥ 12 cmH₂O was an independent predictor of bad compliance, probably associated with a higher proportion of side-effects, whereas JANSON *et al.* [11] reported that patients who continued using CPAP required a higher pressure than those who stopped the therapy (9 versus 8 cmH₂O, $p < 0.05$). SUCENA *et al.* [20] also found that compliance was significantly correlated with pressure level, so that a higher pressure was linked to a better adherence during follow-up. Other authors, however, did not find that pressure level influenced

TABLE 3 Variables associated with continuous positive airway pressure (CPAP) dropout: results of the adjusted multivariate Cox regression analysis

Variables	Adjusted model [#]	
	Hazard ratio (95% CI)	p-value
Age	1.01 (1.00–1.03)	0.043
Psychoactive medication	1.47 (1.03–2.08)	0.031
CPAP pressure	0.89 (0.81–0.96)	0.007

[#]: adjusted for age, body mass index, Epworth Sleepiness Scale, CPAP pressure, apnoea/hypopnoea index, psychoactive medication use, arterial hypertension, diabetes mellitus and CPAP titration method.

adherence when other confounders were adjusted for [12–14]. In our study, higher CPAP pressures were independently associated with continued treatment. Although higher pressure suggests greater OSA severity [15], in our study, determinants of OSA severity such as AHI and oximetric parameters were not associated with adherence in the adjusted model. We hypothesise that higher pressures may have been needed to control other variables more subtly linked with OSA severity, such as snoring or respiratory effort-related arousals, which are known to be associated with clinical complaints of OSA and may explain why these females were more adherent. Unfortunately, these variables were not assessed in this study.

Unlike other researchers [12–14], we did not find OSA severity to be an independent predictor of CPAP adherence. In our study, OSA severity measured by the AHI was associated with adherence in the univariate analysis, but it was no longer associated with compliance when other confounders were adjusted for. Oximetric parameters were not associated with adherence in either the univariate or multivariate analyses. As most studies that have analysed adherence have either predominantly or exclusively included males, it may be possible that this association between OSA severity and adherence cannot be applied to females. In fact, it is known that females usually have a lower AHI (and, therefore, a lower OSA severity) than males [22], so this variable may not be an independent predictor of adherence in females, as we have found in our study. Nevertheless, given the high proportion of females with severe OSA in our study (70.1%), a possible selection bias with regard to the association between OSA severity and compliance cannot be ruled out.

Females with increasing age were at higher risk of CPAP dropout in our cohort, which concurs with the findings of JANSON *et al.* [11], who reported that a greater age was an independent predictor of noncompliance and CPAP dropout, mainly due to nasal and pharyngeal side-effects. Other comorbidities, such as nocturia, have been found to be independently associated with poorer CPAP adherence in an elderly OSA cohort [17]. Although age has not been acknowledged as an independent predictor of adherence in other studies [10, 12, 14, 15], the median age of our cohort was 60 years, which is significantly higher than the 50–55 years of the participants in those studies. These findings concur with the knowledge that females are usually diagnosed with OSA at a greater age than males [2, 22]. It is, therefore, possible that older females may be more prone to stopping CPAP due to additional problems, such as neurological impairment, dementia and physical disability, which may be more closely linked to age than to sex. Nevertheless, given that the aforementioned studies were conducted in a predominantly male population (males accounted for 83–92% of the samples in these studies), it cannot be ruled out that females may behave differently regarding the association between age and adherence.

Some psychiatric disorders, such as anxiety and depression, are common in females with OSA, and they are usually frontline complaints in individuals referred for suspicion of this sleep disorder. Moreover, OSA females have been reported to be heavier users of psychoactive medications, such as anxiolytic and antidepressant drugs, than OSA males [5, 32]. Although one study has observed that CPAP adherence was not correlated with baseline levels of depression, anxiety and stress, some psychological variables have been implicated in the prediction of adherence to CPAP [19, 31]. In our cohort, the use of psychoactive medication independently predicted CPAP dropout, suggesting that it may be either a risk factor *per se* or a marker of an underlying psychiatric disorder, or may simply reflect a poorer perceived health status and quality of life, a feature that has been associated with poorer CPAP adherence in females [15].

The lack of any association between CPAP compliance and EDS measured by the ESS was not unexpected, as this score may not be an adequate tool for assessing daytime somnolence in females. BALDWIN *et al.* [33] observed that the ESS was a more sensitive measure of subjective sleepiness in males than in females, and recent data from the Wisconsin Sleep Cohort showed that sleep-disordered breathing was not associated with significant increased subjective sleepiness (measured by the ESS) in females of any age [34].

Our study has some limitations. Although it is a prospective observational cohort study, the main end-points were cardiovascular outcomes and not treatment adherence, so some potentially interesting variables, such as type of interface, use of humidifiers, adherence during the first weeks of use, specific side-effects and social factors, have not been evaluated. In addition to EDS, other symptoms or questionnaires that may have been useful in determining the women's quality of life or health status were not recorded; more subtle determinants of OSA severity, such as snoring, arousals or respiratory effort-related arousals, were also not recorded. Finally, although the use of psychoactive drugs was strongly associated with CPAP dropout, we did not separately record the different types of medication included in this group (hypnotics, antidepressants, anxiolytics, *etc.*); we also did not investigate the presence of baseline comorbid psychiatric disorders, which may have provided us with a more precise understanding of the association between this variable and CPAP adherence. It is therefore possible that these patients were less compliant as a result of concomitant comorbid depression or insomnia, or even side-effects associated with these treatments, rather than any direct effect of the psychoactive medication.

In conclusion, in a large cohort of OSA females with a prolonged follow-up, we have shown that most of them are still using CPAP 5 years after starting the treatment. Psychoactive medication and increasing age independently predicted CPAP dropout, whereas a higher CPAP pressure level was associated with continued use of the therapy. These findings imply that older females under psychoactive medication should be carefully followed up to detect adherence problems.

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