Cognitive Effects of Treating Obstructive Sleep Apnea in Alzheimer's Disease: A Randomized Controlled Study

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OBJECTIVES: To examine whether treatment of obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) in patients with Alzheimer's disease (AD) results in better cognitive function.

DESIGN: Randomized double-blind placebo-controlled trial. Participants were randomized to therapeutic CPAP for 6 weeks or placebo CPAP for 3 weeks followed by therapeutic CPAP for 3 weeks.

SETTING: General clinical research center.

PARTICIPANTS: Fifty-two men and women with mild to moderate AD and OSA.

INTERVENTION: CPAP.

MEASUREMENTS: A complete neuropsychological test battery was administered before treatment and at 3 and at 6 weeks.

RESULTS: A comparison of subjects randomized to 3 weeks of therapeutic versus placebo CPAP suggested no significant improvements in cognition. A comparison of pre- and posttreatment neuropsychological test scores after 3 weeks of therapeutic CPAP in both groups showed a significant improvement in cognition. The study was underpowered to make definitive statements about improvements within specific cognitive constructs, although exploratory post hoc examination of change scores for individual tests suggested improvements in episodic verbal learning and memory and some aspects of executive functioning such as cognitive flexibility and mental processing speed.

CONCLUSION: OSA may aggravate cognitive dysfunction in dementia and thus may be a reversible cause of cognitive loss in patients with AD. OSA treatment seems to improve some cognitive functioning. Clinicians who care for patients with AD should consider implementing CPAP treatment when OSA is present. **J Am Geriatr Soc 56:2076–2081, 2008.**

Key words: dementia; Alzheimer's disease; obstructive sleep apnea; CPAP; cognitive impairment

Obstructive sleep apnea (OSA) is characterized by complete cessations (apneas) or partial decreases (hypopneas) in respiration or both caused by pharyngeal collapse during sleep. The sleep fragmentation and the accompanying hypoxemia result in negative consequences including neuropsychological impairment.[1] The treatment of choice for OSA is nasal continuous positive airway pressure (CPAP).

The prevalence of OSA in patients with dementia has been estimated to be high, with 70% to 80% having five or more apneas or hypopneas per hour of sleep and 38% to 48% having 20 or more.[2] A relationship between symptoms of OSA and cognitive impairment has been identified in adults[3,4] and in patients with dementia.[5] In one of the largest studies of nursing home patients, those with severe dementia had significantly more-severe OSA than those with mild to moderate or no dementia, and those with more-severe OSA had significantly more-severe dementia.[2]

Although it is unlikely that OSA causes dementia, the hypoxia and sleep fragmentation associated with OSA might worsen cognitive function. Most studies examining the effect of CPAP on OSA in patients without dementia have reported improvement in neuropsychological deficits.[3] Any intervention that improves cognition in patients with dementia is likely to have a broad effect, because better daily function implies greater independence for the patient, less caregiver burden, fewer nursing service and social support needs, and generally lower disease-associated costs. This study examined whether CPAP treatment in elderly

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patients with mild to moderate Alzheimer's disease (AD) and OSA would result in better cognitive function.

METHODS

Participants

Patients with AD were recruited from the University of California, San Diego (UCSD) Alzheimer's Disease Research Center through referrals and advertisements that asked for participants with memory problems and trouble sleeping or snoring. Of 420 participants screened by telephone, 52 were randomized (Figure 1).

Participants were eligible for screening if they had a diagnosis of probable mild AD (diagnosed according to the National Institute of Neurological and Communicative Disorders and Stroke—Alzheimers Disease and Related Disorders Association criteria[6]) a computed tomography or magnetic resonance imaging scan of the brain consistent with AD done within 24 months, stable health, and a live-in caregiver. Only English-speaking patients with a Mini-Mental State Examination (MMSE) 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 2 months before participation and agreed to continue on the same dose for the 6-week duration of the study.

Exclusion criteria included a prior diagnosis of a sleep disorder or current treatment for OSA. Participants with severe medical or psychiatric illnesses (e.g., chronic obstructive pulmonary disease, coronary disease, or cerebrovascular disease) were excluded, because these conditions could put the subject at special risk or interfere with primary and secondary variable evaluations.

Written informed consent was obtained from the patients and from each patient's legally authorized representative. The UCSD Human Research Protections Program approved the study.

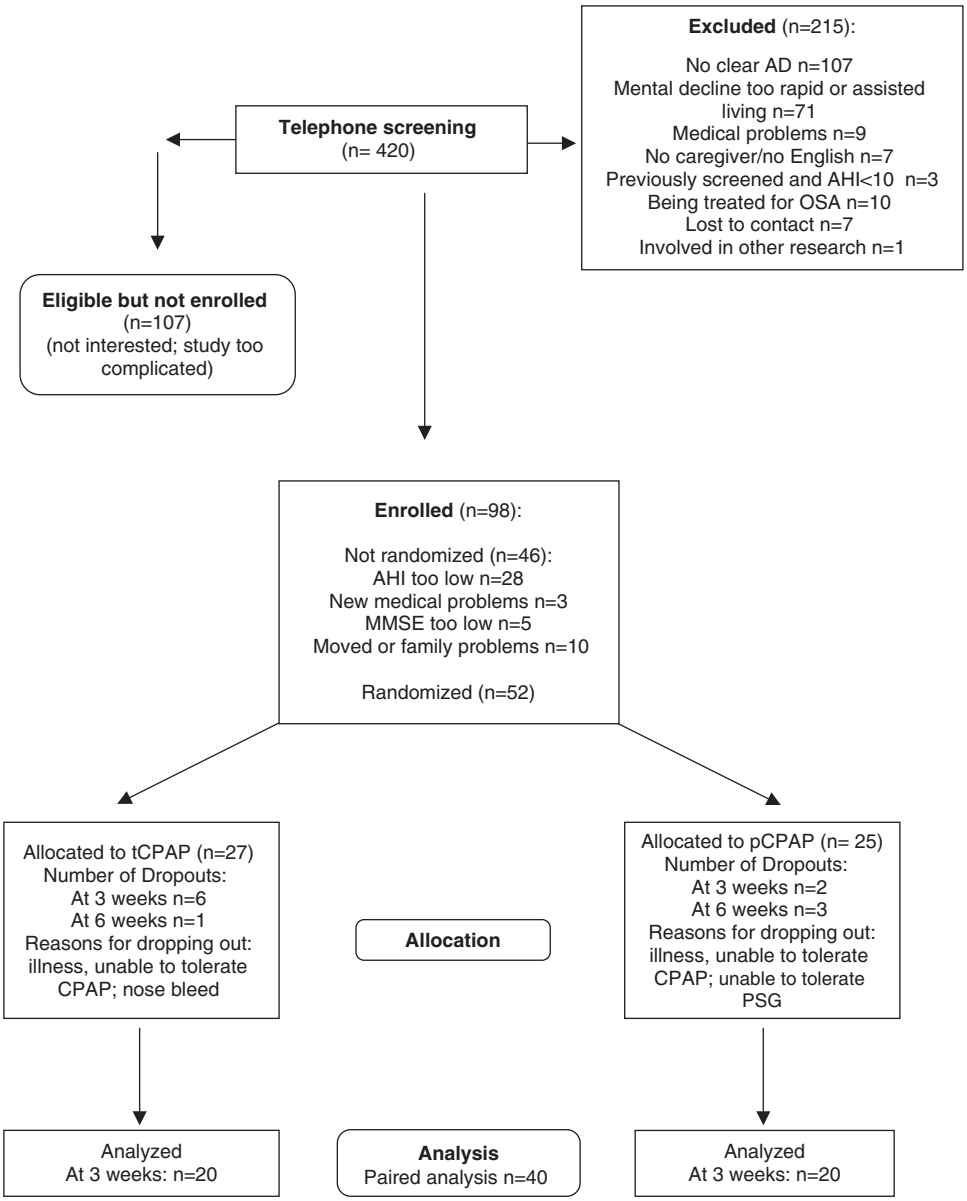

Figure 1. CONSORT diagram showing the flow of participants through each stage of the randomized trial.

Procedure

Screening

Once consents were signed, participants were scheduled for a screening OSA polysomnogram (PSG; Embla, Embla-Global Headquarters, Broomfield, CO), conducted in the home. Electroencephalogram (C3, C4, O1, and O2 derivations), electrooculogram (left oculogram and right oculogram derivations), submental and anterior tibialis electromyogram, thoracic and abdominal respiratory efforts (piezoelectric bands), airflow (measured with a nasal cannula), electrocardiography, and oximetry were recorded. Sleep staging was scored according to Rechtshaffen and Kales criteria.[7] The record was also scored for apneas (a drop in airflow amplitude of $\geq$90% from the immediate baseline lasting at least 10 seconds), hypopneas (a reduction in airflow amplitude of $\geq$50% but $<$90% from the immediate baseline, lasting at least 10 seconds and followed by an arousal or oxygen desaturation of $\geq$3%), and the apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) was computed.

Randomization

Patients with an AHI of 10 or greater were randomized to 6 weeks of therapeutic CPAP (tCPAP) or 3 weeks of placebo (pCPAP) followed by 3 weeks of tCPAP. The placebo CPAP consisted of a placebo mask with ten 1/4″ drill holes to create a large air leak and to allow for adequate air exchange with a pressure reducer placed between the whisper swivel and the CPAP tubing connected to the mask.[8,9] The CPAP unit's pressure was fixed at 8 cm of water (H_2O) pressure to control for machine noise. With this system, the mask's pressure varied from 0.5 cm H_2O at end-expiration to 0.0 cm H_2O during inspiration.

Protocol

Each participant was admitted to the UCSD General Clinical Research Center Gillin Laboratory of Sleep of Chronobiology (GCRC-GLSC) for 2 nights on two occasions (at the start of the study and after the first 3 weeks of CPAP). On the first night of the first admission, participants and their caregivers were trained in the use of the CPAP unit (REMstar Plus CPAP with a built-in heated humidifier; Comfort Select CPAP mask; Respironics, Murrysville, PA). All participants and caregivers received similar instruction on and orientation to the CPAP systems and were kept blind to their condition. The adequacy of the blind was tested by asking patients and caregivers after completion if they thought they had real or placebo CPAP.

Those randomized to the tCPAP group underwent a standard CPAP titration PSG to establish the optimal therapeutic pressure, defined as that which eliminated most apneas and hypopneas. Participants assigned to the pCPAP group underwent a mock CPAP titration PSG using the placebo CPAP system.

On the second night of the GCRC-GLSC admission, all participants slept with the CPAP set to the level determined on the first night and underwent a repeat PSG. In the morning, participants were discharged home with CPAP.

Three weeks later, all participants were readmitted to the GCRC-GLSC and told that their CPAP needed adjustment. The tCPAP group slept in the laboratory for 2 nights with no change in pressure. The pCPAP group was crossed over to tCPAP and given new masks and underwent formal CPAP titration PSG to establish the therapeutic pressure. On the second night, all participants slept with the CPAP machine set at the therapeutic level. In the morning, both groups were discharged home; the pCPAP group now for 3 weeks of therapeutic CPAP and the tCPAP group for a second 3-week period of therapeutic CPAP.

Adherence to therapy was monitored using hidden clocks that recorded the number of hours of compressor use. The research associate visited the home weekly to retrieve data and encourage continued participation.

Neuropsychological Testing

To characterize the sample in terms of premorbid functioning and severity of dementia at the time of enrollment, all subjects were evaluated using the word recognition subtest (tan form) from the Wide Range Achievement Test—Third Edition[10] and the Mattis Dementia Rating Scale.[11]

In addition, participants completed a neuropsychological test battery at baseline and 3 and 6 weeks. Each assessment was completed before admission to the GCRC-GLSC. Cognitive abilities of particular relevance to AD (learning/memory), to OSA-related hypoxia and its treatment (learning/memory and frontal/executive skills), to sleepiness and sleep-disturbance (attention, vigilance), and to normal aging (mental processing speed) were targeted. Specifically, the test battery included basic attention and vigilance (raw score from the Digit Span of the Wechsler Adult Intelligence Scale—Third Edition (WAIS-III),[12] and total correct on the Digit Cancellation task[13]), psychomotor speed (time to complete (seconds) the Trail Making Test Part A[14] and raw scores from the WAIS-III digit symbol and symbol search subtests), verbal episodic memory (total recall on learning trials 1 through 3 from the Hopkins Verbal Learning Test—Revised (HVLT-R)[15,16]), tests sensitive to various aspects of executive functioning (Trail Making Part B (seconds to complete),[14] conceptual-level responses from the 64-card version of the Wisconsin Card Sorting Test [WCST-64],[17,18] total words completed on the Color–Word Interference Trial of the Stroop Color and Word Test,[19] and total correct words generated on the Letter Fluency Test and on the Category (Animals) Fluency Test[20]). Published parallel forms for the HVLT-R were used in fixed order to reduce item content familiarity.

A composite score was computed for the neuropsychological test battery. The composite score was defined as the mean of 14 standardized subscale scores on each of the subscales of the neuropsychological battery described above. Each observed subscale score was converted to a *z*-score (standardized by subtracting the baseline mean and dividing by the standard deviation of the sample). This standardization was done for each scale at each of the three time points (baseline and 3 and 6 weeks). The standardized scores were then averaged to yield a composite score for each time point. This composite score was used as a measure of overall neuropsychological functioning.

Data Analysis

Distributions (mean, standard deviations, frequencies) of baseline demographic and neuropsychological variables were calculated and compared using *t*-tests for continuous variables and Fisher exact tests for categorical variables to

ensure that randomization resulted in comparable treatment groups. The analysis of the primary hypothesis consisted of a two-sample nonparametric Wilcoxon rank sum test to compare changes in neuropsychological functioning from baseline to 3 weeks between treatment groups (comparing 3 weeks of tCPAP with 3 weeks of pCPAP).

This study was designed to have more than 80% power to detect a standardized mean difference of 0.6 in cognitive functioning between the treatment and placebo arms with 50 subjects per treatment arm. Because of unexpected difficulties with recruiting in this patient population, the targeted recruitment was not achieved, and hence the study was underpowered to test the primary hypothesis based on the randomized design. Therefore, a paired analysis of changes in neuropsychological measures after 3 weeks of therapeutic CPAP treatment in both groups was also undertaken (defined as baseline to 3 weeks in the tCPAP group, and 3 to 6 weeks in the pCPAP group) using a Wilcoxon signed rank test. A further exploratory analysis investigated the effect of 6 versus 3 weeks of therapeutic CPAP treatment using two-sample Wilcoxon rank sum tests. Although the primary hypothesis tested whether the change in composite score from baseline to 3 weeks was significantly different across treatment groups, changes in individual subscales from baseline to 3 weeks were examined to assess whether CPAP treatment resulted in improvements in specific neuropsychological domains of functioning. All hypotheses were two sided and were tested at the 5% significance level.

RESULTS

Participant Characteristics

A total of 52 participants were randomized (tCPAP, n = 27; pCPAP, n = 25). There were no significant differences between the two groups in terms of demographic variables or severity of pretreatment OSA, depression, estimation of premorbid verbal intelligence quotient, or neuropsychological functioning (Table 1). During pCPAP, there was no significant change in AHI (mean AHI 26.9 ± 15.5, range 10.8–76.4, during screening vs mean AHI 34.6 ± 22.3, range = 7.1–71.8, after 3 weeks of pCPAP). During tCPAP, the AHI fell from a group mean of 29.7 ± 15.8 (range 13.7–84.2) to a group mean of 6.4 ± 8.1 (range 0.4–31.2).[21]

Thirteen participants (25%) dropped out before the 6-week time point. Attrition rates were comparable across treatment arms (n = 5 of 25 cases in the pCPAP arm; n = 7 of 27 cases in the tCPAP arm). There were no differences in demographic or clinical characteristics between participants who dropped out and those who completed the study.

Credibility of Blinded Condition

Based on the Fisher exact test, there were no significant differences between the two groups of patients or caregivers in their responses to the question about which condition the patient was in (patients: 60% in the tCPAP group and 46% in the pCPAP group believed they had tCPAP; $P = .59$; caregivers: 44% in the tCPAP group and 46% in the pCPAP group believed the patient had tCPAP; $P = .40$), suggesting an effective blind.

Table 1. Participant Baseline Characteristics

Characteristic	Therapeutic CPAP (n = 27)	Placebo CPAP (n = 25)
Female, n (%)	8 (29.6)	5 (20.0)
Ethnicity, n (%)		
Hispanic	3 (11.1)	1 (4.0)
Non-Hispanic	24 (88.9)	24 (96.0)
Race, n (%)		
Caucasian	26 (96.3)	25 (100.0)
African American	0	0
Asian American	0	0
Pacific Islander	1 (3.7)	0
Age, mean ± SD	78.6 ± 6.8	77.7 ± 7.7
Education, years, mean ± SD	14.7 ± 3.1	15.6 ± 2.7
Apnea-hypopnea index, mean ± SD	29.8 ± 16.1	26.9 ± 15.5
Body mass index, mean ± SD	26.1 ± 4.2	25.0 ± 3.6
Mini-Mental State Examination, mean ± SD*	24.3 ± 2.8	24.8 ± 4.2
Patients stable on medications, n (%)		
Acetylcholinesterase inhibitors	25 (92.6)	20 (80.0)
Analgesics	18 (66.7)	17 (68.0)
Anticonvulsants	1 (3.7)	1 (4.0)
Antidepressants	14 (51.9)	5 (20.0)
Antihistamines	3 (11.1)	5 (20.0)
Major tranquilizers	2 (7.4)	1 (4.0)
Minor tranquilizers	3 (11.1)	0
Over the counter (diphenhydramine)	0	1 (4.0)
Cornell Depression Score, mean ± SD	5.1 ± 3.9	4.7 ± 3.3
Neuropsychological functioning composite score, mean ± SD	−0.17 ± 0.57	0.13 ± 0.87
Wide Range Achievement Test—Third Edition Reading Recognition Standard Score, mean ± SD†	106.6 ± 9.1	108.5 ± 9.1
Mattis Dementia Rating Scale total, mean ± SD‡	116.0 ± 13.0	120.1 ± 15.4

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

* Range 0 (severely demented) to 30 (cognitively intact).

† Normative mean 100 ± 15; higher score indicates better premorbid verbal intelligence quotient.

‡ Range 0 (severely demented) to 144 (cognitively intact).

CPAP = continuous positive airway pressure; SD = standard deviation.

CPAP Adherence

Adherence was measured by calculating the number of hours and percentage of nights CPAP was used. During the first 3 weeks (3 weeks of tCPAP in the tCPAP group and pCPCP in the pCPAP group), there were no significant differences in the number of hours used ($P = .34$) or percentage of nights used ($P = .75$). The tCPAP group used their CPAP for 5.8 ± 2.1 hours a night for 73 ± 27% of the nights. The pCPAP group used their CPAP for 6.4 ± 2.5 hours a night for 67 ± 35% of the nights.

In paired analyses (3 weeks of tCPAP in the tCPAP and pCPAP groups), there were still no significant differences between the groups in number of hours per night ($P = .21$) or percentage of nights used ($P = .52$). The pCPAP group, when switched to tCPAP, used it for a mean of 4.9 ± 2.4 hours a night for $62 \pm 36\%$ of the nights.

Neuropsychological Test Battery Results

Composite Neuropsychological Score

Two-sample comparisons of changes in neuropsychological functioning comparing 3 weeks of therapeutic CPAP with 3 weeks of pCPAP resulted in no significant differences, although in the paired analysis, after 3 weeks of therapeutic CPAP for both groups, there was significant improvement in the composite neuropsychological score, with a mean change of 0.077 points ($P = .01$).

Individual Test Results

Change scores on 10 individual neuropsychological tests were also examined, with no significant changes in the two-sample comparisons. In the paired analysis, after 3 weeks of therapeutic CPAP for both groups, there was significant improvement in HVLT-R (mean pre- to post-treatment 3.3 ± 1.5 to 4.0 ± 1.9; $P = .03$) and Trail Making Test Part B (mean pre- to post-treatment 205.3 ± 95.8 to 182.8 ± 96.1; $P = .049$).

There were no significant changes in the other neuropsychological tests, and there were no differences in neuropsychological test scores after 6 versus 3 weeks of therapeutic CPAP, suggesting that additional treatment beyond 3 weeks did not result in further improvement.

DISCUSSION

To the authors' knowledge, this is the first report of a randomized placebo-controlled CPAP trial in patients with AD with OSA. Although changes in neuropsychological functioning across treatment groups (comparing 3 weeks of tCPAP with 3 weeks of pCPAP) were not statistically different, the composite neuropsychological scores from combined therapeutic periods suggested modest but statistically significant improvements in cognitive functioning associated with 3 weeks of therapeutic CPAP.

Results of two separate meta-analyses concluded that OSA most affects vigilance, executive functioning, and coordination.[3,22] Published literature reviews suggest much variability in which cognitive deficits are seen in OSA and in whether these deficits are reversible after treatment. As noted in a previous review,[23] most studies have shown at least trends toward better performance with CPAP than with placebo. The authors concluded that the small changes may have been due to the mild OSA in the study population, poor CPAP adherence, or an irreversible component in cognitive impairment. Nevertheless, at least three studies comparing neuropsychological test scores of patients with OSA before and after 6 months of CPAP treatment with healthy controls found some cognitive improvement.[24–26] The present results are consistent with these studies of cognitive effects of CPAP in patients with OSA without dementia.

A recent study exploring the effect of CPAP on memory impairment in patients with OSA without dementia suggested that impaired verbal memory improved in those using CPAP for an average of 6 hours a night.[27] In the current study, patients with AD used their CPAP for an average of 5 hours a night.[28] Future studies will need to examine whether longer use per night in patients with AD results in greater cognitive improvements.

Standard treatment of AD is aimed at improving memory by ameliorating the cholinergic deficit. Acetylcholinesterase inhibitors have shown the most promising results, with reported treatment effects of approximately 1 point on the MMSE over 6 months compared with placebo.[29] The treatment in the current study lasted only 3 to 6 weeks, and although there was no effect on MMSE score, significant improvement in cognition was found. It is possible that this study was underpowered or of too short duration to see improvement in MMSE score.

This is the one limitation of the study (i.e., because of the difficulty in participant recruitment, the study was underpowered to detect meaningful changes across treatment arms). With the available sample size, there was 80% power to detect an effect size of 0.8 when comparing changes across treatment arms. The only analysis that compared treatment with placebo for which the randomization ensured a valid interpretation was from baseline to 3 weeks. The paired analysis did not allow for comparison between treatment groups but did test the hypothesis that there was a change in scores with treatment within groups, although in the tCPAP group mean, change in composite score from baseline to 3 weeks was greater than the minimal change seen during pCPAP (mean change score of 0.028 vs 0.008), yielding an effect size of 0.11.

The study was also underpowered to make definitive statements about improvements within specific cognitive constructs. The composite score has not been validated on a population basis, although exploratory post hoc examination of change scores for individual tests suggested improvements in episodic verbal learning and memory and some aspects of executive functioning, such as cognitive flexibility and mental processing speed.

In summary, there were significant improvements in cognition while patients were on tCPAP but not on pCPAP, although the direct 3-week comparison of subjects randomized to tCPAP and pCPAP did not result in significant differences. Thus, the findings tentatively suggest that patients with AD with OSA may show some general cognitive benefits from OSA treatment, but more confidence in such conclusions awaits independent replication with sufficiently powered studies.

This study was not an epidemiological study, and the prevalence of OSA in those with mild to moderate AD is uncertain, although the data show there is a nontrivial proportion of patients with AD for whom OSA is a clear problem. It has been suggested that OSA might be a reversible cause of cognitive loss and dementia and that treatment of OSA, especially in the early stages of dementia when patients are still largely independent, may slow dementia progression.[30] The results of this study in which CPAP treatment of OSA improved cognitive function in patients with mild to moderate AD, lend support to that hypothesis. Further studies will need to determine whether CPAP treatment of OSA in patients with AD might slow dementia progression. In the meantime, clinicians who care

for patients with AD with OSA need to consider implementing CPAP treatment.

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