EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

The role of CPAP treatment in elderly patients with moderate obstructive sleep apnea. A Multicenter Randomised Controlled Trial

S. Ponce, E. Pastor, B. Orosa, G. Oscullo, P. Catalán, A. Martinez, L. Hernandez, A. Muriel, E. Chiner, M.A. Martinez-Garcia

Please cite this article as: Ponce S, Pastor E, Orosa B, *et al*. The role of CPAP treatment in elderly patients with moderate obstructive sleep apnea. A Multicenter Randomised Controlled Trial. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00518-2019).

Journal. *European Respiratory Journal*
Original Contribution

Title

The role of CPAP treatment in elderly patients with moderate obstructive sleep apnea. A Multicenter Randomized Controlled Trial.

Ponce S. (1), Pastor E. (2), Orosa B. (1), Oscullo G. (3), Catalán P. (4), Martinez A. (5), Hernandez L. (6), Muriel A. (7), Chiner E. (2), Martinez-Garcia MA. (3) on behalf the group of sleep respiratory disorders of the Sociedad Valenciana de Neumología.

(1) Pneumology Department. Hospital Universitario Dr Peset. Valencia. Spain
(2) Pneumology Department. Hospital Universitario San Juan. Alicante. Spain
(3) Pneumology Department. Hospital Universitario y Politécnico La Fe. Valencia. Spain.
(4) Internal Medicine Department. Hospital General de Requena. Valencia. Spain
(5) Pneumology Departmenty. Hospital General Universitario de Castellón. Spain
(6) Pneumology Department. Hospital General Universitario de Alicante. Valencia
(7) Clinical Biostatistics Unit, Hospital Universitario Ramón y Cajal, IRYCIS. CIBERESP. Nursing Department, Alcala University, Madrid, Spain.

Correspondence to:
Miguel Ángel Martínez-García
Pneumology Department
Hospital Universitario and Politécnico La Fe.
Bulevar Sur s/n
46012-Valencia. Spain
Mail: mianmartinezgarcia@gmail.com

Phone (+34) 609865934

This article has an online data supplement, which is accessible from this issue's table of contents online

Author Contributions:

Ponce Perez S. and Martinez-Garcia MA participated in the study's conception and design, supervised the study and wrote the manuscript.

Muriel A participated in the data interpretation.

Pastor E., Catalán P, Martinez A, Hernandez L., Orosa B, Oscullo G and Chiner E. participated in the data collection.

All the other authors contributed to data acquisition and interpretation, critically revised the manuscript and approved the final version for publication.

All the authors take responsibility for the accuracy and completeness of the data and analyses reported, and for the fidelity of the studies to the protocols. The first manuscript draft was written by the first and last authors (SP and MAMG.), with input from all the authors. All authors made the decision to submit the manuscript for publication and approved the manuscript for submission.

Financial support: Fundación Valenciana de Neumología

ABSTRACT

The efficacy of continuous positive airway pressure (CPAP) treatment in elderly patients with non-severe obstructive sleep apnea (OSA) is controversial.

The objective of this study was to assess the effect of CPAP treatment in elderly patients with moderate OSA on clinical, quality of life and neurocognitive spheres.

Open-label, randomized, multicenter clinical trial in 143 elderly (⩾70 years old) patients with confirmed moderate OSA (apnea-hypopnea index between 15 and 29.9 events/hour^{-1}) randomized to receive CPAP (n=73) or no CPAP (n=72) for 3 months. The primary endpoint was the Epworth Sleepiness Scale (ESS) value, and the secondary endpoints included quality of life (Quebec Sleep Questionnaire [QSQ]), sleep-related symptoms, presence of anxiety/depression, office-based blood pressure measurements and some neurocognitive tests. The analysis was performed according to the intention-to-treat principle.

Mean (SD) age was 74.9 (4.6) years. The CPAP group achieved a greater improvement in the EES value (adjusted difference of 2.6 [95%CI: 3.6-1.6], effect size: 1), in some sleep-related symptoms and in some dimensions of the QSQ questionnaire (nocturnal symptoms: 0.7 [95%CI: 0.3-1];p<0.0001, and emotions: 0.4 (0.1-0.7);p=0.023). However, CPAP did not demonstrate any effect on either the neurocognitive tests (including anxiety and depression) or the blood pressure levels. There was a positive correlation between the effect of CPAP and the improvement in EES values and quality of life domains.

CPAP treatment resulted in a significant improvement in diurnal hypersomnia and some sleep-related symptoms and quality of life domains in elderly patients with moderate OSA.

Clinical trial registered with www.clinicaltrials.gov (NCT03079466)

Key-words: Sleep-disordered breathing, sleep apnea, CPAP, continuous positive airway pressure, elderly

INTRODUCTION

Obstructive sleep apnea (OSA) is one of the most commonly found diseases in the general population, and its prevalence is expected to rise in the future, for various reasons: the endemia of obesity, greater access to diagnostic techniques, and increased life expectancy [1,2]. The prevalence of OSA in the elderly is higher than that in the middle-aged population but little is known about the effect of OSA and continuous positive airway pressure (CPAP) on the elderly population [3,4]. This is basically because there is a physiological increase in the number of sleep-related respiratory events with age [5]. However it is not know what is the cut-off point on the apnea-hypopnea index (AHI) that distinguishes the physiological from the pathological in elderly, although it is likely higher than the AHI ≥5 events/hour that is habitually used to define OSA [5]. It is therefore difficult to establish which elderly patients will benefit from CPAP treatment, especially in non-severe forms of OSA.

A recent clinical trial undertaken by our work group demonstrated the efficacy of 3 months of CPAP, in terms of both clinical findings and quality of life in patients ⩾70 years with severe OSA (AHI ⩾30) [6]. Similarly, another clinical trial reported a positive effect of 12 months of CPAP treatment on hypersomnia, but not on the quality of life, in patients ⩾ 65 years with symptomatic OSA (Epworth Sleepiness Scale [ESS] ⩾9) [7]. In the light of these results, the main objective of the present study was to analyze the effect of CPAP in patients ⩾70 years referred to sleep units on suspicion of OSA in whom a moderate OSA was diagnosed by respiratory polygraphy (RP) or full polysomnography (PSG).

METHODS

Design overview and setting

This was an open-label, randomized, multicenter clinical trial of parallel groups with a blinded end-point design, conducted in 6 teaching clinical centers in Spain in elderly patients sent to sleep laboratories because of clinical suspicion of OSA, and diagnosed with moderate OSA. Patients were randomly assigned to either CPAP or no therapy for 3 months. The study was approved by the Ethics Committee of each participating center. All the participants provided informed signed consent. The study's quality was evaluated according to the Consolidated Standards of Reporting Trials (CONSORT) items. The trial was registered in clinicaltrials.gov with the identifier number: NCT03079466

Participants

Consecutive patients referred to the sleep laboratories due to clinical suspicion of OSA were recruited from the participating centres. Patients were initially eligible for participation in the study if they were aged $\geqslant$70 years and had an AHI between 15 and 29.9 events/hour^{-1}. (8). Exclusion criteria included current use of CPAP treatment, central sleep apnea (defined as at least 50% of respiratory events with a pattern of apnea or hypopnea without any respiratory effort), respiratory failure (defined as diurnal oxygen saturation below 90%), severe heart failure (New York Heart Association functional class III–IV), a cardiovascular event in the month prior to inclusion in the study, disabling hypersomnia (ESS$\geqslant$18), and previous severe impairment of cognitive performance that, in the opinion of the researchers, ruled out their inclusion in the study.

Procedures

Sleep study and CPAP pressure titration

Each participant was subjected to a sleep study, either full standard polysomnography (PSG) (Alice 5. Respironics, Inc), or respiratory polygraphy (RP) (Alice Pdx, Respironics, Ins), with a device previously validated against PSG. All the data were interpreted manually. We followed the Spanish Society of Pneumology and Thoracic Surgery guidelines for the diagnosis and treatment of OSA [9] (more information in supplemental material).

Initial visit

At the initial visit after the sleep study, all the patients completed a standardized protocol that included general and anthropometric data, personal history especially related to cardiovascular, depression, anxiety or other neurocognitive diseases, current medication, and clinical history related to OSA, including chronic snoring, witnessed apneas, daytime hypersomnolence, nightmares, choking, and nocturia (based on the patient's report that he/she would wake up to go to the toilet at least 2 times during the night). The validated Spanish version of the ESS was used to quantify daytime somnolence [10]

All patients completed a specific sleep-related quality-of-life questionnaire: the validated Spanish-language version of the Quebec Sleep Questionnaire (QSQ). The QSQ includes the quantification of diurnal and nocturnal symptoms, hypersomnolence, and social interactions and emotional aspects [11,12] Cognitive function was assessed by an extensive neuropsychological battery administered at the same time of day in each evaluation (09:00 h) by trained, blinded personnel; this covered subjective sleepiness, executive function, visual

attention, speed of processing and mental flexibility (Trail Making Test (TMT) A and B) [13], working memory (digit symbol and digit span tests) [14], and symptoms of anxiety or depression (hospital anxiety and depression tests) [15]. Finally, three office-based blood pressure measurements were taken, following international recommendations [16].

Follow-up

The follow-up period was 3 months, during which the patient (with or without CPAP) had direct contact with the research team at all times for the resolution of clinical problems or doubts related to the study. Medical appointments were scheduled for all patients at 4 and 12 weeks after randomization, to ensure the same number of medical visits in all patients (with or without CPAP). Every medical appointment involved protocol-based assessments of the following: adherence to CPAP and side effects (for CPAP group) and changes in treatment, and reevaluation of the exclusion criteria. At the last medical appointment, after 12 weeks, all the patients again completed a standardized protocol that included sleep-related symptoms, neurocognitive tests, QSQ, and blood pressure measurements taken at the same time as the pre-randomization tests. Adherence to CPAP was always objectively assessed by reading the device's time counter from the start of treatment to the end of the follow-up. Patients were classified as being adequately treated with CPAP if the treatment had started and the average cumulative adherence was $\geqslant$4 h/day−1.

Primary outcome

The primary outcome is the change (from the beginning of the study to the end of follow-up) of the ESS. Secondary outcomes include quality of life (Quebec Sleep Questionnaire [QSQ]), sleep-related symptoms, presence of anxiety/depression, office-based blood pressure measurements and some neurocognitive tests

Statistical analysis

Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartil range), while categorical variables were reported as absolute numbers and percentages.

The sample size was calculated on the basis of a clinically significant change in the primary endpoint (ESS) of 2 points (based on McMillan et al results (7)) and assuming an alpha error of 5%, a statistical power of 80% and a 10% of withdrawals during the follow-up, with a result of 71 patients needed per randomized arm. The analysis was performed according to the intention-to-treat (ITT) principle. Secondary endpoints included quality of life (QSQ domains), sleep-related symptoms, neurocognitive tests, and office-based blood pressure measurements changes.

Patients with an AHI between 15 and 29.9 events/hour^{-1} were eligible for randomization by software specifically designed to allocate groups for the patients. Random allocation stratified by site was used, without any other restriction. The software only revealed the allocation group when an investigator provided the data of a fully eligible patient, which guaranteed the concealment of the randomization sequence.

The intra-group differences from the beginning to the end of the study were evaluated with the paired t-test and the inter-group comparisons were assessed by analysis of covariance (ANCOVA), with adjustment for the corresponding baseline variable of the outcome. The x2 test was used to compare dichotomous variables. The effect size was estimated by dividing this difference by the standard deviation of the baseline measurement. As proposed by Cohen [17], an effect size of 0.20, 0.50 and 0.80 was considered as small, medium and large, respectively. Correlation between quantitative variables was analyzed using the Pearson test. Logistic regression analysis was used to estimate the odds ratio (OR) and 95% CIs of having clinical symptoms (as dichotomic variables) and/or EES ≥10 points in the CPAP group compared with the control group without CPAP, adjusting for the baseline status.

A 2-sided p-value <0.05 was considered significant. A multiple imputation method was implemented in 10 patients with missing follow-up data in the ESS value (n=3) or QSQ domain values (n=7), under the assumption that these data were missing at random. Stata (StataCorp), version 11 and SPSS predictive analytics software (IBM), version 21, were used for analysis.

RESULTS

183 patients were initially recruited between March 2017 to July 2017 and 145 were randomized: 73 to the CPAP arm and 72 to the no CPAP (Figure 1). No statistical or clinical differences were observed between the randomized groups (Table 1). Mean age was 74.9 (4.6) years; 87 (60.8%) patients were men; mean body mass index (BMI) was 30.5 (5.5) $kg \cdot m^{-2}$. 37.8% showed an ESS⩾10. None of the patients presented central sleep apnea. The mean AHI was 21.7

(4.8) events/h^{-1} (93% of events were obstructive), which was very similar to that for ODI3% 20.4 (9.9).

The average use of CPAP treatment was 5.2 (2.5) h/$night^{-1}$, with 20 patients presenting <4 h per night (72.6% with good adherence). The mean CPAP pressure used was 7.9 (1.8) cmH2O. The residual AHI following the application of CPAP during the titration study was 4 (3.2) events/h^{-1}. No change in BMI was observed between randomized groups over the course of the study (30.4 (5.5) versus 30.6 (5.7) $kg \cdot m^{-2}$; p=0.87). An RP was performed in 82.5% of the studies. No baseline differences were observed between those patients under RP and those under PSG.

Effect on the primary outcome (Epworth Sleepiness Scale) and other sleep-related symptoms

The EES values were 9.4 (4.1) and 8.9 (3.7) at baseline and 5.9 (3.5) and 8.3 (3.8) at the end of the follow-up for the CPAP (effect size 1) and control groups (effect size 0.2), respectively. After adjusting for the baseline ESS value, a significant decrease of 2.6 (95%CI -3.6 to -1.6) points was observed in the CPAP group compared with the control group. Those patients under CPAP treatment had 13.1 (95%CI 4.7-36.5; p>0.0001) more probability of decreasing the EES value to below 10 points than those not treated with CPAP (Table 2). There was a positive correlation between the change in EES values between groups and the number of hours of CPAP use (r=0.31, p=0.007). Although there was an increased dispersion of the ESS changes in those patients with increased use of CPAP, there were no differences in either the age or the AHI

values between the groups usng CPAP less than 6 hours/day and those using it more than 6 hours/day (Figure 2).

On the other hand, there was a significant improvement in snoring (OR: 20.8), witnessed apneas (OR: 8.7), and choking (OR 3.3), but not in nocturia (OR 0.6) and nightmares (OR 1.3), in the CPAP group (Table 2).

Effect on sleep-related quality of life

Table 3 shows that only the QSQ domains referred to nocturnal symptoms and emotions improved significantly in the CPAP group, compared with the control group, adjusting for their corresponding baseline values, especially the noctunal symptoms with an effect size of 0.88. There was a positive correlation between the changes between groups in the noctunal symptoms ($r=0.29$; $p=0.01$), emotional domain ($r=0.33$, $p=0.005$), and social domain ($r=0.35$, $p=0.003$) and the number of hours of CPAP use (Figure 3).

Effect on anxiety and depression scores and neurocognitive function

Twenty-six (17.7%) patients scored $\geqslant$11 points in depression on the Hospital Anxiety and Depression Scale (HADS), and 30 (20.4%) patients scored $\geqslant$11 points in HADS anxiety. Table 4 shows that CPAP treatment did not achieve a significant improvement in the HADS-depression and HAS-anxiety scores as well as any neurocognitive test

The TMT-A median [interquartil range] values were 94 (56-125) and 68.5 (50-132) at baseline and 70 (49-121) and 60 (47-100) at the end of the follow-up for

the CPAP and control groups, respectively. The TMT-B values were 200 (162-300) and 198 (127-300) at baseline and 186 (121-299) and 180 (113-300) at the end of the follow-up for the CPAP and control groups, respectively. No statistical differences were found in the intergroup analysis after adjusting for their corresponding baseline measures (-5.6 [95CI: -14.3 to 3], p=0.2) and -9.4 [95%CI -24 to 5.3], p=0.21) for TMT-A and TMT-B, respectively.

Effect on office-based blood pressure levels

Finally, no differences were observed in changes in either office-based systolic blood pressure (−0.9 versus −0.2 mmHg; p=0.9) or diastolic blood pressure (−1.3 versus −1.2 mmHg; p=0.8) measurements when comparing the CPAP and control groups.

Per protocol (PP) analysis

Those patients who tolerated CPAP for at least 4 hours per day (n=53) were compared with the control group without CPAP (n=71) in a per protocol analysis. (see supplemental data).

DISCUSSION

This study develops and expands previous trials in older people, by evaluating the efficacy of CPAP treatment in elderly patients with moderate to severe OSA. According to our results, CPAP improved the clinical picture related to OSA, including hypersomnia, as well as some aspects of the quality of life, without any changes in the neurocognitive sphere or blood pressure readings.

Only two clinical trials on the effect of CPAP on exclusive series of elderly OSA patients have been published to date. McMillan et al observed 12 months of CPAP treatment in patients aged over 65 years with OSA of any degree of severity: although they found an improvement in the degree of hypersomnia (2.1 points in the EES at 3 months and 2 points at 12 months), this was not the case in variables linked to the cost-effectiveness of the treatment, the quality of life, the neurocognitive state, and the blood pressure readings [7]. For their part, Martinez-Garcia et al observed a significant improvement in the clinical symptoms (the EES improved by 3.4 points), in the quality of life, and in some neurocognitive tests associated with working memory in patients aged over 70 years with a diagnosis of severe OSA (IAH ≥30) [6]. As the number of sleep-related respiratory events increases with age for physiological reasons [4,5,18-20], and as we do not know the AHI value that distinguishes the physiological from the pathological, it seemed reasonable to perform an RCT similar to the one performed by our group on severe OSA, using the same variables and a diagnostic method that would make it possible to calculate both the ODI and the AHI (RP or PSG) in elderly patients with moderate OSA (defined as an AHI between 15 and 29.9 events.hour^{-1}) [8].This also allowed us to make a direct comparison of the effects of CPAP on the results of the two clinical trials (severe OSA versus moderate OSA).

Although in the present study the effect on the main variable (ESS) improved on both a statistically and clinically significant basis, in keeping with the minimum important difference of 2 points recently calculated by Crook et al (20), this improvement (2.6 points) was not as substantial as the one attained with severe OSA (3.4 points). This difference is probably due to the greater

degree of baseline hypersomnia present with severe OSA as well as the probable greater etiological responsibility of severe OSA for hypersomnia, compared to moderate OSA. As regards other sleep-related symptoms, there was a similar improvement in severe OSA, although to a lesser extent, but there was no statistical difference in the incidence of nightmares or the degree of nocturia (although the nocturia did significantly improve in those patients with good compliance with CPAP). Maybe these two symptoms are less closely related to OSA itself in moderate cases but instead have a greater connection with other comorbidities common to elderly people.

One basic difference between the two studies is that all the domains of the quality of life improved with CPAP in severe OSA patients, whereas only two did so in moderate ones (nighttime symptoms and emotions). This could concur wth the improvements seen in the energy and vitality domains of the SF-36 questionnaire in the McMillan´s study [7]. However, the improvement was much more substantial in all the domains in the PP analysis, as this was only applied to patients with good CPAP compliance. It is possible that elderly patients with moderate OSA need more hours of CPAP to improve their quality of life than their counterparts with severe OSA, as the latter's quality of life is more markedly impacted by the disease [21-23] and is therefore more susceptible to improvement with CPAP. It is worth noting that although all the domains of QSQ presented a significant statistical improvement with CPAP compared to the control group, they did not reach the minimum clinically significant difference established by the authors of the QSQ [11]. However, it is important to bear in mind that the clinically significant differences of the QSQ were validated in a population with a mean age of 55 years, 20 years lower than

that of the patients included in the present study. Therefore, these minimum differences may not be applicable to the present study.

Another fundamental difference between the two studies was the lack of improvement (even in the PP analysis) in the questionnaires on anxiety and depression in moderate OSA, in contrast with the results in severe OSA, where there was a clear improvement even in the ITT analysis. The explanation for this phenomenon could be similar to that for the improvement in other symptoms like nocturia and nightmares, since it is possible that the presence of anxiety and depression (both very common in the elderly [24]) is more closely associated with severe OSA than with moderate OSA, and so an improvement with CPAP would be more likely in the former case.

Similarly, it was not possible to corroborate the neurocognitive improvement observed in severe OSA in moderate OSA, even in the PP analysis. This could be because only a low percentage of patients with moderate OSA and neurocognitive deficits are seen in the consulting room and are therefore susceptible to improvement. Accordingly, when patients with this type of deficit (such as those associated with Alzheimer's disease) have in fact been included, some studies have demonstrated a significant improvement with CPAP [25,26].

Finally, the initial rate (at 3 months) of compliance with CPAP was good (over 70%) in moderate OSA patients, with at least 4 hours a day; this was very similar to the readings for severe OSA, which shows that at this age the CPAP use is not very different to that observed in middle-aged patients, in contrast with the results of some other authors [22, 23].

Among the strengths of the present study, apart from the methodology of the multicenter clinical trial used, is the application of a methodology similar to that of the previous study conducted with elderly patients with severe OSA by our own group [6], which enabled us to directly compare the results of the two groups. Furthermore, there were very few lost patients or missing data.

The limitations of the study include the fact that 75% of the sleep tests were conducted with home polygraphy and 25% with full PSG. This situation was tolerated in order to be able to include hospitals with limited access to PSG. In any case, no patients were selected beforehand for one test or the other; this choice depended entirely on the equipment available in each hospital. Moreover, a comparison of the baseline variables of those patients who received PSG and those who received PR did not produce any statistically different results. Another potential limitation of the study is the absence of a placebo group receiving sham-CPAP, although in our opinion sham-CPAP is not a true placebo, as several authors have indicated [27,28]. Finally, only 20 of the 144 patients were aged over 80 years, so the results in very elderly people cannot be inferred from this study.

In conclusion, in patients aged 70 and over referred to sleep units on suspicion of OSA, CPAP treatment significantly reduce the degree of hypersomnia and other sleep-related symptoms, along with improvements in some health-related quality of life domains, but it has no effect on neurocognitive variables, blood pressure readings, or the degree of anxiety and depression. The improvement in the quality of life largely depends on good compliance with CPAP, and so elderly patients selected for CPAP treatment must be closely monitored in this respect.

REFERENCES.

1. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. Lancet 2009; 374: 1196-1208.
2. Levy P, Kohler M, McNocholas WT, Barbe F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea symdrome. Nature Reviews 2015; 1: 1-20
3. Martinez-García M.A, Amibilia J, Chiner E, Queipo C, Diaz M, Carmona C, et al. Sleep apnea in patients of elderly: care activity in Spain (2002-2008). Arch Bronconeumología 2010; 46:502-507.
4. Netzer NC, Ancoli-Israel S, Bliwise DL, Fulda S, Roffe C, Almeida F, et al. Principles of practice parameters for the treatment of sleep disordered breathing in the elderly and frail elderly: the consensus of the International Geriatric Sleep Medicine Task Force. Eur Respir J 2016; 48: 992-1018
5. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men. Prevalence and severity. Am Respir J Crit Care Med 1998; 157: 44–148.
6. Martínez-García MA, Chiner E, Hernández L, Cortes P, Catalán P, Ponce S, et al. Obstructive sleep apnoea in the elderly: role of continuous positive airway pressure treatment. A randomised, controlled trial. Eur Resp J 2015; 46:142-51.
7. McMillan A, Bratton DJ, Faria R, Laskawiec-Szkonter M, Griffin S, et al. PREDICT investigators. Continuous positive pressure in the respiratory tract in elderly people with obstructive sleep apnea syndrome: a randomized, multicenter, 12-month trial. Lancet Respir Med.2014;2: 804-814.
8. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep. 1999;22:667–89.
9. Lloberes P, Durán-Cantolla J, Martínez-García MA, Marín JM, Ferrer A, Corral J, et al. Diagnosis and treatment of sleep apnea-hypopnea syndrome. Arch Bronconeumol 2011; 47: 143-156

10. Chiner E, Arriero JM, Signes-Costa J, Marco J, Fuentes I. Validación de la versión española del test de somnolencia Epworth en pacientes con síndrome de apnea de sueño. Arch Bronconeumol 1999; 35: 422–427.
11. Lacasse Y, Bureau MP, Sériès. A new standardised and self-administrated quality of life questionnaire specific to obstructive sleep apnoea. Thorax 2004; 59: 494–499.
12. Catalán P, Martínez A, Herrerón A, Chiner E, Martinez-Garcia MA, et al. Consistencia interna y validez de la versión española del cuestionario de calidad de vida “Québec Sleep Questionnaire” para apnea obstructiva del sueño. Arch Bronconeumol 2012; 48: 107–113.
13. Lezack MD. Neuropsychological Assessment. 3rd Edn. New York, Oxford University Press, 1995.
14. Wechsler DA. Wechsler Adults Intelligence Scale (WAIS). Madrid, Tea Ediciones, 1976.
15. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–370.
16. 2007 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. World Health Organization-International Society of Hypertension guidelines for the management of hypertension. J Hypertens 2007; 25: 1115–1187.
17. Cohen J. Statistical Power Analysis for the Behavioral Sciences. NewYork, Academic Press, 1969.
18. Duran J, Esnaola S, Rubio R, De la Torre G. Obstructive apnea-hipopnea and related clinical features in a population based simple of subjects aged 30 to 70 years. Am J Respir Crit Care Med 2001;163: 685-689
19. Martinez-Garcia MA, Duran-Cantolla J, Monserrat JM. Sleep apnea-hypopnea syndrome in elderly. Arc Bronconeumol 2012; 46:479-488.
20. Crook S, Sievi NA, Bloch KE, Stradling JR, Frei A, Puhan MA, et al. Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomized controlled trials. Thorax. 2018 Aug 12. pii: thoraxjnl-2018-211959. doi: 10.1136/thoraxjnl-2018-211959

21. Martinez-Garcia MA, Soler JJ, Román P, Gonzalez V, Amorós C, Montserrat JM. Obstructive sleep apnea has little impact on quality of life in the elderly. Sleep Med 2009; 10: 104-11
22. Weaver TE, Chasens ER. Continuous positive airway pressure treatment for sleep apnea in older adults. Sleep Med Rev 2007; 11: 99–111.
23. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008; 5: 173–178.
24. Saunamaki T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2007; 116: 277–288.
25. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensud KE, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older woman. JAMA 2011; 306: 613–619.
26. Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natajaran L, et al. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. J Am Geriatr Soc 2008; 56: 2076–2081.
27. Hein H. Is sham CPAP a true placebo? Am J Respir Crit Care Med 2002; 165: 305.
28. Schwartz SW, Cimino CR, Anderson WM. CPAP or placebo-effect? Sleep 2012; 35: 1585–1586

Figure Legends

Figure 1. Flow-chart of the study.

Figure 2. Correlation between intergroup changes between groups in the Epworth Sleepiness Scale and the number of hours of CPAP use.

Figure 3. Correlation between intergroup changes in the Quebec Sleep Questionnaire domains and the number of hours of CPAP use.

Table 1. Baseline characteristics of randomized patients.

Variable	All patients	CPAP treatment	No CPAP treatment
Subjects	143	73	72
Age, yrs	74.9 (4.6)	74.6 (4.2)	75 (5)
Gender, % males	95 (65.5%)	50 (68.5%)	45 (62.5%)
BMI, Kg/m2	30.4 (5.5)	31.1 (6.2)	29.6 (4.8)
BMI ≥30 mg/m2	74 (51.8%)	39 (53.4%)	35 (48.6%)
Neck circumference, cm	40.9 (3.6)	41.4 (3.5)	40.3 (3.9)
ESS	9.2 (4)	9.4 (4.2)	9 (3.7)
ESS ≥ 10	54 (37.8%)	28 (38.4%)	26 (36.1%)
Sleep study, respiratory polygraphy	118 (82.5%)	57 (78.1%)	61 (84.7%)
Arterial hypertension	100 (69.9%)	50 (68.5%)	50 (69.4%)
Diabetes	41 (28.7%)	19 (26%)	22 (30.6%)
Dyslipidemia	83 (58%)	42 (57.5%)	41 (56.9%)
Past CVE	28 (19.6%)	16 (21.9%)	12 (16.7%)
Atrial fibrillation	19 (13.3%)	9 (12.3%)	10 (13.9%)
COPD	16 (11.2%)	12 (16.4%)	4 (5.6%)
Insomnia	30 (21%)	16 (21.9%)	14 (19.4%)
Depression	24 (16.8%)	10 (13.7%)	14 (19.4%)
AHI, event h-1	21.7 (4.8)	22.2 (4.3)	21.3 (5.2)
ODI3%, event h-1	20.4 (9.9)	21.3 (7.8)	19.6 (11.7)
Tsat<90%, %	14.4 (25.5)	14.2 (28.1)	14.6 (22.7)
Central AHI, events h-1	1.43 (2.48)	1.32 (2.4)	1.53 (2.6)
Minimum 02 saturation, %	78.5 (10.4)	77.9 (8.7)	79.1 (11.9)

CVE: ischemic heart disease + cerebrovascular disease; ESS: Epworth Sleepiness Scale; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; AHI: Apnea-hypopnea index; ODI3%: Oxugen desaturation index at 3%; CPAP: Continuous positive airway pressure

Table 2. Changes in sleep-related symptoms between randomized groups in an intention-to-treat principle, adjusted for baseline measurements.

	CPAP treatment (n=73)		**Conservative treatment (n=72)**		**OR (95% CI)***	**p-value**
	Baseline	Follow-up	Baseline	Follow-up		
Snoring	70 (96%)	15 (20.5%)	66 (91.7%)	58 (80.6%)	20.8 (8.6-50.1)	<0.0001
Witnessed apneas	53 (73%)	11 (15.1%)	56 (77.8%)	42 (58.3%)	8.7 (3.7-19.9)	<0.0001
Choking	18 (24.7%)	4 (5.5%)	12 (16.7%)	9 (12.5%)	3.3 (1.1-12.2)	0.041
Nocturia	41 (56.2%)	31 (42.5%)	39 (54.2%)	23 (31.9%)	0.6 (0.3-1.2)	0.109
Nightmares	15 (20.5%)	9 (12.3%)	14 (19.4%)	10 (13.9%)	1.3 (0.4-3.8)	0.68
EES >10	28 (42.5%)	8 (11%)	26 (32%)	23 (33.3%)	13.1 (4.7-36.5)	<0.0001

Data are expressed as mean (SD), unless otherwise stated. ESS: Epworth Sleepiness Scale

*Adjusted for baseline data

Table 3. Changes in sleep-related quality of life (Quebec Sleep Questionnaire [QSQ]) between randomized groups in an intention-to-treat principle, adjusted for baseline measurements.

Variables	**CPAP treatment (n=73)**				**Conservative treatment (n=72)**				**Intergroup difference (95%CI)**	**p-value**
	Baseline	Follow-up	Effect size	Intragroup difference	Baseline	Follow-up	Effect size	Intragroup difference		
QSQ quality of life										
Hypersomnolence	5.5 (1.3)	5.9 (1.2)	0.31	-0.4 (1.3)	5.7 (1.1)	5.8 (1.3)	0.1	-0.1 (1)	-0.3 (-0.6, 0.1)	0.12
Diurnal symptoms	5 (1.5)	5.5 (1.3)	0.33	-0.5 (1.2)	5.2 (1.4)	5.3 (1.3)	0.1	-0.1 (0.9)	-0.3 (-0.6,-0.1)	0.12
Nocturnal symptoms	4.6 (1.4)	5.8 (1.2)	0.86	-1.2 (1.4)	4.7 (1.3)	5 (1.3)	0.23	-0.3 (1)	-0.7 (-1,-0.3)	<0.0001
Emotions	5.4 (1.4)	5.9 (1.3)	0.36	-0.5 (1.3)	5.5 (1.2)	5.4 (1.3)	0.1	0.1 (1)	-0.4 (-0.7,-0.1)	0.023
Social interaction	5.6 (1.4)	6.1 (0.9)	0.29	-0.4 (1.5)	5.8 (1.2)	6 (1.1)	0.16	-0.2 (0.9)	-0.1 (-0.4, 0.2)	0.38

Data are expressed as mean (SD), unless otherwise stated. QSQ: Quebec Sleep Questionnaire

Table 4. Changes in neurocognitive tests between randomized groups in an intention-to-treat principle, adjusted for baseline measurements.

Variables	**CPAP treatment (n=72)**				**Conservative treatment (n=73)**				**Intergroup difference (95% CI)***	**p-value**
	Baseline	Follow-up	Effect size	Intragroup difference	Baseline	Follow-up	Effect size	Intragroup difference		
HADS Anxiety	6.6 (4.4)	5.7 (4.5)	0.2	0.9 (3.5)	6.1 (4.9)	6.1 (4.9)	0	0 (2.4)	0.8 (0.2,1.7)	0.12
HADS Depression	6.7 (4.9)	6.4 (4.4)	0.1	0.3 (2.7)	5.8 (4.5)	5.8 (4.6)	0	0 (2.1)	0.2 (-0.9,0.5)	0.57
Digit Span	8.3 (4)	8.6 (2.1)	0.1	-0.3 (3.5)	8.4 (2.7)	8.3 (2.6)	0.03	0.1 (1.6)	-0.2 (-0.6,0.9)	0.63
Digit Symbol	21.2 (11.1)	23.2 (11.5)	0.2	-2 (6.3)	20.4 (10)	21.7 (11.2)	0.1	-1.3 (7.2)	-0.9 (-2.5,4.3)	0.59

Data are expressed as mean (SD), unless otherwise stated. HADS: Hospital Anxiety and Depression Scale; TMT: Trail Making Test

*Adjusted by baseline values

Figure 1

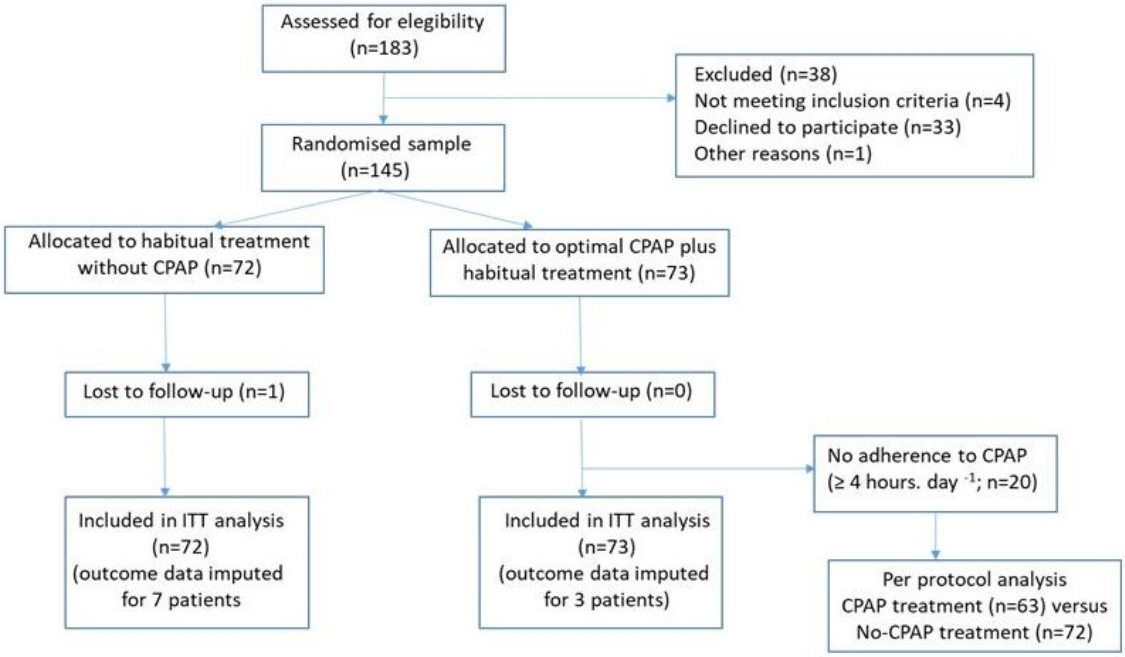

Assessed for elegibility (n=183)
Excluded (n=38)
Not meeting inclusion criteria (n=4)
Declined to participate (n=33)
Other reasons (n=1)
Randomised sample (n=145)
Allocated to habitual treatment without CPAP (n=72)
Allocated to optimal CPAP plus habitual treatment (n=73)
Lost to follow-up (n=1)
Lost to follow-up (n=0)
No adherence to CPAP (≥ 4 hours. day -1; n=20)
Included in ITT analysis (n=72) (outcome data imputed for 7 patients
Included in ITT analysis (n=73) (outcome data imputed for 3 patients)
Per protocol analysis CPAP treatment (n=63) versus No-CPAP treatment (n=72)

Figure 2

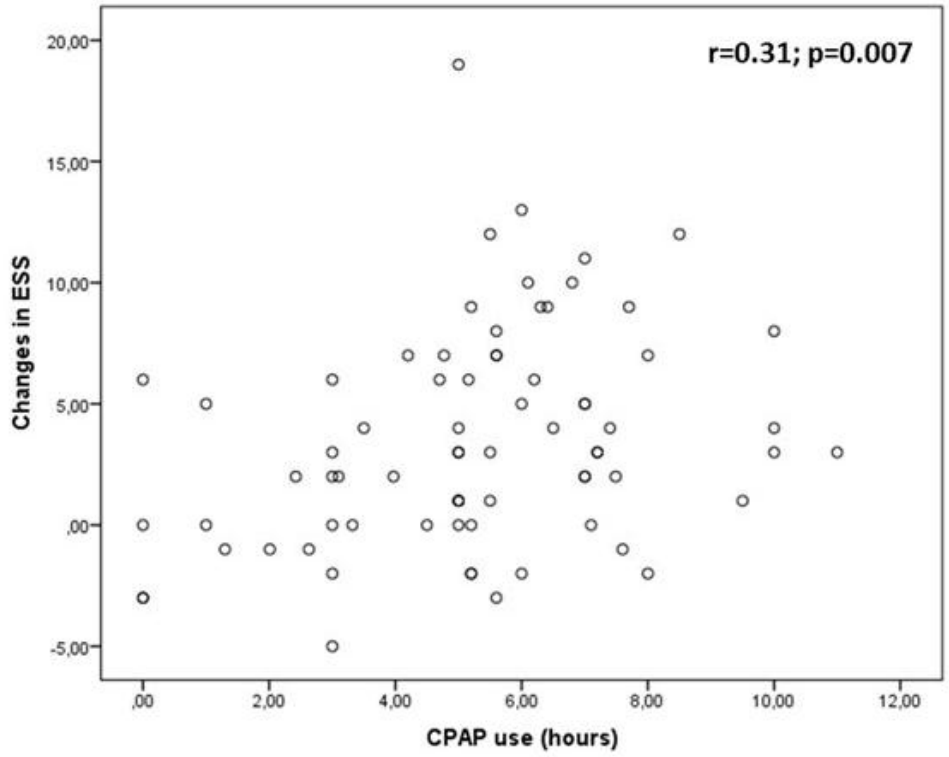
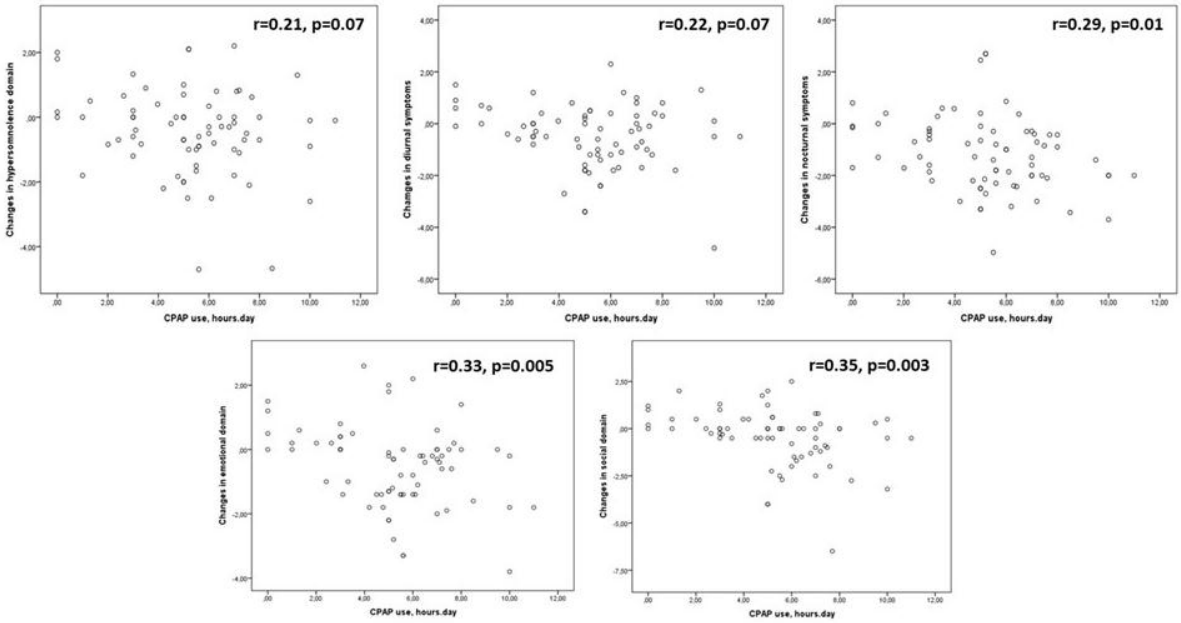

r=0.31; p=0.007
Changes in ESS
20,00
15,00
10,00
5,00
,00
-5,00
,00
2,00
4,00
6,00
8,00
10,00
12,00
CPAP use (hours)

Figure 3


r=0.21, p=0.07
Changes in hypersomnolence domain
CPAP use, hours.day
r=0.22, p=0.07
Changes in diurnal symptoms
CPAP use, hours.day
r=0.29, p=0.01
Changes in nocturnal symptoms
CPAP use, hours.day
r=0.33, p=0.005
Changes in emotional domain
CPAP use, hours.day
r=0.35, p=0.003
Changes in social domain
CPAP use, hours.day

Supplemental material

Sleep study and CPAP pressure titration

Each participant was subjected to a sleep study, either full standard polysomnography (PSG) (Alice 5. Respironics, Inc), or respiratory polygraphy (RP) (Alice Pdx, Respironics, Ins) with a device previously validated against PSG [1]. PSG included continuous recording of electro-encephalogram, electro-oculogram, electro-myogram, electro-cardiogram, evaluations of the nasal airflow, thoracic and abdominal band movements, and arterial oxygen saturation (SaO2), according to standard criteria [2]. RP included continuous recording of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements, and SaO2. All the patients undergoing RP who showed recording artefacts, discrepancy between the result of the RP and the pre-test clinical probability (pre-test clinical suspicion) of sleep apnea (especially in patients with high pre-test probability and unaltered RP results), predominance of central events, or a subjective sleep time of <3 h had a full PSG. Apnea was defined as interruption (>90%) of oronasal airflow for $\geqslant$10 s, and it was classified as obstructive or central, depending on whether respiratory effort was present or absent. Hypopnea was defined as a 30–90% reduction in the oronasal airflow for $\geqslant$10 s associated with a desaturation of $\geqslant$3% (and/or an arousal in the case of a PSG study). The AHI was defined as the number of apneas plus hypopneas per hour of sleep (PSG) or recording (RP). All data were recorded manually by the investigators.

Optimal CPAP pressure was titrated by an auto-CPAP device (S9 Autoset, Resmed Ltd) over three consecutive nights. The optimal pressure was determined, based on the visual evaluation of the raw data recording from the night study, with no significant leaks (<0.40 leaks/s^{-1}). This fixed pressure was then maintained throughout the study in those patients assigned to the CPAP arm.

Per protocol analysis

Per protocol analysis was also perfomed by comparing those patients with good adherence to CPAP treatment (n=66) with the control group without CPAP (n=72). For quantitative variables, baseline characteristics were compared using the t-test or U-Mann Whitney test, depending on the normal or non-normal distribution, and the x2 test was used for dichotomic variables. Intra-group and inter-group differences were analyzed using the same protocol as that used in the ITT analysis, in this case adjusting the results not only for the corresponding baseline measures but also for those baseline variables that demonstrated a statistical difference between groups ($p<0.1$), or for those variables that the researchers considered as clinically meaningful, regardless of the presence or otherwise of differences between groups.

When those patients who tolerated CPAP for at least 4 hours per day (n=53) were compared with the control group without CPAP (n=71), a statistically significant difference was observed in their baseline variables with respect to the domains of quality of life (except for that of diurnal symptoms, which was better in patients with poor tolerance), without any differences in any other parameter, although the EES value was 1.1 points higher in those who tolerated CPAP (without reaching statistical significance) (Table 1 suppl). When a PP analysis was applied, however, the treatment with CPAP improved significantly, not only in the parameters observed in the ITT but also in those related to all the quality-of-life domains (Table 2 suppl). The EES values were 9.7 (4.1) and 8.9 (3.7) at baseline and 5.2 (2.7) and 8.3 (3.8) at the end of the follow-up for the CPAP (effect size 1.1) and control groups (effect size 0.2), respectively. After adjusting for the baseline ESS value, a significant decrease of -3.5 (95%CI -4.5 to -2.5) points was observed in the CPAP group compared with the control group. Furthermore, CPAP was shown to provide protection against nocturia (OR 0.37 [95%CI: 0.2-0.9], p=0.025). However, there were no significant improvements, even in the PP analysis, in any of the neurocognitive tests analyzed (including those for anxiety and depression), or in the incidence of nightmares or in the blood pressure readings (Table 3 suppl)

References

1. Nilus G, Domanski U, Schroeder M, Franke KJ, Hogrebe A. Margarit L. Ensayo controlado aleatorio para validar el equipo ambulatorio Alice Pdx. El sueño de Nat Sci. 2017;9:171-180.
2. Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages Q5 Q6 of human subjects. Los Angeles, University of California, 1968.

Table 1 suppl. Comparative baseline characteristics of those patients randomized to CPAP with good (at least 4 hours/day) and bad compliance with the treatment.

Variable	**Good CPAP tolerance (n=53)**	**Bad CPAP tolerance (n=20)**	**p**
Age, yrs	74.6 (4.2)	75.5 (4.3)	0.46
Gender, n, (% males)	35 (66%)	15 (75%)	0.58
BMI, Kg/m2	30.8 (4.8)	31.9 (8.9)	0.49
AHI, events/hour-1	22.2 (4.2)	22.1 (4.9)	0.99
Tc90%, %	14.6 (30.9)	13.1 (19.6)	0.83
ODI3%, events/hour-1	21.5 (8.1)	20.6 (7.3)	0.67
CPAP pressure, cmH20	7.9 (1.9)	7.5 (1.6)	0.47
EES	9.7 (4.1)	8.6 (4.2)	0.28
QSQ domains			
Hipersomnolence	5.3 (1.4)	5.8 (1)	0.13
Diurnal symptoms	4.7 (1.5)	5.4 (1.4)	0.08
Nocturnal symptoms	4.1 (1.4)	5 (1)	0.01
Emotions	5 (1.4)	5.9 (1.3)	0.01
Social aspects	5.4 (1.6)	6.2 (0.9)	0.03
SBP, mmHg	128.7 (14.7)	128.4 (12.7)	0.32
DBP, mmHg	73.5 (8.7)	74 (8.8)	0.33
Neurocognitive measures			
TMT-A	108.5 (71.5)	88.6 (60.1)	0.27
TMT-B	215.2 (82.7)	197 (79.4)	0.39
Digital spam	8.4 (4.6)	8 (1.4)	0.68
Digital symbol	20.8 (11.7)	22.1 (9.4)	0.65
HADS test			
Depression	7 (4.8)	5.9 (5.2)	0.41
Anxiety	7.1 (4.2)	5.2 (4.6)	0.09

ESS: Epworth Sleepiness Scale; BMI: Body Mass Index; AHI: Apnea-hypopnea index; ODI3%: Oxygen desaturation index at 3%; CPAP: Continuous positive airway pressure; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; QSQ: Quebec Sleep Questionnaire; HADS: Hospital Anxiety-Depression Scale

Table 2 suppl. Changes in sleep-related quality of life (Quebec Sleep Questionnaire) between randomized groups in a per-protocol principle, adjusted for baseline measurements and baseline ESS value.

Variables	**CPAP treatment (n=53)**				**Conservative treatment (n=72)**				**Intergroup difference (95% CI)***	**p-value**
	Baseline	Follow-up	Effect size	Intragroup difference	Baseline	Follow-up	Effect size	Intragroup difference		
QSQ, quality of life										
Hypersomnolence	5.3 (1.4)	5.9 (1.2)	0.4	-0.6 (1.4)	5.7 (1.1)	5.8 (1.3)	0.1	-0.1 (1)	0.4 (0.02-0.8)	0.04
Diurnal symptoms	4.7 (1.5)	5.4 (1.3)	0.1	-0.7 (1.3)	5.3 (1.4)	5.4 (1.3)	0.1	-0.1 (0.1)	0.4 (0.06-0.8)	0.023
Nocturnal symptoms	4.1 (1.4)	5.5 (1.2)	1	-1.4 (1.5)	5 (1.3)	5.2 (1.3)	0.2	-0.2 (0.2)	0.8 (0.4-1.2)	0.0001
Emotions	5 (1.4)	5.8 (1.3)	0.6	-0.8 (1.2)	5.7 (1.2)	5.6 (1.3)	0.1	0.1 (0.1)	0.7 (0.3-1.1)	0.001
Social interaction	5.4 (1.6)	6.2 (0.9)	0.5	-0.8 (1.6)	5.8 (1.3)	6 (1.1)	0.2	-0.2 (0.2)	0.3 (0.1-0.65)	0.04

Data are expressed as mean (SD), unless otherwise stated. QSQ: Quebec Sleep Questionnaire.

*Adjusted by baseline measure and baseline EES (Epworth Sleepiness Scale).

Table 3 suppl. Changes in neurocognitive tests between randomized groups in a per-protocol principle, adjusted for baseline measurements and baseline EES value.

Variables	**CPAP treatment (n=53)**				**Conservative treatment (n=72)**				**Intergroup difference (95% CI)***	**p-value**
	Baseline	Follow-up	Effect size	Intragroup difference	Baseline	Follow-up	Effect size	Intragroup difference		
HADS Anxiety	7.1 (4.2)	6.3 (4.9)	0.2	0.8 (3.6)	6.1 (4.9)	5.8 (4.6)	0.1	0.3 (2.4)	-0.6 (-1.7, 0.5)	0.28
HADS Depression	7 (4.8)	6.3 (4.6)	0.1	0.7 (2.7)	5.8 (4.5)	6.1 (4.9)	0.1	-0.3 (2.1)	-0.5 (-1.3, 0.3)	0.23
Digit Span	8.4 (4.6)	8.6 (2.2)	0	-0.2 (4)	8.4 (2.7)	8.3 (2.6)	0	0.1 (1.6)	0.2 (-0.5,0.9)	0.58
Digit Symbol	20.8 (11.7)	23.1 (11.9)	0.1	-2.3 (6.9)	20.4 (10)	21.7 (11.2)	0.1	-1.3 (7.2)	0.7 (-3,1, 4.5)	0.68

*Adjusted for baseline measurements and baseline EES (Epworth Sleepiness Scale). HADS: Hospital Anxiety-Depression Scale