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

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Abstract

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

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

SETTING: General clinical research center

PARTICIPANTS: 52 men and women with mild-moderate AD and OSA

INTERVENTION: Continuous positive airway pressure

MEASUREMENTS: A complete neuropsychological test battery was administered before treatment, at three and at six-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- versus post-treatment 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. However, 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.

CONCLUSIONS: OSA may aggravate cognitive dysfunction in dementia and thus may be a reversible cause of cognitive loss in AD patients. OSA treatment seems to improve some of the cognitive functioning. Clinicians who care for AD patients should consider implementing CPAP treatment when OSA is present.

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Keywords

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

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by complete cessations (apneas) and/or partial decreases (hypopneas) in respiration 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%-80% having five or more apneas-hypopneas per hour of sleep and 38%-48% having 20 or more. (4) A relationship between symptoms of OSA and cognitive impairment has been identified in adults (2;12), and in patients with dementia (3). In one of the largest studies of nursing home patients, those with severe dementia had significantly more severe OSA compared to those with mild-moderate or no dementia, and those with more severe OSA had significantly more severe dementia (4).

While 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 non-demented patients have reported improvement in neuropsychological deficits (2). Any intervention that improves cognition in patients with dementia is likely to have broad impact, since improved daily function implies greater independence for the patient, less caregiver burden, fewer nursing service and social support needs, and generally reduced disease-associated costs. This study examined whether CPAP treatment in elderly patients with mild-moderate Alzheimer's disease (AD) and OSA would result in improved cognitive function.

METHODS

Participants:

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

Participants were eligible for screening if they had a diagnosis of mild probable AD (diagnosed according to the National Institute of Neurological and Communicative Disorders & Stroke-Alzheimers Disease and Related Disorders Association criteria (23)) a CT or MRI 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 Status 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 two months prior to 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 or cerebral vascular disease) were excluded as 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 study was approved by the UCSD Human Research Protections Program.

Procedure:

Screening: Once consents were signed, participants were scheduled for a screening OSA polysomnogram (PSG; Embla, Flaga Medical Devices/Medcare, Reykjavik, Iceland), conducted in the home. Electroencephalogram (C3, C4, O1 and O2 EEG derivations), electrooculogram (LOC and ROC derivations), sub-mental 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 (26). The record was also scored for apneas (a drop in airflow amplitude of ≥ 90% from the immediate baseline lasting at least 10 seconds), hypopneas (a reduction in airflow amplitude ≥ 50% but < 90% from the immediate baseline, lasting at least 10 seconds and followed by an arousal or oxygen desaturation ≥ 3%), and the apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) was computed.

Randomization: Patients with an AHI≥10 were randomized to either six weeks of therapeutic CPAP (tCPAP) or three weeks of placebo (pCPAP) followed by three weeks of tCPAP. The placebo CPAP consisted of a placebo mask with ten ¼-inch 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 (15;21). The CPAP unit's pressure was fixed at 8 cm 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 two nights on two occasions (at the start of the study and after the first three weeks of CPAP). On the first night of the first admission, participants and their caregivers were trained on 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 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 night one and underwent a repeat PSG. In the morning, participants were discharged home with CPAP.

Three weeks later, all participants were re-admitted to the GCRC-GLSC and told that their CPAP needed adjustment. The tCPAP group slept in the laboratory for two nights with no change in pressure. The pCPAP group was crossed over to tCPAP, 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.

Compliance with therapy was monitored by 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 with the Word Recognition subtest (tan form) from the Wide Range Achievement Test – Third Edition (29) and the Mattis Dementia Rating Scale (DRS) (22).

In addition, participants completed a neuropsychological test battery at baseline, 3-weeks, 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/or its treatment (learning/memory, and "frontal/executive skills"), to sleepiness/sleep-disturbance (attention, vigilance), as well as to normal aging (mental processing speed) were targeted. Specifically, the test battery included the following: 1) Basic attention and vigilance (raw score from the Digit Span of the Wechsler Adult Intelligence Scale - Third Edition [WAIS-III] (28), and total correct on the Digit Cancellation task(24)), 2) Psychomotor speed (time to complete [seconds] the Trail Making Test Parts A (27), and raw scores from the WAIS-III Digit Symbol and Symbol Search subtests), 3) Verbal episodic memory (total recall on learning trials 1 through 3 from the Hopkins Verbal Learning Test – Revised (HVLT-R)(8;10)), 4) tests sensitive to various aspects of "executive functioning" (Trail Making Part B [seconds to complete] (27), conceptual level responses from the 64-card version of the Wisconsin Card Sorting Test [WCST-64] (18;19), total words completed on the Color-Word Interference trial of the Stroop Color and Word Test (17), and total correct words generated on the Letter fluency (FAS) test and on the Category (Animals) Fluency test(16)). 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 (i.e., 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, three weeks, six 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 (i.e., compare 3-weeks of therapeutic CPAP to 3-weeks of placebo CPAP).

Our study was designed to have >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. Due to 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-week to 6-weeks in the pCPAP group) using a Wilcoxon signed rank test. A further exploratory analysis

investigated the effect of 6 weeks versus 3 weeks of therapeutic CPAP treatment using 2-sample Wilcoxon rank sum tests. While 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 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 on demographic variable or on severity of pre-treatment OSA, depression, estimation of premorbid Verbal IQ or neuropsychological functioning (Table 1). During placebo CPAP, there was no significant change in AHI (mean AHI=26.9 [SD=15.5, range=10.8–76.4] during screening vs. mean AHI=34.6 [SD=22.3, range=7.1–71.8] after three weeks of placebo CPAP). During therapeutic CPAP use, the AHI was reduced from a group mean of 29.7 [SD=15.8, range=13.7-84.2] to a group mean of 6.4 (SD=8.1, range=0.4-31.2).(11)

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 of participants who dropped out vs. those who completed the study.

Credibility of blinded condition

Based on Fisher's 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 patiaent was in (patients: 60% in the tCPAP group and 46% in the pCPAP group believed they had therapeutic CPAP; p=0.59; caregivers: 44% in the tCPAP group and 46% in the pCPAP group believed the patient had therapeutic CPAP; p=0.40), suggesting an effective blind.

CPAP Compliance

Compliance was measured by calculating the number of hours and percent of nights CPAP was used. During the first three weeks (i.e., 3 weeks of therapeutic CPAP in the tCPAP group and placebo in the pCPAP group), there were no significant differences in either the number of hours used (p=0.34) or in the percent of nights used (p=0.75). The tCPAP group used their CPAP for 5.8 hours a night (SD 2.1) for 73% (SD 27%) of the nights. The pCPAP group used their CPAP for 6.4 hours a night (SD 2.5) for 67% (SD 35%) of the nights.

In paired analyses (i.e., 3 weeks of therapeutic CPAP in both the tCPAP and pCPAP group), there were still no significant differences between the tCPAP group and pCPAP group in either number of hours per night (p=0.21) or in percent of nights used (p=0.52). The pCPAP group, when switched to therapeutic CPAP, used it for a mean of 4.9 hours a night (SD 2.4) for 62% (SD 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 to 3-weeks of placebo CPAP resulted in no significant differences. However, in the paired analysis, after three 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=0.01).

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 three weeks of therapeutic CPAP for both groups, there was significant improvement in HVLT-R (mean (SD) pre- to post-treatment: 3.3 [SD=1.5] to 4.0 [SD=1.9]; p=0.029) and Trail Making test (mean (SD) pre- to post-treatment 205.3 [SD=95.8] to 182.8 [SD=96.1]; p=0.049).

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

DISCUSSION

To our knowledge, this is the first report of a randomized placebo controlled CPAP trial in AD patients with OSA. While changes in neuropsychological functioning across treatment groups (i.e., comparing 3-weeks of therapeutic CPAP to 3-weeks of placebo CPAP) 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 vigilance, executive functioning, or coordination are most affected by OSA (2;7). Published literature reviews suggest much variability in which cognitive deficits are seen in OSA and in whether these deficits are reversible after treatment. As reviewed by Engleman et al. (14), most studies have shown at least trends towards better performance after CPAP compared to placebo. The authors concluded that the small changes may have been due to the relatively mild study population, poor CPAP compliance or to an irreversible component in cognitive impairment. Nevertheless, at least three studies comparing neuropsychological test scores of OSA patients before and after six months of CPAP treatment with healthy controls found some cognitive improvement (6;20;25). The present results are consistent with these studies of cognitive effects of CPAP in non-demented OSA patients.

A recent study, exploring the effect of CPAP on memory impairment in non-demented OSA patients, suggested that impaired verbal memory improved in those using CPAP for an average of six hours a night (30). In the current study, AD patients used their CPAP for an average of five hours a night (5). Future studies will need to examine if 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. To date, acetylcholinesterase inhibitors have shown the most promising results, with reported treatment effects of approximately one point on the MMSE over six months compared to placebo (13). Our treatment lasted only three-six weeks and although there was no effect on MMSE, we did find significant improvement in cognition. It is possible that our study was underpowered or of too short duration to see improvement in the MMSE.

This in fact is the one limitation of the study, i.e., due to 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 vs. placebo for which the randomization ensured a valid interpretation was from baseline to three 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. However, in the

therapeutic CPAP group mean, change in composite score from baseline to 3 weeks was greater than the minimal change seen during placebo CPAP (mean change score of 0.028 vs. 0.008 respectively), yielding an effect-size of 0.11.

The study was also underpowered to make definitive statements about improvements within specific cognitive constructs. Our composite score has not been validated on a population basis. However, 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 therapeutic CPAP but not on placebo CPAP. It must be noted, however, that the direct 3-week comparison of those randomized to therapeutic versus placebo CPAP did not result in significant differences. Thus our findings tentatively suggest that AD patients with OSA may show some general cognitive benefits from OSA treatment, but more confidence in such conclusions await independent replication with sufficiently powered studies.

This study was not an epidemiological study and the prevalence of OSA among those with mild-moderate AD is uncertain; however, our data clearly show there is a non-trivial proportion of AD patients for whom 0SA is a clear problem. Bliwise 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 (9). The results of this study in which CPAP treatment of OSA improved cognitive function in patients with mild-moderate AD, lend support to Bliwise's hypothesis. Further studies will need to determine whether CPAP treatment of OSA in AD patients might actually slow dementia progression. In the meantime, clinicians who care for AD patients with OSA need to consider implementing CPAP treatment.

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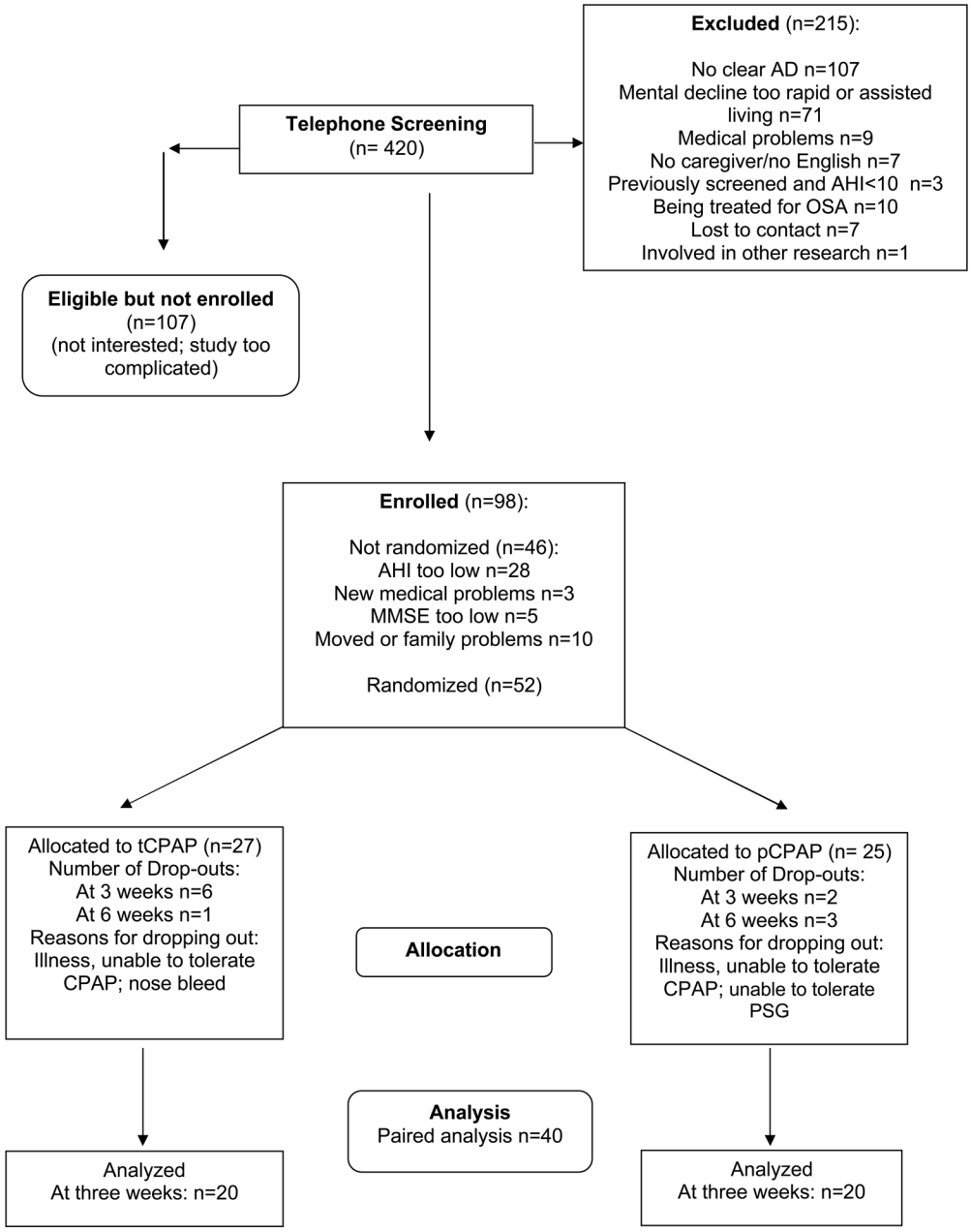

Figure 1.
CONSORT diagram showing the flow of participants through each stage of the randomized trial.

Table 1

Participant Baseline Characteristics[1]

	Therapeutic CPAP (n=27)	Placebo CPAP (n=25)
Gender; n (% female)	8 (30%)	5 (20%)
Ethnicity, n(%)		
Hispanic	3 (11%)	1 (4%)
Non-Hispanic	24 (89%)	24 (96%)
Race; n (%)		
Caucasian	26 (96%)	25 (100%)
African American	0	0
Asian American	0	0
Pacific Islander	1 (4%)	0
Age; mean years (±SD)	78.6 (6.8)	77.7 (7.7)
Education; mean years (±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 (3.60)
MMSE[2]; mean (±SD)	24.3 (2.8)	24.8 (4.2)
N (%) on stable medications		
acetylcholinesterase inhibitors	25 (93%)	20 (80%)
analgesics	18 (66.7%)	17 (68%)
anticonvulsants	1 (3.7%)	1 (4%)
antidepressants	14 (51.9%)	5 (20%)
antihistamines	3 (11.1%)	5 (20%)
major tranquilizers	2 (7.4%)	1 (4%)
minor tranquilizers	3 (11.1%)	0
over-the-counter (diphenhydramine)	0	1 (4%)
Cornell Depression Scores; mean (±SD)	5.1 (3.9)	4.7 (3.3)
Neuropsychological functioning composite score; mean (±SD)	−0.17 (0.57)	0.13 (0.87)
WRAT-III[3] Reading Recognition Standard Score; mean (±SD)	106.58 (9.08)	108.54 (9.07)
Mattis DRS[4] total; mean (±SD)	116.04 (12.98)	120.12 (15.38)

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

[2] Mini Mental Status Exam with a range of 0 (severely demented) to 30 (cognitively intact).

[3] Wide Range Achievement Test – Third Edition; normative mean=100 (SD=15); higher score indicates better premorbid verbal IQ

[4] Mattis Dementia Rating Scale with a range 0 (severely demented) to 144 (cognitively intact)