Review Article

©2020 NRITLD, *National Research Institute of Tuberculosis and Lung Disease, Iran*
ISSN: 1735-0344 *Tanaffos 2020; 19(3): 176-185*

TANAFFOS

Alzheimer's Disease in Patients with Obstructive Sleep Apnea Syndrome

Dimitra I. Siachpazidou [1], Vasileios T. Stavrou [2], Kyriaki Astara [3], Chaido Pastaka[1], Eudoxia Gogou [4], Chrissi Hatzoglou [3], Nicholas-Tiberio Economou [5], Konstantinos I. Gourgoulianis [1,2,4]

[1] Laboratory of Respiratory Sleep Disorders, Department of Respiratory Medicine, Faculty of Medicine University of Thessaly, Biopolis, Larissa, Greece, [2] Laboratory of Cardio-Pulmonary Testing and Pulmonary Rehabilitation, Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Biopolis, Larissa, Greece, [3] Faculty of Medicine, University of Thessaly, Biopolis, Larissa, Greece, [4] Department of Physiology, Faculty of Medicine, University of Thessaly, Biopolis, Larissa, Greece, [5] Sleep Study Unit, Eginition Hospital, University of Athens Medical School, Athens, Greece.

Received: 30 March 2020
Accepted: 28 June 2020

Correspondence to: Vasileios T. Stavrou
Address: Laboratory of Cardio-Pulmonary Testing and Pulmonary Rehabilitation, Department of Respiratory Medicine, Faculty of Medicine, University of Thessaly, Biopolis, Larissa, Greece,
Email address: vasileiosstavrou@hotmail.com

Background: Obstructive sleep apnea syndrome (OSAS) is a disorder with high prevalence among adults and is an independent risk factor for various diseases, especially those affecting the central nervous system (CNS). Continuous positive airway pressure (CPAP) is usually the optimal choice of treatment for OSAS. Alzheimer's disease (AD) is a neurodegenerative disease affecting a large proportion of the elderly population. The purpose of this study was to collect information concerning the two pathological entities and investigate the effectiveness of CPAP in the treatment of AD.
Materials and Methods: In this review, Twenty articles were found concerning OSAS and AD, of which one article was about treatment with donepezil and seven articles considered treatment with CPAP.
Results: Serious OSAS and short sleep duration are associated with a high risk of developing dementia. Respiratory distress during sleep is associated with developing mild cognitive impairment at younger ages. The cerebrovascular damage of AD patients is correlated with the severity of OSAS. Lower cerebrospinal fluid levels are associated with memory disturbances and oxygen saturation parameters in patients with OSAS-AD. Continuous use of CPAP is related to the delayed onset of cognitive impairment and is suggested as an effective method of protecting cognitive function, depression, sleep quality and architecture, and daytime sleepiness in AD patients with good compliance. Treatment of CPAP patients with OSAS-AD is suggested as an effective method of protecting cognitive function.
Conclusion: Clinicians dealing with AD patients should consider CPAP treatment when OSAS coexists.

Key words: Sleep Disorders; Alzheimer's Disease; CPAP Treatment; Adults

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a chronic condition characterized by repetitive repression of breathing in the upper airway during sleep leading to intermittent hypoxia and recurrent arousals. It is a prevalent disorder, particularly among middle-aged and obese men; however, its occurrence in women as well as in individuals with normal body mass index (BMI) is widely reported (1). OSAS has been recognized as a heterogeneous disorder with multiple contributing pathophysiological causes, affecting mainly the anatomy of the upper airway and the determinants of its collapsibility (2). The severity of OSAS is estimated through the apnea-hypopnea index (AHI), which calculates the total apnea and hypopnea episodes per hour of sleep. In the general population, 6-17% of people suffer from moderate OSAS, which results from AHI ≥15 events/h, with higher rates appearing in men and the elderly (3). It is globally estimated that at least

20% of the general population has symptoms compatible with OSAS, but even in countries where the syndrome is widely recognizable, a large proportion of patients remain undiagnosed (4). The first-line treatment of OSAS in most adult patients is the continuous positive airway pressure (CPAP), which reduces the AHI effectively and normalizes the oxyhemoglobin saturation and the number of arousals/awakenings by restoring the airflow of the upper airway during sleep (5). OSAS is a risk factor in several diseases, like hypertension, diabetes, metabolic syndrome, stroke, and cognitive deficiencies (6). Some epidemiological studies have suggested a pathophysiological link between OSAS and Alzheimer's disease (AD). The mechanism by which sleep disturbance may affect cognitive impairment is not clear yet (7). Patients with AD often show impaired sleep behavior as well as excessive daytime sleepiness. The degree of daytime sleepiness is significantly related to the severity of AD. Sleep disturbances as well as circadian rhythm disturbance precede the clinical onset of AD (8). Sleep has been suggested as a potential agent for preventing and treating AD. The treatment of OSAS has been shown to delay mild cognitive impairment and improve cognition in AD patients. Excessive and prolonged neuronal activity that develops during OSAS periods of cortical arousal can help the age of onset and accelerate the progress of AD. The mechanisms that affect the central nervous system (CNS) in OSAS have been investigated for a long time; however, they have not been clarified yet. The explanation is perhaps a synthesizer interaction (9). AD is one of the most important challenges of the 21st century for public health. AD is a systemic neurodegenerative disorder of unknown etiology. The clinical manifestation of this disorder usually occurs with cognitive deficits in the memory of elderly patients (10). Some estimates show that 50% of the population aged over 80 suffers from such dementia (11). AD is one of the top 10 causes of death in the developed world that cannot yet be treated or slowed down (12). It is mostly characterized by progressive memory decline and other cognitive deficits. The neuropathologic hallmark is neuronal loss with cerebral atrophy, β-amyloid plaques, and neurofibrillary tangles composed of tau (13).

The relationship between OSAS and AD has not been fully elucidated. Although this relationship has been recently proposed to be bidirectional (14), the information so far points towards an OSAS - induced AD (15). However, the pathophysiology behind these theories has not been established yet. Therefore, the purpose of this review was to summarize information on published studies on the relationship between OSAS and AD, assess the degree of severity of OSAS as a confounding factor, and investigate whether CPAP treatment in AD patients is effective while determining the degree of CPAP use compliance.

MATERIALS AND METHODS

The choice of literature was done aiming at comprehensive coverage of the topic during the period November 2017 to December 2019 with keywords ”Obstructive Sleep Apnea Syndrome”, “Sleep disorders”, “Alzheimer's disease”, “Continuous Positive Airway Pressure”, “treatment”, and “adults”, and their combinations using PubMed, Scopus, the Cochrane Library, and Embase databases. The primary research was scientific research, to find both qualitative and quantitative studies on adult patients published in international scientific journals. Articles that included patients with co-morbidities, review articles, and meta-analyses were excluded, while the articles in English were selected. The results of the treatment are shown in Table 1 and Table 2 shows the results of studies on AD regarding biomarkers.

Relationship between OSAS and AD

A recent review by Irwin and Vitiello (14), suggests a bidirectional relationship between sleep and AD, in the context of sleep disturbance and inflammation. This has also been proposed indirectly in the review by Bao et al. (16) regarding the association between sleep disturbances and depression. Concerning the OSAS - induced AD, Pan and Kastin (15) reported that OSAS activates neurodegenerative processes as a result of two major contributing processes: sleep fragmentation and intermittent hypoxia. However, the mechanisms that occur on a cellular level and on the blood-brain barrier (BBB) level have not been established (15). Carvalho et al. indicated a link between the main symptoms of OSAS, such as excessive daytime sleepiness (EDS), fatigue, and neurodegenerative processes, and consequently preclinical AD (17). Additionally, in another research, the authors connected EDS with β-amyloid (Aβ) accumulation (18). Bubu et al. (19) indicated not only changes in Aβ but also increased levels of CSF T-tau and P-tau in OSAS patients. Liguori et al. (20) evaluated the cerebrospinal fluid (CSF) β-amyloid isoforms (Aβ40, Aβ42) and orexin levels in OSA patients compared with AD patients and controls. The results showed that OSAS induced orexinergic system and dysregulated cerebral β-amyloid metabolism, supporting the current hypothesis of OSAS – induced AD. Although it has been mentioned above that AD – induced OSAS also might exist, evidence related to the pathophysiologic mechanisms is scarce. The apolipoprotein E epsilon 4 (APOE-ε4) gene is regarded as a major risk factor for the development of AD. Some studies examined the possible association with OSAS and found that APOE-ε4 can predispose to the syndrome (21, 22).

Although the evidence is limited, it could be suggested that AD and OSAS are bidirectionally related. Further research regarding their relationship, especially in terms of the AD - induced OSAS, is required to clarify the underlying mechanisms that, in turn, might affect the treatment approaches.

Treatment-off

In a study by Lutsey et al. (23) on 1667 people for 15 years, it was found that only serious OSAS is associated with a high risk of developing dementia. Sleeping for <7 h versus 8 to ≤9 h was also correlated significantly with a higher risk of dementia and AD. Finally, the effect of OSAS on dementia and AD was found to be mainly through cardiovascular pathways and diabetes (23). Lutsey et al. (24) studied 312 participants who underwent a multiple - sleep study and magnetic resonance imaging (MRI) scanning twice; once during 1996 – 1998, and then fifteen years later. They were stratified according to the sleep duration (<7 h, 7-to ≤8 h, and ≥8 h) and 19% had moderate-sleeping sleep apnea. No significant relationship was found between OSAS and short sleep, and cerebral markers of vascular dementia and AD (24). Finally, Buratti et al. (25) assessed 162 participants with AD (69 subjects in the control group (71.95 years old) and 93 patients with OSAS (72.83 years old)) who underwent ultrasound assessment of the external and internal cranial arteries, and it was found that in patients with OSAS and AD, common lesions of these arteries, as well as the extent of cerebrovascular damage was correlated with the severity of OSAS. Similar findings were observed in the overview by Bista et al. (26), assessing the cerebrovascular effects of OSAS.

In order to understand the effect of one pathological entity on the other, some studies have examined patients without interventions. Two studies (23, 24) have shown a correlation between lack of sleep and increased risk of dementia. Others proposed that the underlying factor connecting the pathophysiology of the two diseases is the vascular system; thus, they examined whether abnormalities occur to support this proposal. MRI scanning (24) did not reveal any significant biomarkers but ultrasound assessment (25) showed similar vascular lesions in OSAS and AD patients. The exact mechanisms behind these lesions remain to be unveiled.

Effect of Treatment: Donepezil

The research by Moraes et al. (27) studied patients with AD and OSAS who underwent a sleep study, a cognitive evaluation using AD assessment scale-cognitive (ADAS-cog) and donepezil (n=11) and placebo (n=12) were administrated, three months before and after the treatment. Patients with OSAS and AD treated with donepezil experienced a decrease in the apnea-hypopnea index, increased blood oxygenation, improved neurologic array scores, and an increase in the rapid eye movement (REM) stage compared with the placebo group (27). This is the only study to our knowledge that estimated the effectiveness of donepezil. Despite the encouraging results, the small sample is a significant limitation of the study, signifying that more research is necessary to support the evidence.

Effect of Treatment: CPAP

Liguori et al. (28) looked at sleep parameters, cognitive function, and CSF biomarkers, such as β-amyloid and tau protein in patients with OSAS and AD. After the end of the study, they observed that patients with OSAS and AD showed low concentrations of β-amyloid, higher levels of lactic acid, and a higher tau protein/β-amyloid ratio in CSF compared with controls and patients with OSAS-AD and the use of CPAP. Patients with OSAS-AD experienced reduced sleep quality and lower memory and executive performance. Lower levels of β-amyloid in CSF have been associated with memory impairment and oxygen saturation parameters in patients with OSAS-AD (28).

A study by Osorio et al. (29) conducted in 767 people found that breathing difficulty during sleep is associated with a younger age of mild cognitive impairment or onset of AD. Continuous use of CPAP is associated with the delayed onset of cognitive impairment and it is suggested as an effective method for cognitive function protection (29). Additionally, Richards (30) studied 5 patients with mild to moderate dementia, OSAS, and who used CPAP (after 6 weeks and after 1 year of treatment) and 5 patients without CPAP. At the end of the study, they found that prolonged use of CPAP in patients with AD and OSAS led to the improvement in cognitive function, depressive symptoms, daytime sleepiness, and sleep quality of patients and caregivers (30).

The attention of Cooke et al. (2009) focused on the long-term benefits of using CPAP in patients with AD and OSAS. The researchers studied 5 patients using CPAP (mean use =13.3 months) and 5 patients without CPAP. In this study, it was observed that patients using CPAP resulted in less cognitive decline and stabilization of depressive symptoms and somnolence. The results of this study increase the likelihood that long-term CPAP treatment for AD and OSAS patients may lead to sustained improvement in sleep and mood as well as retardation of cognitive impairment (31). Cooke et al. (31) examined the effect of treatment with CPAP (after one night and after 3 weeks of treatment) and the placebo in 52 patients with AD and OSAS. They noted that in patients with mild to moderate AD and OSAS following a treatment night, the CPAP group had significantly less % stage 1 and more % stage 2 sleep compared with the placebo group. After 3 weeks of CPAP, there was a significant reduction in stage 1, wake-ups, and an increase in stage 3 (32).

In addition, Cooke et al. (33) examined treatment with CPAP (n=27) and placebo (n=25) in patients with AD and OSAS after 3 and 6 weeks. A complete neuropsychological test battery was administered prior to treatment and after 3 and 6 weeks. Comparison of the neuropsychological pre-treatment and post-treatment scores showed a significant improvement in the cognitive function of patients using CPAP versus placebo. Therefore, they concluded that OSAS may worsen the cognitive function of AD patients, and CPAP therapy can improve cognitive impairment. Clinical doctors who care for AD patients should consider CPAP treatment when OSAS is present (33).

Finally, the study by Ayalon et al., which studied 9 patients with AD and OSAS using CPAP and 12 patients with AD and OSAS without CPAP for six weeks in total, observed that AD and OSAS patients using CPAP (4.8 h per night) had fewer depression symptoms. It was surprising that the average number of hours of CPAP per night use in patients with AD was 4.8 h, which did not differ greatly from the compliance of only OSAS patients. This study is the first to report that patients with AD and OSAS can comply with CPAP therapy (34).

The strength of evidence in most of the studies on the effects of CPAP on AD is limited due to the small sample size. In order to assess cognitive health, one study searched the possible correlation of CSF biomarkers with sleep parameters (28). Several other studies estimated the short-term effects of CPAP and their results were similar (29, 31, 33, 34). Although it was assessed by only one study, the long term effects of the use of CPAP showed similar benefits (32). Therefore, it could be concluded that its use is beneficial for delaying dementia and reversing cognitive symptoms to some extent. However, there is not enough evidence to recommend CPAP for cognitive decline.

Table 1. Treatment results in patients with obstructive sleep apnea syndrome and Alzheimer's disease.

Reference	Sample	Treatment	Results
Ju et al. (35)	n=35 OSAS	auto-PAP/CPAP	OSA on SWA and Aβ—and possibly tau—is a probable proximal step in a cascade whereby OSA increases the risk of AD
Elias et al. (36)	n=42/119 OSAS	CPAP (n=14)	CPAP↓ amyloid PET findings and APOE4 related to with Aβ amyloidburden than OSA.
Liguori et al. (28)	n=25 OSA, n=10 OSA-CPAP, n=15 C	CPAP	OSA ↓ sleep quality and ↑ intermittent hypoxia, inducing biomarkers alterations
Osorio et al. (29)	n=133 AD + SDB	CPAP (35 pts)	CPAP ↓ onset of cognitive impairment
Troussière et al. (37)	n=23 AD and SAS (14 of whom underwent CPAP treatment)	CPAP	CPAP$_{treatment}$ of severe SAS in mild-to-moderate AD patients was associated with significantly slower cognitive decline over a three-year follow-up period
Singh et al. (38)	n=20 OSAS	CPAP + Vitamin E + C	Improving number of apnoeic episodes and the oxidative profile
Richards (30)	n=10 AD + OSAS	CPAP (5 pts) at 6 weeks and after 1 year of treatment	CPAP$_{treatment}$ ↓ symptoms
Cooke et al. (31)	n=10 AD + OSAS	CPAP (5 pts) at 6 weeks and after 13.3 months of treatment	CPAP$_{treatment}$ ↑ sleep and mood as well as retardation of cognitive impairment
Ancoli-Israel et al. (32)	n=52 AD + OSA	CPAP and placebo after one night and after 3 weeks of treatment	Improvement in sleep architecture
Cooke et al. (33)	n=52 AD + OSA	CPAP + placebo (after 3 weeks placebo + 3 CPAP or 6 weeks of CPAP treatment)	↑ cognition
Ayalon et al. (34)	n=21 AD + OSAS	CPAP (9 pts) for 3 weeks CPAP or 3 placebo and 3 weeks CPAP	↓depression symptoms
Sukys-Claudino et al. (39)	n=21 OSAS (n=11 Donezepil, n=10 placebo)	Donezepil	↑ breathing regulation in OSA patients
Moraes et al. (27)	n=23 AD + OSAS = (n=11 Donezepil, n=12 placebo)	Donezepil	Donepezil treatment improved AHI and oxygen saturation in patients with AD
La et al. (40)	n=25 AD under trazodone, n=25 AD non – users	Trazodone	↑ cognitive in patients with AD
Smales et al. (41)	n=15 OSAS (6 under CPAP)	Trazodone	Trazodone may be beneficial for cognition and AD prevention
Eckert et al. (42)	n=7 OSAS	Trazodone	Trazodone may be beneficial for cognition and AD prevention
Kryscio et al. (43)	n=3,786 men	Selenium + Vitamin E	The antioxidant agents did not prevent the onset of dementia
Albuquerque et al. (44)	-	Selenium	↓ oxidative stress in patients with OSA
Kim et al. (45)	n=14 patients with probable AD	Rivastigmine transdermal patch	↑ RDI
Cho et al. (46)	n=12,664 OSAS under Uvulopalatopharyngoplasty and n=112,753 OSAS with no surgery	Uvulopalatopharyngoplasty	In the no-surgery$_{group}$, the incidence of dementias was higher
Kheirandish-Gozal et al. (47)	n=74 OSAS children,n=105 obesity OSAS, n=63 OB,n=44 C (24 of which underwent Adenotonsillectomy)	Adenotonsillectomy	OSA and OSA+OB are associated with increased plasma levels of AD biomarkers ↓ treatment of OSA

Note: AD = Alzheimer's disease, **Aβ** = amyloid-beta, C = control, CPAP = continuous positive airway pressure, OB = obesity, OSAS = obstructive sleep apnea syndrome, PAP = positive airway pressure, PET = positron emission tomography, SAS = sleep apnea syndrome, SWA = slow wave activity during sleep.

Table 2. Biomarkers results in patients with obstructive sleep apnea syndrome and Alzheimer's disease

Reference	Sample	Method	Results
Lee et al. (48)	n=727 SDB,n=3635 non-SDB	Cohort stud via propensity score matching	SDB group more likely to develop AD after matching and adjusting for other risk factors
Gaeta et al. (49)	n=116/128 mild-moderate AD were diagnosed with OSAS	PSG for assessing the severity of OSAS and Mini-Mental State Examination + EES + APOE status for AD severity	The prevalence of APOE ε4 was not significantly different between patients with and without severe OSA
Przybylska-Kud et al. (50)	n=31 C, n=38 mild-moderate OSAS, n=43 severe OSAS	Aβ 1–40 and Aβ 1–42 plasma concentrations	OSA_{severe} demonstrated higher concentrations of Aβ 1–40 compared with the rest groups
Gonzalez Vicente et al. (51)	Rats	Under intracerebro-ventricular streptozotocin, a drug that has been described to cause Alzheimer-like behavioral and histopathological impairments	↑ sensitivity to CO_2 during wakefulness, ↑ Aβ in the Locus Coeruleus, no change in tau protein phosphorylation and sleep disruption
Mendes et al. (52)	n=318 AD	assessed for multimorbidity and neuroimaging biomarkers	OSA was associated with lower amyloid-PET SUV ratios
Lutsey et al. (23)	n=1667	OSAS and risk for dementia	Sleeping <7 versus8-≤9 hours, also correlated significantly with a higher risk of dementia and AD
Kahya et al. (53)	n=36 [APOE ε4 carriers (n=9), non- carriers (n=27)] cognitively normal older adults without self-reported sleep apnea	Actigraph + PSQI + ESS	Cognitively normal older APOE ε4 carriers without self-reported sleep apnea had disrupted sleep compared to non-carriers
Ju et al. (54)	n=10 OSA, n=31 C	PSG and lumbar puncture for CSF biomarkers	SWA is decreased in moderate-to-severe OSA and neuronally derived proteins, but not total protein, were also decreased in the OSA group
Lutsey et al. (24)	n=312	PSG and MRI twice. They were stratified according to the sleep duration (<7 hours, 7-to-<8 hours and ≥8 hours)	No significant statistical relationship between OSAS and short sleep with cerebral markers of vascular dementia and Alzheimer's disease
Bu et al. (55)	n=45 OSAS, n=49 C	The cognitively normal OSAS patients exhibited significantly higher serum Aβ40, Aβ42 and total Aβ levels, and each of these levels were positively correlated with the severity of OSAS and the extent of hypoxia. In OSAS patients, the serum P-tau 181 levels were higher and correlated with the Aβ levels	↑ Aβ levels in the serum are correlated with the severity of chronic intermittent hypoxia in OSAS patients and may contribute to the pathogenesis of AD
Buratti et al. (25)	n=162 AD, n= 69 C, n=93 OSAS	U/S of external and internal arteries	Common lesions of external and internal cranial arteries as well as that the extent of cerebrovascular damage was correlated with the severity of OSAS
Osorio et al. (56)	n=19 severe SDB,n=51 mild, n=25 normal elderly cognitive normal	SDB severity, CSF measures of phosphorylated-tau (P-Tau), total-tau (T- Tau), and amyloid beta 42 (Aβ42), as well as ApoE allele status	SDB in ApoE3+ and ApoE2+ normal elderly is associated with changes in specific biomarkers of Late onset Alzheimer's disease
Nikodemova et al. (57)	n=755 adults evaluated for their sleep characteristics	PSG + APOE4 + neurocognitive test battery	The combination of moderate to severe SDB and APOE4 genotype is associated with poorer performance on some neurocognitive tests with memory and executive function components
Shiota et al. (58)	Mice triple transgenic AD	Were evaluated Aβ profile, cognitive brain function, and brain pathology.	CIH directly increased levels of Aβ42 in the AD model (but not Aβ40 and HIF-1α), no significant changes in cognitive function. Therefore, OSA may aggravate AD
Kaushal et al. (59)	Murine models (adult male human ApoE4-targeted replacement mice (hApoE4) and wild-type (WT) controls)	Sleep disorder such as sleep apnea (i.e., IH, SF, or both) would lead to a more pronounced disruption of sleep integrity in a murine model of AD	IH, SF and IH+SF, are sufficient to elicit sleep deficits, excessive sleepiness, and hApoE4 exacerbates such effects

Note: AD = Alzheimer's disease, **Aβ** = amyloid-beta, C = control, CSF = cerebrospinal fluid, ESS = Epworth sleep scale, IH = intermittent hypoxia, MRI = magnetic resonance imaging, PET = positron emission tomography, PSG = polysomnography study, PSQI = Pittsburg sleep quality index, SDB = sleep-disorders breathing, SF = sleep fragmentation, SWA = slow wave activity during sleep.

DISCUSSION

The scientific community has recently begun to address AD and OSAS patients; as far as the effects of CPAP treatment are concerned, international literature is generally limited. After the synopsis of information in this literature review, 20 articles were found that studied the relationship between AD and OSAS patients. There is a separate section that reviews the information on the relationship between these two entities. According to the available data, increasing evidence is suggesting an OSAS - induced direction towards AD (15, 17, 18, 19, 35, 21, 22). However, it has been suggested that there might be an AD – induced OSAS, through inflammatory pathways (14, 16). The pathophysiologic mechanisms have not yet been fully clarified. Treatment strategies, including using donepezil and CPAP were analyzed in the corresponding sections. OSAS with severe AHI and respiratory distress during sleep as well as sleep fragmentation were associated with cognitive impairment with varying degrees and beginning at an earlier age (23, 24, 29). A separate reference to the cerebrovascular damage of AD patients was cited to indicate the correlation with the severity of OSAS (25, 26). Lower levels of β-amyloid, higher levels of lactic acid, and a higher tau protein / β-amyloid ratio in CSF might demonstrate possible biomarkers associated with memory decline and oxygen saturation parameters in patients with OSAS and AD (28). Regarding studies without treatment, Lutsey et al. recently noted that severe OSAS, as well as disturbed sleep architecture, are associated with a high risk of developing dementia. On the other hand, after a study of about 15 years, in 2016, they found that sleeping shortness and OSAS are not associated with brain neuroimaging markers (23,24).

A large part of this bibliographic review refers to the treatment of CPAP patients with OSAS and AD. The CPAP has been shown to delay the appearance of cognitive impairment (29) and has been proposed as an effective method of protecting and even restoring cognitive function, depression, quality of sleep, sleep structure, and daytime sleepiness in AD patients (30). Additional studies (30, 31, 32) observed that the use of CPAP increased sleep quality and improved neurocognitive and depressive symptoms. The short – term effects of OSA seem to be a significant reduction in stages I and II sleep duration (32) and in awakening, and also an increase in stage III sleep duration (33). Moraes et al. who examined the effects of donepezil, observed an improvement in the objective indices of sleep in pneumogastric array scores and in the REM stage (27).

Finally, Ayalon et al. noted that the AD-OSAS group using CPAP (4.8 h per night) did not show significant differences compared with the group OSAS group. This study is the first to report that patients with AD and OSAS can comply with CPAP therapy (34).

Limitations

The articles were selected using the keywords, including obstructive sleep apnea syndrome, AD, and CPAP. The exclusion criteria were the age of below 18 years old, co-morbidities, as well as meta-analyses articles. Only English articles were used. The studies included were published up to 15 years ago due to the lack of data. In addition to the limited literature on the relationship between AD and OSAS and the effects of CPAP treatment, no comparison can be made with other reviews or meta-analyses.

CONCLUSION

In conclusion, based on the limited available published studies, the severity of OSAS, as well as the short duration of sleep is significantly associated with a high risk of developing dementia. Treatment with CPAP seems effective for OSAS and AD patients because it not only treats OSAS but also delays cognitive impairment and protects against it. It remains the gold standard for treatment; thus, clinical doctors who treat AD patients should consider CPAP treatment when OSAS coexists. Further research is needed because few studies have evaluated the relationship between OSAS and AD as well as the effect of treatments with a CPAP device. Future research could help elucidate the pathophysiologic relationship between the two entities and answer questions that are still unknown to the scientific community.

REFERENCES

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. ***Am J Respir Crit Care Med*** 2002;165(9):1217-39.
2. Pham LV, Schwartz AR. The pathogenesis of obstructive sleep apnea. ***J Thorac Dis*** 2015;7(8):1358-72.
3. Ferini-Strambi L, Lombardi GE, Marelli S, Galbiati A. Neurological Deficits in Obstructive Sleep Apnea. ***Curr Treat Options Neurol*** 2017;19(4):16.
4. Partinen M. Epidemiology of obstructive sleep apnea syndrome. ***Curr Opin Pulm Med*** 1995;1(6):482-7.
5. Rowley JA, Lareau S, Fahy BF, Garvey C, Sockrider M. What Is Obstructive Sleep Apnea in Adults? ***Am J Respir Crit Care Med*** 2017;196(1):P1-P2.
6. Osman AM, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. ***Nat Sci Sleep*** 2018;10:21-34.
7. Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of sleep on the risk of cognitive decline and dementia. ***Curr Opin Psychiatry*** 2014;27(6):478-83.
8. Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. Sleep disturbance in mild to moderate Alzheimer's disease. ***Sleep Med*** 2005;6(4):347-52.
9. Polsek D, Gildeh N, Cash D, Winsky-Sommerer R, Williams SCR, Turkheimer F, et al. Obstructive sleep apnoea and Alzheimer's disease: In search of shared pathomechanisms. ***Neurosci Biobehav Rev*** 2018;86:142-149.
10. Frost GR, Li YM. The role of astrocytes in amyloid production and Alzheimer's disease. ***Open Biol*** 2017;7(12):170228.
11. Fishman E. Risk of Developing Dementia at Older Ages in the United States. ***Demography*** 2017;54(5):1897-1919.
12. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. ***Alzheimer's & Dementia*** 2017;13(4):325-73.
13. Malhotra RK. Neurodegenerative Disorders and Sleep. ***Sleep Med Clin*** 2018;13(1):63-70.
14. Irwin MR, Vitiello MV. Implications of sleep disturbance and inflammation for Alzheimer's disease dementia. ***Lancet Neurol*** 2019;18(3):296-306.
15. Pan W, Kastin AJ. Can sleep apnea cause Alzheimer's disease? ***Neurosci Biobehav Rev*** 2014;47:656-69.
16. Bao YP, Han Y, Ma J, Wang RJ, Shi L, Wang TY, et al. Cooccurrence and bidirectional prediction of sleep disturbances and depression in older adults: Meta-analysis and systematic review. ***Neurosci Biobehav Rev*** 2017;75:257-273.
17. Carvalho DZ, St Louis EK, Boeve BF, Mielke MM, Przybelski SA, Knopman DS, et al. Excessive daytime sleepiness and fatigue may indicate accelerated brain aging in cognitively normal late middle-aged and older adults. ***Sleep Med*** 2017;32:236-243.
18. Carvalho DZ, St Louis EK, Knopman DS, Boeve BF, Lowe VJ, Roberts RO, et al. Association of Excessive Daytime Sleepiness With Longitudinal β-Amyloid Accumulation in Elderly Persons Without Dementia. ***JAMA Neurol*** 2018;75(6):672-680.
19. Bubu OM, Pirraglia E, Andrade AG, Sharma RA, Gimenez-Badia S, Umasabor-Bubu OQ, et al. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes. ***Sleep*** 2019;42(6):zsz048.
20. Liguori C, Mercuri NB, Nuccetelli M, Izzi F, Cordella A, Bernardini S, et al. Obstructive sleep apnea may induce orexinergic system and cerebral β-amyloid metabolism dysregulation: is it a further proof for Alzheimer's disease risk? ***Sleep Med*** 2019;56:171-176.
21. Kadotani H, Kadotani T, Young T, Peppard PE, Finn L, Colrain IM, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. ***JAMA*** 2001;285(22):2888-90.
22. Gottlieb DJ, DeStefano AL, Foley DJ, Mignot E, Redline S, Givelber RJ, et al. APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the Sleep Heart Health Study. ***Neurology*** 2004;63(4):664-8.
23. Lutsey PL, Misialek JR, Mosley TH, Gottesman RF, Punjabi NM, Shahar E, et al. Sleep characteristics and risk of dementia and Alzheimer's disease: The Atherosclerosis Risk in Communities Study. ***Alzheimers Dement*** 2018;14(2):157-166.

24. Lutsey PL, Norby FL, Gottesman RF, Mosley T, MacLehose RF, Punjabi NM, et al. Sleep Apnea, Sleep Duration and Brain MRI Markers of Cerebral Vascular Disease and Alzheimer's Disease: The Atherosclerosis Risk in Communities Study (ARIC). ***PLoS One*** 2016;11(7):e0158758.
25. Buratti L, Viticchi G, Falsetti L, Cagnetti C, Luzzi S, Bartolini M, et al. Vascular impairment in Alzheimer's disease: the role of obstructive sleep apnea. ***J Alzheimers Dis*** 2014;38(2):445-53.
26. Bista SR, Barkoukis TJ. Medical disorders impacted by obstructive sleep apnea. ***Dent Clin North Am*** 2012;56(2):373-86.
27. Moraes W, Poyares D, Sukys-Claudino L, Guilleminault C, Tufik S. Donepezil improves obstructive sleep apnea in Alzheimer disease: a double-blind, placebo-controlled study. ***Chest*** 2008;133(3):677-83.
28. Liguori C, Mercuri NB, Izzi F, Romigi A, Cordella A, Sancesario G, et al. Obstructive Sleep Apnea is Associated With Early but Possibly Modifiable Alzheimer's Disease Biomarkers Changes. ***Sleep*** 2017;40(5).
29. Osorio RS, Gumb T, Pirraglia E, Varga AW, Lu SE, Lim J, et al. Sleep-disordered breathing advances cognitive decline in the elderly. ***Neurology*** 2015;84(19):1964-71.
30. Richards KC. Comorbid Alzheimer's disease and OSAS: does CPAP slow cognitive decline? ***J Clin Sleep Med*** 2009;5(4):310.
31. Cooke JR, Ancoli-Israel S, Liu L, Loredo JS, Natarajan L, Palmer BS, et al. Continuous positive airway pressure deepens sleep in patients with Alzheimer's disease and obstructive sleep apnea. ***Sleep Med*** 2009;10(10):1101-6.
32. Ancoli-Israel S, Palmer BW, Cooke JR, Corey-Bloom J, Fiorentino L, Natarajan L, et al. Cognitive effects of treating obstructive sleep apnea in Alzheimer's disease: a randomized controlled study. ***J Am Geriatr Soc*** 2008;56(11):2076-81.
33. Cooke JR, Ayalon L, Palmer BW, Loredo JS, Corey-Bloom J, Natarajan L, et al. Sustained use of CPAP slows deterioration of cognition, sleep, and mood in patients with Alzheimer's disease and obstructive sleep apnea: a preliminary study. ***J Clin Sleep Med*** 2009;5(4):305-9.
34. Ayalon L, Ancoli-Israel S, Stepnowsky C, Marler M, Palmer BW, Liu L, et al. Adherence to continuous positive airway pressure treatment in patients with Alzheimer's disease and obstructive sleep apnea. ***Am J Geriatr Psychiatry*** 2006;14(2):176-80.
35. Ju YS, Zangrilli MA, Finn MB, Fagan AM, Holtzman DM. Obstructive sleep apnea treatment, slow wave activity, and amyloid-β. ***Ann Neurol*** 2019;85(2):291-295.
36. Elias A, Cummins T, Tyrrell R, Lamb F, Dore V, Williams R, et al. Risk of Alzheimer's Disease in Obstructive Sleep Apnea Syndrome: Amyloid-β and Tau Imaging. ***J Alzheimers Dis*** 2018;66(2):733-741.
37. Troussière AC, Charley CM, Salleron J, Richard F, Delbeuck X, Derambure P, et al. Treatment of sleep apnoea syndrome decreases cognitive decline in patients with Alzheimer's disease. ***J Neurol Neurosurg Psychiatry*** 2014;85(12):1405-8.
38. Singh TD, Patial K, Vijayan VK, Ravi K. Oxidative stress and obstructive sleep apnoea syndrome. ***Indian J Chest Dis Allied Sci*** 2009;51(4):217-24.
39. Sukys-Claudino L, Moraes W, Guilleminault C, Tufik S, Poyares D. Beneficial effect of donepezil on obstructive sleep apnea: a double-blind, placebo-controlled clinical trial. ***Sleep Med*** 2012;13(3):290-6.
40. La AL, Walsh CM, Neylan TC, Vossel KA, Yaffe K, Krystal AD, et al. Long-Term Trazodone Use and Cognition: A Potential Therapeutic Role for Slow-Wave Sleep Enhancers. ***J Alzheimers Dis*** 2019;67(3):911-921.
41. Smales ET, Edwards BA, Deyoung PN, McSharry DG, Wellman A, Velasquez A, et al. Trazodone Effects on Obstructive Sleep Apnea and Non-REM Arousal Threshold. ***Ann Am Thorac Soc*** 2015;12(5):758-64.
42. Eckert DJ, Malhotra A, Wellman A, White DP. Trazodone increases the respiratory arousal threshold in patients with obstructive sleep apnea and a low arousal threshold. ***Sleep*** 2014;37(4):811-9.
43. Kryscio RJ, Abner EL, Caban-Holt A, Lovell M, Goodman P, Darke AK, et al. Association of Antioxidant Supplement Use and Dementia in the Prevention of Alzheimer's Disease by Vitamin E and Selenium Trial (PREADViSE). ***JAMA Neurol*** 2017;74(5):567-573.
44. Albuquerque RG, Hirotsu C, Tufik S, Andersen ML. Why Should We Care About Selenium in Obstructive Sleep Apnea? ***J Clin Sleep Med*** 2017;13(7):931-932.

45. Kim H, Joo E, Suh S, Kim JH, Kim ST, Hong SB. Effects of long-term treatment on brain volume in patients with obstructive sleep apnea syndrome. ***Hum Brain Mapp*** 2016;37(1):395-409.
46. Cho JH, Suh JD, Han KD, Jung JH, Lee HM. Uvulopalatopharyngoplasty May Reduce the Incidence of Dementia Caused by Obstructive Sleep Apnea: National Insurance Service Survey 2007-2014. ***J Clin Sleep Med*** 2018;14(10):1749-1755.
47. Kheirandish-Gozal L, Philby MF, Alonso-Álvarez ML, Terán-Santos J, Gozal D. Biomarkers of Alzheimer Disease in Children with Obstructive Sleep Apnea: Effect of Adenotonsillectomy. ***Sleep*** 2016;39(6):1225-32.
48. Lee JE, Yang SW, Ju YJ, Ki SK, Chun KH. Sleep-disordered breathing and Alzheimer's disease: A nationwide cohort study. ***Psychiatry Res*** 2019;273:624-630.
49. Gaeta AM, Benítez ID, Jorge C, Torres G, Dakterzada F, Minguez O, et al. Prevalence of obstructive sleep apnea in Alzheimer's disease patients. ***J Neurol*** 2020;267(4):1012-1022.
50. Przybylska-Kuć S, Zakrzewski M, Dybała A, Kiciński P, Dzida G, Myśliński W, et al. Obstructive sleep apnea may increase the risk of Alzheimer's disease. ***PLoS One*** 2019;14(9):e0221255.
51. Gonzalez-Vicente A, Hong NJ, Yang N, Cabral PD, Berthiaume JM, Dominici FP, et al. Dietary Fructose Increases the Sensitivity of Proximal Tubules to Angiotensin II in Rats Fed High-Salt Diets. ***Nutrients*** 2018;10(9):1244.
52. Mendes A, Tezenas du Montcel S, Levy M, Bertrand A, Habert MO, Bertin H, et al. Multimorbidity Is Associated with Preclinical Alzheimer's Disease Neuroimaging Biomarkers. ***Dement Geriatr Cogn Disord*** 2018;45(5-6):272-281.
53. Kahya M, Vidoni E, Burns JM, Thompson AN, Meyer K, Siengsukon CF. The Relationship Between Apolipoprotein ε4 Carrier Status and Sleep Characteristics in Cognitively Normal Older Adults. ***J Geriatr Psychiatry Neurol*** 2017;30(5):273-279.
54. Ju YE, Finn MB, Sutphen CL, Herries EM, Jerome GM, Ladenson JH, et al. Obstructive sleep apnea decreases central nervous system-derived proteins in the cerebrospinal fluid. ***Ann Neurol*** 2016;80(1):154-9.
55. Bu XL, Liu YH, Wang QH, Jiao SS, Zeng F, Yao XQ, et al. Serum amyloid-beta levels are increased in patients with obstructive sleep apnea syndrome. ***Sci Rep*** 2015;5:13917.
56. Osorio RS, Ayappa I, Mantua J, Gumb T, Varga A, Mooney AM, et al. Interaction between sleep-disordered breathing and apolipoprotein E genotype on cerebrospinal fluid biomarkers for Alzheimer's disease in cognitively normal elderly individuals. ***Neurobiol Aging*** 2014;35(6):1318-24.
57. Nikodemova M, Finn L, Mignot E, Salzieder N, Peppard PE. Association of sleep disordered breathing and cognitive deficit in APOE ε4 carriers. ***Sleep*** 2013;36(6):873-80.
58. Shiota S, Takekawa H, Matsumoto SE, Takeda K, Nurwidya F, Yoshioka Y, et al. Chronic intermittent hypoxia/reoxygenation facilitate amyloid-β generation in mice. ***J Alzheimers Dis*** 2013;37(2):325-33.
59. Kaushal N, Ramesh V, Gozal D. TNF-α and temporal changes in sleep architecture in mice exposed to sleep fragmentation. ***PLoS One*** 2012;7(9):e45610.