Alzheimer's Disease, Sleep Apnea, and Positive Pressure Therapy

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Invited Commentary: Alzheimer's Disease, Sleep Apnea, and Positive Pressure Therapy

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Keywords

Alzheimer's disease; Sleep apnea; Positive pressure therapy; Impaired cognition; Clinical trials

OPINION STATEMENT

Numerous lines of evidence converge in suggesting that sleep apnea may play a causal role in severe cognitive impairment, most likely Alzheimer's Disease (AD) but also including Vascular Dementia. Until recently, most of these studies have been based on small samples of clinic patients or population-based, descriptive studies of sleep apnea and cognition. Although randomized clinical trials have been completed for treating sleep apnea in middle-aged cognitively intact patients with sleep apnea using continuous positive airway pressure (CPAP), systematic intervention studies in well-characterized AD patients are very rare, and have been published from only a single research group. Results suggest some very modest improvement in selected aspects of cognition over a very limited period of time. There is thus lack of conclusive evidence that treating sleep apnea in AD is likely to have a major impact on dementia, although it may benefit daytime hypersomnolence, excessive napping and lethargy so common in many dementia patients. Additionally, anecdotal evidence suggests that in some selected cases, treatment can have relatively dramatic effects. At this point in time, the best indications for pursuing treatment for sleep apnea with nasal CPAP in AD patients would be factors promoting adherence, such as presence of a caregiver/family member invested in treatment, and a realistic appraisal of what goals of intervention should be expected (e.g., increasing daytime functionality by enhancing alertness) over a reasonable window of time. Speculative factors implicating a potentially causal role for sleep apnea in dementing illness would be comorbid diseases well-established to be associated with both sleep apnea and dementia (cardiovascular disease, diabetes) and presence of the Apolipoprotein-E4 genotype. None of these factors have been shown conclusively to influence CPAP efficacy in dementia, but to the extent that they lie on a putative causal pathway for sleep apnea and dementia (either as moderators or mediators of CPAP efficacy), their presence might be expected to enhance, rather than mitigate, a more favorable response in the domain of cognition.

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This article does not contain any studies with animal subjects performed by the author. With regard to the author's research cited in this paper, all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

Compliance with Ethics Guidelines
Conflict of Interest
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EVIDENCE SUPPORTING AN ASSOCIATION BETWEEN IMPAIRED COGNITION AND SLEEP APNEA

Although sleepiness has long been appreciated as a cardinal symptom of sleep apnea, early psychometric studies [1] demonstrated that impairments in neuropsychological tests were associated with measures of sleep apnea. The literature in this area has expanded exponentially in the last 30 years [2, 3], perhaps deriving from the alluring possibility that if sleep apnea was indeed a cause of serious cognitive decline, it might well constitute one of the most common causes of potentially reversible dementia ever described [4]. Many different lines of evidence from divergent sources converge as the basis for this speculation. Perhaps the single most compelling line of evidence derives from studies of populations known to have high rates of severe cognitive impairment. This includes both nursing home populations and outpatient populations presenting in memory clinics. In nursing homes, a series of studies in San Diego, California documented a very high prevalence of sleep disordered breathing (i.e., the rate of the Apnea/Hypopnea Index was nearly double that of an ambulatory, independent living population sampled from the same geography and demographics [5–8]. This is also detectable in institutionalized populations using pulse oximetry [9, 10], or even simple behavioral observation [11]. Moreover, in the San Diego nursing home studies, although nearly all of the patients were cognitively impaired, even within this population, more severe levels of impairment (as assessed with the 144-point Dementia Rating Scale) were associated with higher levels of sleep disordered breathing [7]. It is significant that in this population the correspondingly high prevalence of concurrent cardiovascular, cerebrovascular, and pulmonary disease [7, 8] may have enhanced the likelihood of detecting such relationships [12, 13]. For example, relationships between various measures of cognitive impairment and indices of broadly defined cardiovascular disease and other medical comorbidities (e.g., diabetes or insulin resistance) have been reported frequently in population-based studies of independently living populations, such as the Framingham Heart Study, the Atherosclerosis Risk in Communities Study, and the Swedish Uppsala cohort [14–18].

Although there are some exceptions (e.g., [19]), data from memory clinic populations generally complement the aforementioned studies in nursing home populations. Yamout et al [20*] reported that measures of nocturnal hypoxia were associated with cognitive impairment but that those relationships were limited to patients with comorbid medical disease. Additional data generated cross-sectionally from a memory clinic database of 405 (149 men; 256 women; mean [SD] age = 74.6 [9.1]) are presented in Table 1. For these analyses, severe dementia was defined as a Mini-Mental State Exam score of ≤ 18. Cardiovascular disease (CVD) was defined in a manner similar to the approach described in Yamout et al [20*]: clinic measured systolic and/or diastolic blood pressure of > 140 or > 90 mm Hg, respectively; history of cardiovascular event (myocardial infarct, stroke, cardiac revascularization procedures); or use of cardiovascular medications (defined as diuretics, beta blockers, calcium channel inhibitors, ACE inhibitors). Likelihood of sleep apnea here was defined by self- or caregiver-reported snoring, defined using a previously validated snoring question [21]. A positive snoring response was defined as a frequency of “sometimes,” “usually” or “almost always” over the preceding 6 months. Because of the additive risk conferred by sleep related breathing abnormalities and cardiovascular risk factors jointly, a single combined risk of positive snoring and positive cardiovascular disease was retained in the logistic models. Table 1 indicates that, even when controlling for age, education and sex, the likelihood of sleep apnea with concurrent CVD represented a risk for severe dementia in a memory clinic population.

Table 2 summarizes other diverse domains of evidence that indicate dementia may be related to sleep apnea. This includes selected neuroimaging studies, as well as several basic

science reports indicating the effects of models of intermittent hypoxia, and its effects on neurotransmitters and neuronal integrity (i.e., apoptosis). Although this evidence and the congruence across domains are impressive, there continue to be some cohort studies suggesting few associations [22, 23], as well as the baseline analyses from the Sleep Heart Health Study, including both studies of psychometrics [24, 25] and neuroimaging [26, 27] that present conflicting data. Generally, however, taken together the overall evidence indicates at least five of nine of Hill's criteria for causality [28], including strength and consistency of cross-sectional associations, dose response (biologic gradient), biological plausibility, and (in the context of longitudinal studies) temporal precedence. Issues related to reversibility are discussed in the following section.

POSITIVE AIRWAY PRESSURE CLINICAL TRIALS: EFFECTS ON COGNITION

Results from two major clinical trials the Apnea Positive Pressure Long-term Efficacy Study (APPLES) [24, 29; Class I] and the Continuous Positive Airway Pressure Apnea Trial North American Program (CATNAP) [30; Class I] have been published in the last few years. There are several notable features in these trials. First, in both of these studies was an emphasis on neurobehavioral or functional (c.f., cardiovascular) outcomes as the primary, pre-specified outcomes. Secondly, patients with all types of dementia, as well as Mild Cognitive Impairment, were excluded. Results have been decidedly mixed, if not frankly negative, regarding whether CPAP is associated with improvements in the neurobehavioral domain [29, 30]. Major decisions in the exclusion criteria for patients entering the APPLES trial, may have portended such negative outcomes in the cognitive domain. A description of some of these considerations has been provided elsewhere [31], but in brief, selection of a patient population with extremely high functioning cognition when combined with known medical interventions for cognition known to have extreme small effect sizes (Cohen's d values of less than .01) make for insurmountable and unreasonable expectations for seeing such neurobehavioral outcomes. Therefore, neither APPLES nor CATNAP, certain to see many future citations as providing conclusive evidence that neurobehavioral markers are ***unchanged*** by CPAP, are far from the best studies to address what behavioral effects might be expected when CPAP is applied to dementia patients.

Anecdotal evidence has suggested that treatment of sleep apnea with nasal CPAP in AD patients can offer some dramatic results. For example, cases like those of an elderly woman who had long given up playing bridge and had become relatively reclusive who resumed her social activities, card-playing and actively sought out increased contact with grandchildren foretell some of the potential benefits of CPAP over periods of 2 to 3 months [32]. Unfortunately, cases like this, although encouraging, can never substitute for well-done, prospective randomized clinical trials with pre-specified outcomes like that performed by Ancoli-Israel and colleagues in San Diego [33–37; Class II). This trial, which was published in several component parts, showed that, without question, AD patients could tolerate CPAP, became subjectively more alert with its use, incurred improved mood and experienced improved sleep architecture when treated with CPAP relative to a sham CPAP control. Although functional outcomes did not change, the study also showed that, in principle, at least some AD patients can and are willing to engage in this modality of treatment. More equivocal were clinically significant changes in cognition. The patients were in mild-to-moderate range of severity (range of mean Mini-Mental State Exam across groups was 24 to 25; range of mean Dementia Rating Scale across groups was 116–120) suggesting that late-stage disease was probably ***not*** a mitigating factor in the strength of the results. However, the sample size may have been underpowered (N = 27 and 25 in active and sham groups at point of randomization), the active treatment exposure (6 weeks for the

CPAP group; 3 weeks for the sham CPAP group who was then crossed over to receive real CPAP) may have been too short, and effects indicating statistically significant improvements (2 of 14 individual neuropsychological tests) may not have withstood adjustment for multiple comparisons and were only significant when combining both arms at the end of the treatment (i.e., when the 3 weeks of active treatment after sham group was crossed over and combined with the active group, who had 6 weeks of treatment). In short, the effects that were seen with CPAP were modest. Also, unspecified in this trial was any indication of how much cardiovascular disease burden was carried by the participants and their genotype with respect to the APO-E4 allele, both factors known to predispose for AD in their own right [38–42]. Taken together, these considerations would suggest that within the context of judicious and tempered expectations on the basis of patients and their caregivers and family members, CPAP use can certainly be entertained and attempted (Table 3). But care should be exercised so as not to foster unrealistic expectations of what may change or what is likely to change. Few other clinical trials for treatment of sleep apnea in AD exist, the rare exception being a study reporting benefit with the cholinesterase inhibitor, donepezil [43], which showed some modest results in both sleep disordered breathing and levels of oxygen desaturation, findings also noted in non-demented patients with sleep apnea [44]. Studies of so-called “salvage” nocturnal oxygen therapy in AD patients with sleep apnea and associated hypoxemia have not yet appeared in the literature, though in the nocturnal oxygen therapy trial (performed in non-dementia patients) was associated with improvement in cognitive function [45], so the potential for benefit is not beyond the realm of possibility.

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Table 1

Cross-sectional prediction of severe dementia (MMSE ≤18) in a memory clinic population

	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio (95% CI)
Variable		
Education	3.82 (2.35–6.21)	3.35 (2.03–5.53)
Race	2.73 (1.53–4.86)	2.12 (1.15–3.90)
Age	1.45 (0.95–2.20)	1.01 (0.99–1.04)
Gender	0.60 (0.39–0.94)	0.69 (0.43–1.10)
Snoring + CVD	1.91 (1.18–3.08)	1.77 (1.07–2.94)

MMSE: Mini-Mental State Exam

CVD: Cardiovascular disease

Table 2

Domains of evidence suggesting a causal relationship between sleep apnea and dementia

DOMAIN OF EVIDENCE	REFERENCES
Animals models of intermittent hypoxia experimentally mimicking sleep apnea are related to enhanced cortical lipid peroxidation and higher rates of cleaved caspase 3 (suggesting apoptosis) in CA1 hippocampal layer; upregulation of dopamine transport also observed	[46–48]
In non-demented, middle-aged, Clinic populations, a wide range of neuropsychological morbidities have been associated with measures of sleep apnea	[24, 49, 50–52]
Cross-sectional, population-based studies indicating that PSG-based measures of sleep apnea are related to poorer executive and memory function	[53, 54]
Longitudinal, epidemiologic studies showing that symptoms of sleep apnea are associated with incident cognitive decline	[55, 56**]
Nursing home patients with high prevalence of vascular disease demonstrate associations between measures of sleep apnea and more profound levels of dementia and impairments in activities of daily living	[7, 10]
Caregiver reports of sleep apnea signs and symptoms (e.g., snoring, irregular breathing in sleep, daytime sleepiness) are more common in well-characterized AD patients than in non- demented controls	[57, 58]
Structural neuroimaging techniques including MRI and DTI have shown sleep apnea is associated with volumetric measures in vulnerable regions such as hippocampus, cingulate cortex and selected cerebellar regions	[59–63]
Structural neuroimaging studies show that CPAP use leads to increases in hippocampal and cortical volumes	[64]
Functional neuroimaging tech niques such as fMRI and PET have shown hypometabolism in regions sensitive to cognitive performances, as well as increased BOLD activation, throughout prefrontal cortex and selected subcortical regions in sleep apnea patients	[65–68]
EEG slowing in OSA shows improvement of CPAP treatment	[69]
Within a closed health care system (Veterans Administration) comorbidity between AD and sleep apnea is above chance	[70]
APO-E4 allele may represent an at risk variant for both AD and sleep apnea	[38*–42]

Table 3

Factors for possible consideration in attempting to treat sleep apnea in Alzheimer's disease with continuous positive airway pressure

Availability of engaged spouse, adult child or caregiver interested in working with patient
Problem with daytime sleepiness impacting quality of waking life
Presence of cardiovascular risk factors; possibility of concurrent vascular dementia
Family understanding of realistic goals of treatment
Presence of APO-E4 allele