Published in final edited form as:

Sleep Med. 2009 December ; 10(10): 1101–1106. doi:10.1016/j.sleep.2008.12.016.

Continuous positive airway pressure deepens sleep in patients with Alzheimer's disease and obstructive sleep apnea

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Abstract

Objective—Patients with Alzheimer's disease (AD) and obstructive sleep apnea (OSA) experience disrupted sleep. This study examined the effect of continuous positive airway pressure (CPAP) on sleep parameters in AD patients with OSA.

Methods—A randomized placebo-controlled trial of 3 weeks of therapeutic CPAP (tCPAP) vs. 3 weeks placebo CPAP (pCPAP) followed by 3 weeks tCPAP in patients with AD and OSA. Polysomnography data from screening after one night and after three weeks of treatment were analyzed. Records were scored for percent of each sleep stage, total sleep time (TST), sleep efficiency (SE), sleep period (SP), time in bed (TIB), sleep onset (SO), wake time after sleep onset (WASO), and arousals. A randomized design comparing one night of pCPAP to tCPAP and a paired analysis combining 3 weeks of tCPAP were performed.

Results—Fifty-two participants (mean age=77.8 years, SD=7.3) with AD and OSA were included.

After one treatment night, the tCPAP group had significantly less % Stage 1 ($p=0.04$) and more % Stage 2 sleep ($p=0.02$) when compared to the pCPAP group. In the paired analysis, 3-weeks of tCPAP resulted in significant decreases in WASO ($p=0.005$), % Stage 1 ($p=0.001$), arousals ($p=0.005$), and in an increase in % Stage 3 ($p=0.006$).

Conclusion—In mild to moderate AD patients with OSA, the use of tCPAP resulted in deeper sleep after just one night, with improvements maintained for three weeks.

Keywords

sleep; obstructive sleep apnea; dementia; CPAP

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Introduction

Alzheimer's disease (AD) patients have disrupted sleep relative to aged controls [1,2], with less slow wave sleep (SWS) and more frequent awakenings and wake time after sleep onset (WASO) [1]. Some have hypothesized that there is an important association between the severity of these sleep disruptions and worsening cognitive function in AD [3,1].

In addition to the sleep disruptions associated with AD, patients with AD also have a reported increased incidence of obstructive sleep apnea (OSA) [4,5,6,7,8]. Our laboratory has previously shown that the sleep of AD patients with OSA is characterized by less rapid eye movement (REM) sleep compared to AD patients without OSA [9]. Continuous positive airway pressure (CPAP) is the most effective treatment for OSA and its effect on restoring consolidated sleep in patients without dementia is characterized by an increase in SWS and REM [10,11, 12,13].

As part of a larger study exploring the effect of CPAP on cognitive functioning in patients with mild to moderate AD and OSA [14], this study examined the effect of CPAP on sleep parameters in this population of patients. Although patients with AD without OSA have sleep disturbances, we hypothesized that treatment with CPAP would result in deeper, less disrupted sleep (manifested by increases in SWS and REM sleep and decreases in Stage 1 sleep, WASO, and arousals).

Methods

Participants

Four hundred and twenty persons with AD were screened for this study from several sources including the University of California San Diego (UCSD) Alzheimer's Disease Research Center, the UCSD Seniors Only Care Program, advertisements, referrals from neurologists at UCSD and in the general San Diego community, and from word of mouth. Ninety-eight participants were ultimately enrolled and fifty-two were eventually randomized (see Fig. 1). All participants were assessed for decisional making capacity. Written informed consent was obtained from the patient or from his/her legally authorized representative (if the patient did not have decisional making capacity). This protocol was reviewed and approved by the UCSD Human Research Protections Program.

Inclusion criteria included being over the age of 50 years, a diagnosis of possible or probable mild to moderate Alzheimer's Dementia (diagnosed by a neurologist according to the National Institute of Neurological and Communicative Disorders & Stroke-Alzheimer's Disease and Related Disorders Association [NINCDS-ADRDA] criteria) [15], having stable medical conditions and a reliable live-in caregiver. Only English-speaking patients with a Mini Mental Status Examination (MMSE) [16] score greater than 17 were enrolled. Patients were allowed to continue acetylcholinesterase inhibitors, psychotropic medications, memory enhancers, and health food supplements, as long as they had been stable on the same dose for at least two months prior to participation and agreed to continue on the same dose for the six-week duration of the study. Symptoms or manifestations of OSA including snoring and excessive daytime sleepiness or a suspicion of having OSA were not recruitment inclusion criteria.

Exclusion criteria included having a prior diagnosis of a sleep disorder or currently receiving treatment for OSA. Participants with severe underlying medical or psychiatric illnesses such as symptomatic chronic obstructive pulmonary disease, renal failure, symptomatic coronary or cerebral vascular disease, uncontrolled seizure disorder, or current substance abuse were excluded as these conditions could interfere with sleep quality.

Study Design—After informed consent was obtained, participants were scheduled for an overnight screening home polysomnogram (PSG) to determine the presence of OSA. Patients with an apnea hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) ≥ 10 were randomized to either six weeks of therapeutic CPAP (tCPAP) or three weeks of placebo CPAP (pCPAP) followed by three weeks of tCPAP.

Each participant was admitted to the UCSD General Clinical Research Center Gillin Laboratory of Sleep of Chronobiology (GCRC-GLSC) for two nights at the start of the study and another two nights three weeks later. At the end of the six weeks, all participants underwent an overnight PSG in their homes.

Polysomnographic Evaluation—All PSGs, both at home and on the GCRC-GLSC, were performed with the Embla recording system (Flaga Medical Devices/Medcare, Reykjavik, Iceland). Electroencephalogram (EEG; C3 and C4 derivations), electrooculogram (LOC and ROC derivations), sub-mental electromyogram (EMG), thoracic and abdominal respiratory efforts (piezoelectric bands), oral and nasal airflow (nasal pressure transducer and naso-oral thermistor), electrocardiogram (ECG), tibialis EMG, and peripheral oxygen saturation (SpO₂ via finger pulse oximetry) were recorded.

All sleep recordings were scored using the Rechtschaffen and Kales criteria [17]. The following standard parameters were computed: percent Stage 1, percent Stage 2, percent Stage 3, percent Stage 4, percent REM sleep, wake after sleep onset (WASO), sleep period (SP), sleep onset (SO), sleep efficiency (SE), time in bed (TIB), and total sleep time (TST). EEG arousals were scored according to the 1992 American Sleep Disorders Association criteria [18], and an arousal index (ArI; total number of arousals per hour of sleep) was computed. An arousal from sleep was defined as a sudden rise in EEG frequency (to alpha or theta) for 3 seconds or longer but less than 15 seconds [12].

CPAP and Placebo CPAP Titration—The REMstar Plus CPAP system with a built-in heated humidifier and the Comfort Select CPAP mask (Respironics, Murrysville, PA) were used by participants in both treatment groups. On the first night of the first admission to the GCRC-GLSC, those randomized to the tCPAP group underwent a standard CPAP titration PSG to establish the therapeutic pressure. CPAP pressure was started at 4 cm H₂O and was increased by two cm H₂O increments until 8 cm H₂O was reached. Further increases in pressure were achieved by 1 cm H₂O increments. Optimal therapeutic CPAP pressure was defined as that which eliminated most apneas and hypopneas, snoring, and sleep disruption associated with effort related arousals.

Participants in the pCPAP group were given a CPAP mask that contained ten ¼-inch drill holes to create a large air leak and to allow for adequate air exchange to prevent rebreathing. There was also a valve placed in the CPAP end of the hose to further reduce the pressure with the actual measured pressure at the CPAP mask ranging from 0.0 cm H₂O during inspiration to 0.5 cm H₂O at end-expiration. To create machine noise that was consistent with therapeutic CPAP, the placebo CPAP was set at a fixed 8 cm H₂O pressure (although as described, the actual pressure was less than 1 cm H₂O pressure). Participants assigned to the pCPAP group underwent a mock CPAP titration PSG using the placebo CPAP system set at a fixed 8 cm H₂O to control for noise.

On the second night of the GCRC-GLSC admission, all participants had a repeat PSG using the CPAP machine set at the titrated pressure determined on night one (i.e., either the therapeutic CPAP pressure or placebo CPAP). In the morning, participants were discharged to home with their assigned CPAP systems.

Three weeks later, participants were re-admitted to the GCRC-GLSC for another two nights. Both groups were told that their CPAP systems needed to be adjusted. The tCPAP group underwent a repeat PSG without a change in their previously determined CPAP pressure. Those in the pCPAP group were crossed over to tCPAP. They were given new masks and underwent a formal CPAP titration PSG to establish the therapeutic CPAP pressure, as described above. On the second night, all participants underwent a repeat PSG while using the CPAP machine set at the therapeutic pressure. In the morning, both groups were discharged (the pCPAP group for 3 weeks of therapeutic CPAP and the tCPAP group for a second three-week period of therapeutic CPAP).

Compliance with therapy was monitored by built-in clocks that recorded the number of hours the CPAP blower was switched on at the prescribed pressure and in use. The research associate visited the home once a week to retrieve the compliance data and to answer any questions.

All participants and caregivers received similar instruction and orientation to the CPAP systems. Research assistants made weekly calls or visits to ensure that the participants still understood how to use CPAP and answer any questions.

All participants and caregivers were kept blind to their randomization condition; this adequacy was tested by asking patients and caregivers after completion of the protocol if they thought they had real or placebo CPAP. As previously reported, there was no significant difference between responses in the two groups of patients (60% in the tCPAP group and 46% in the pCPAP group believed they had therapeutic CPAP; $p=0.59$) [14].

Data Analysis

The therapeutic versus placebo groups were compared at baseline to ensure that groups were comparable on demographic and clinical characteristics. A randomized design comparing one night of placebo to one night of therapeutic CPAP and a paired design analysis combining three weeks of therapeutic CPAP in both groups were performed. Although 52 patients were randomized, there were six tCPAP and two pCPAP participants who dropped out of the study at three weeks; one tCPAP and four pCPAP participants dropped out of the study at six weeks. Therefore, the paired analysis included 39 subjects. Two sample t-tests were used to compare sleep measures across groups, while one sample t-test was used for the paired analysis. We also conducted correlation analyses (both Spearman and Pearson) between changes in the Epworth Sleepiness Scale (ESS) score and changes in the sleep parameters after 3 weeks of therapeutic CPAP.

Statistical significance was defined as $p<0.05$ (two tailed). The statistical program R version 2.3.1 was used for all analyses [19].

Results

Demographics: Table 1 lists the participants' baseline demographics characteristics. There were 52 participants (39 men, 13 women) initially randomized. Mean age was 77.8 years ($SD=7.3$, range=53-91), and participants on average were mildly overweight, had mild to moderate dementia (mean MMSE=25.3, $SD=2.9$, range=18-30), and had 14 or more years of education. Although most participants completed the study, a total of 13 participants (25%) dropped out before the 6-week time point. Attrition rates were comparable across treatment arms (24%; $n=6$ in the pCPAP arm; 26%; $n=7$ in the tCPAP). There were no differences in demographic or clinical characteristics of participants who dropped out vs. those who completed the study.

Changes in sleep after one night of CPAP

Table 2 lists the sleep variables at screening and after one night of therapeutic or placebo CPAP treatment. Compared to the pCPAP group, the tCPAP group had a significant decrease in % Stage 1 sleep ($p=0.04$) and an increase in % Stage 2 sleep ($p=0.02$) after one night of therapeutic CPAP. There were no significant changes in % REM, % Stage 3, % Stage 4 sleep, ArI, SP, TIB, SE, or SO in either group.

Changes in sleep after three weeks of CPAP

In the paired analysis as shown in Table 3, three weeks of therapeutic CPAP resulted in significant decreases in mean WASO ($p=0.005$), TIB ($p=0.002$), SP ($p<0.001$), TST ($p=0.05$), ArI ($p=0.005$) and mean % Stage 1 sleep ($p=0.001$) and a significant increase in mean % Stage 3 ($p=0.006$). None of the correlations performed between changes in ESS and changes in sleep parameters after 3 weeks of CPAP were statistically significant.

Discussion

This study demonstrated that in mild to moderate AD patients with OSA, a single night of treatment with therapeutic CPAP, when compared to placebo CPAP, resulted in an immediate deepening of sleep with less time spent in Stage 1 and more time spent in Stage 2 sleep. These improvements in sleep were maintained following three weeks of therapeutic CPAP. In addition, three weeks of therapeutic CPAP resulted in more consolidated sleep with less time spent awake during the night, less arousals from sleep, and more time spent in deeper levels of sleep when compared to pre-CPAP treatment.

Our study's results are similar to those found in non-demented patients with OSA [12,20,21, 22,23,13]. Loredó and colleagues randomized 76 patients with OSA to therapeutic CPAP, placebo CPAP or nocturnal oxygen and found that those patients randomized to therapeutic CPAP had less percent Stage 1 sleep and more percent REM sleep after one night of treatment [12]. Other studies had reported that after one night of therapeutic CPAP, participants with OSA had increased amounts of SWS and decreased amounts of Stage 1 sleep [20,22,24]. It should be noted, however, that most of these “before-and-after” studies with CPAP were not placebo-controlled.

In addition to our study, there have been 14 other placebo-controlled trials of CPAP. Five studies used an oral placebo [25,26,27,28,29]. Two studies compared CPAP to conservative treatment which included counseling about weight loss, sleep hygiene, and sleep posture [30, 31]. Eight studies [12,32,33,34,35,36,37,38] have employed a placebo or subtherapeutic CPAP including the Loredó study [12], which used the same placebo CPAP design as used in our study. In general, results of these studies have been mixed in regard to changes in sleep. As suggested previously, it is possible that the small CPAP pressure used in the subtherapeutic CPAP studies (pressures ranging from 1-3 cm H₂O) had a partial therapeutic effect [38,36, 37]. In order to avoid this potentially confounding factor, our study employed placebo CPAP and insured that there was essentially no pressure (0.0-0.5 cm H₂O) being delivered to the patient.

As shown in Table 3, after 3 weeks of CPAP treatment, there were also some surprising results, specifically the small but significant decreases in TST, TIB, and SP after 3 weeks of therapeutic CPAP. There was also an increase in SO, although it was not statistically significant. As the subjects' TIB decreased, the TST and SP, both of which are a function of TIB, likewise decreased. More importantly, however, despite the small decreases in TST, TIB and SP (all by approximately 30 minutes, which may be related to discomfort due to the CPAP mask and therapeutic CPAP pressure), the subjects' sleep was deeper (as evidenced by the increases in

% Stage 2 and SWS) and sleep efficiency did not change. Additionally, it is important to remember that these are all elderly patients with AD, a condition that as been reported to cause further disruptions in sleep (relative to age-matched controls) [1,2]. And although there are published data showing improvements in sleep parameters with CPAP (as referenced above), these studies have generally not been conducted in older patients; therefore, those results may not be generalizable.

As previously reported, our study participants, all of whom had AD, were highly compliant with CPAP treatment, using their respective machines for close to 5.5 hours on average over the course of the study [14]. Adequate CPAP compliance has been defined as greater than 4.5 hours of CPAP use per night on a routine basis [39]. Most studies of CPAP compliance report “good compliance” as greater or equal to 4 hours, and in a study of older adults without dementia, mean compliance was over six hours per night [40]. Our laboratory has previously reported that the presence of depression was the only factor associated with noncompliance in this patient population [41].

As our group has previously reported [42], CPAP did significantly improve daytime sleepiness, as measured by the ESS, in this same group of patients. Correlations between changes in ESS at three weeks and changes in sleep parameters, however, were not significant, but the results were in the expected direction. The lack of statistical significance may be due to the small effect size and insufficient power. In addition, although the participants' ESS scores improved after three weeks of CPAP treatment, the ESS scores at baseline were not significantly elevated. It is also important to recall that because these patients all had AD, the caregiver and the patient answered this questionnaire about the patient together, which may be less reliable than when patients fill it out themselves [42].

Despite our positive findings, there were several limitations to this study that warrant discussion. First, the main outcome measure of the study was changes in cognitive functioning, and the study was both powered and designed for this outcome. Sleep parameters were examined post-hoc. Therefore, the study may have been underpowered for the sleep measures. Another limitation was the lack of a PSG recording with placebo CPAP after three weeks of use. Since patients had to return for two nights of sleep recordings, adding a third night to evaluate a 3-week post-placebo CPAP night would have created excessive participant burden. While this does limit our ability to assess the effects of placebo vs. CPAP after 3 weeks, we were able to evaluate the difference after one night with very positive results. A third limitation is generalizability. This study included patients with mild to moderate AD. It is unclear if the positive results from our study are generalizable to patients with more severe dementia. Despite these limitations, this study was successful in showing that even one night of therapeutic CPAP can be beneficial to the sleep of patients with mild to moderate AD and OSA.

In summary, a single night of CPAP treatment in patients with mild to moderate AD and OSA resulted in less Stage 1 and more Stage 2 sleep. These improvements in the consolidation and deepening of sleep were maintained after three weeks of therapeutic CPAP. These findings mirror the effects of CPAP treatment on sleep parameters in persons without dementia, providing further evidence that patients with dementia (particularly mild to moderate AD) and OSA can benefit from CPAP treatment.

Acknowledgments

Supported by NIA AG08415, GCRC M01 RR00827, P50 AG05131, and the Research Service of the Veterans Affairs San Diego Healthcare System

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Figure 1.
CONSORT diagram showing the flow of participants through each stage of a randomized trial.

Table 1

Participant Baseline Characteristics*

Demographics	Therapeutic CPAP Group (n=27)	Placebo CPAP Group (n=25)
Age (years $\pm$ SD)	78.6 $\pm$ 6.8	77.7 $\pm$ 7.7
Gender	F=8; M=19	F=5; M=20
Body Mass Index (mean $\pm$ SD)	26.1 $\pm$ 4.2	25.0 $\pm$ 3.6
Education (years $\pm$ SD)	14.7 $\pm$ 3.1	15.6 $\pm$ 2.7
MMSE (mean $\pm$ SD)	24.3 $\pm$ 2.8	24.8 $\pm$ 4.2

* Note: There were no significant differences between the two groups on any of these variables.

Table 2

Sleep Variables during screening and during first night of CPAP vs. Placebo CPAP

Sleep Variable (mean $\pm$ SD)	Therapeutic CPAP Group (n=27)		Placebo CPAP Group (n=25)		p value [*]
	Screening	First night CPAP	Screening	First night PLACERO	
TST (min)	366.9 $\pm$ 91.9	308.0 $\pm$ 71.0	382.7 $\pm$ 93.9	310.5 $\pm$ 63.9	0.84
WASO (min)	117.6 $\pm$ 74.0	89.1 $\pm$ 40.7	130.4 $\pm$ 73.3	110.7 $\pm$ 58.3	0.51
% Stage 1 Sleep	22.9 $\pm$ 14.0	15.5 $\pm$ 8.4	22.0 $\pm$ 14.2	23.5 $\pm$ 14.6	0.04
% Stage 2 Sleep	59.5 $\pm$ 11.6	67.7 $\pm$ 11.5	62.3 $\pm$ 16.6	57.3 $\pm$ 12.2	0.02
% Stage 3 Sleep	2.4 $\pm$ 4.2	3.9 $\pm$ 6.1	1.8 $\pm$ 2.3	3.3 $\pm$ 4.5	0.73
% Stage 4 Sleep	0.1 $\pm$ 0.3	0.1 $\pm$ 0.4	0.0 $\pm$ 0.1	0.0 $\pm$ 0.0	0.28
% REM Sleep	15.1 $\pm$ 8.9	12.8 $\pm$ 8.2	13.9 $\pm$ 8.4	14.9 $\pm$ 7.6	0.43
TIB (min)	494.4 $\pm$ 75.5	436.6 $\pm$ 45.2	519.3 $\pm$ 3	444.0 $\pm$ 50.3	0.85
SP (min)	484.5 $\pm$ 77.5	397.2 $\pm$ 63.5	513.2 $\pm$ 83.8	421.1 $\pm$ 57.8	0.82
SO (min)	9.9 $\pm$ 20.2	39.4 $\pm$ 48.8	6.2 $\pm$ 8.0	23.2 $\pm$ 39.4	0.24
SE (%)	75.9 $\pm$ 14.2	77.2 $\pm$ 10.8	74.7 $\pm$ 13.2	74.1 $\pm$ 12.8	0.39
Arl	8.8 $\pm$ 5.5	5.9 $\pm$ 3.5	7.9 $\pm$ 4.4	9.6 $\pm$ 5.6	0.23

* p-value from randomized analysis is shown.

** Note: There were no significant differences between the two groups on any of these variables on the screening night.

Table 3

Improvements in Sleep after 3 weeks of therapeutic CPAP (paired analysis)

PSG Variable (mean $\pm$ SD)	Screening Night (n=39)	3-Weeks of Therapeutic CPAP (n=39)	p value [*]
% Stage 1 Sleep	23.5 $\pm$ 14.5	16.3 $\pm$ 10.1	0.001
% Stage 2 Sleep	59.6 $\pm$ 13.8	64.2 $\pm$ 11.5	0.06
% Stage 3 Sleep	1.9 $\pm$ 3.1	4.0 $\pm$ 6.2	0.006
% Stage 4 Sleep	0.1 $\pm$ 0.2	0.2 $\pm$ 0.7	0.26
% REM Sleep	15.0 $\pm$ 8.7	15.3 $\pm$ 6.6	0.95
TST (min)	372.0 $\pm$ 87.1	343.6 $\pm$ 72.5	0.05
WASO (min)	126.0 $\pm$ 79.5	92.3 $\pm$ 44.6	0.005
TIB (min)	507.2 $\pm$ 77.0	458.0 $\pm$ 68.6	0.002
SP (min)	498.0 $\pm$ 78.0	435.9 $\pm$ 77.2	<0.001
SO (min)	9.2 $\pm$ 17.2	19.9 $\pm$ 32.2	0.06
SE (%)	75.1 $\pm$ 14.5	78.8 $\pm$ 10.0	0.11
Ari	8.4 $\pm$ 5.1	4.7 $\pm$ 2.7	0.005

* p-value from paired analysis is shown.