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REVIEW

Treatment of Obstructive Sleep Apnea in patients with Alzheimer's Disease: role of Continuous Positive Airway Pressure therapy

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Abstract

Purpose of Review Obstructive Sleep Apnea (OSA) is a frequent comorbidity in patients with Alzheimer's Disease (AD). This narrative review critically examines current evidence on the relationship between OSA and AD, discussing their shared pathogenic mechanisms. Furthermore, the review focuses on the rationale, effectiveness, and feasibility of Continuous Positive Airway Pressure (CPAP) treatment in patients with comorbid OSA and mild cognitive impairment (MCI) or dementia due to AD. Finally, this review provides clinicians with a practical approach for the proper diagnosis, and management of OSA in patients with AD either in the context of memory clinics and sleep medicine centers.

Recent Findings Chronic intermittent hypoxia, glymphatic system failure and sleep disruption are the most important mechanisms connecting OSA to AD pathophysiology. Randomized clinical trials and observational studies show that OSA treatment with CPAP in patients with AD results in improvement of daytime vigilance, mood and executive functions as well as sleep consolidation. Moreover, it has been shown that CPAP has a mild potential effect on cognitive trajectories over time. Interestingly, adherence rates to CPAP treatment are similar to those reported in the general population.

Summary Patients with MCI and AD dementia should be screened for the presence of OSA as part of the routinary clinical evaluation. Given its proven efficacy and feasibility, treatment with CPAP should be offered in patients with comorbid AD and moderate-severe OSA and a proper follow-up should be established to ensure treatment compliance and tolerability.

Keywords Obstructive Sleep Apnea · Alzheimer's Disease · Dementia · Mild cognitive impairment · Continuous positive airway pressure · CPAP therapy

Introduction

Obstructive Sleep Apnea (OSA) is a chronic sleep-related breathing disorder (SDB), caused by repetitive collapse of the upper airways during sleep, and associated with intermittent desaturations and cortical arousals. The severity of OSA is classified by means of the Apnea Hypopnea Index (AHI), defined as the number of apneas plus hypopneas per hour of sleep [1]. AHI comprised between 5 and 14 events/hour identifies mild OSA, between 15–29 events/hour moderate OSA, while an AHI $\geq$ 30 events/hour severe OSA. OSA is a very common condition, and its prevalence increases with age, and body weight [2]. It is estimated that 436 million people are affected by moderate to severe OSA worldwide [3]. However, most of these cases are underdiagnosed or probably asymptomatic [3]. OSA clinical picture is indeed heterogenous, ranging from asymptomatic or mild snoring patients to patients with a wide variety of nocturnal and diurnal symptoms, which concur to the OSA syndrome (OSAS). These symptoms include loud snoring, nocturnal choking, witnessed apneas, dry mouth, nocturia, insomnia, excessive daytime sleepiness (EDS), non-restorative sleep, morning or nocturnal headache and fatigue. EDS is the most common daytime symptom and is associated with higher nocturnal hypoxemia [4], and higher sleep fragmentation [5]. Cardiovascular, metabolic and cerebrovascular sequelae are well-recognized components of OSA-associated morbidity and mortality [6–8]. Furthermore, neuropsychiatric symptoms

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are common in OSA presentation, namely depression, bipolar affective disorder [9], anxiety, irritability [10]. OSA negatively impacts executive functions, attention, vigilance, episodic memory, visuospatial abilities [11], and social cognition [12]. In particular, the hypersomnolent subtype is gravated by a more extensive and complex neurocognitive dysfunction [5].

Moreover, in the last decades growing evidence has linked OSA to dementia pathophysiology, in particular to Alzheimer's Disease (AD) pathology [13]. AD is the most common cause of dementia, accounting for more than 70% of all causes of dementia and, as our society ages, prevalence estimates of dementia are projected to rise from 57 million in 2019 to 153 million cases in 2050 [14], making AD a global health concern. AD is biologically defined by the presence of amyloid β deposition and phosphorylated tau accumulation (which constitutes the so-called 'AD pathology'). This biomarker profile may be accompanied by different syndromal cognitive stages according to presence and severity of symptoms [15]. AD is indeed regarded as a *continuum* extending over decades, in which AD pathology is at first present without symptoms ('AD pre-clinical stage') [16], or is associated with subjective memory complaints not confirmed by objective neuropsychological assessment (subjective cognitive impairment, SCI), progresses into a stage of mild cognitive impairment (MCI) [17], and then advances to overt dementia [18], even if not every patients will follow this path [19]. Thus, the advent of *in-vivo* pathological AD biomarkers has allowed clinicians to identify patients in pre-clinical and early clinical stages of the disease, making urgent the need for effective disease-modifying strategies. In this view, the increasing evidence of a potential link between OSA and accumulation of AD pathology has shed the light of a new potential disease-modifying target.

The aims of the present narrative review are to examine the relationship between OSA and AD, and to review the existing knowledge on the effects and feasibility of CPAP treatment in patients with comorbid OSA and MCI or dementia due to AD. Finally, we discuss clinical management and treatment approaches of OSA in patients with MCI or dementia due to AD.

OSA & AD: Pathogenetic Links

In the last decades, observational studies investigating the association between OSA and AD have multiplicated. A recently published meta-analysis showed that patients with OSA had a higher risk of developing any type of neurocognitive disorder, particularly AD dementia [20]. In a longitudinal 5-year follow-up study older women with sleep disordered breathing (SDB) had an increased risk of developing MCI or dementia, compared to those without SDB, and adjustment for baseline cognitive scores strengthened this association (OR: 2.36; 95% CI: 1.34–4.13) [21]. Moreover, presence of SDB is associated with earlier MCI and AD dementia onset, as shown by a large, longitudinal study of more than 2,000 participants [22]. On the other hand, patients with AD dementia have a five-fold increased chance of being diagnosed with OSA compared to cognitively normal individuals of similar age, as reported by a meta-analysis [23] including three observational studies using polysomnography (PSG) and two studies assessing OSA with polygraphy and respiratory inductive pletismography. When analyzing only the studies assessing OSA with gold-standard methodology (i.e. PSG), such risk becomes as high as seven-fold. Overall, the evidence emerging from the existing literature points out the high prevalence of comorbid OSA and AD, suggesting OSA as a potential risk factor for AD, or at least a reverse causation between these two conditions. Consequently, both the fields of preclinical and clinical research have focused on the possible mechanisms clarifying this association. Several pathways have been proposed.

Chronic intermittent hypoxia (CIH), as a consequence of repetitive collapse of the upper airways in sleep-induced apneas, exposes the brain to oxidative stress and chronic inflammation [24]. Studies conducted on rodents' brain showed that CIH elevates oxidative stress and inflammatory markers in early-stage AD-associated brain regions, such as the entorhinal cortex and dorsal hyppocampus [25, 26]. In another recent experimental study, CIH induced down-regulation of post-synaptic proteins and long-term potentiation dysfunction of the hippocampus in wild type mice; such effects were more pronounced in an animal model of AD (APP/PS1 mice) [27], suggesting OSA may have a more prominent detrimental effect in the presence of AD pathology and may accelerate neurodegeneration. Indeed, CIH exposure, compared to normoxia, was shown to enhance pathological tau seeding and spreading, to increase phospho-tau burden, and to exacerbate AD-like memory and synaptic plasticity deficits in a tau-mouse model [28]. Moreover, CIH increased levels of $A\beta_{42}$ in transgenic AD mice, compared to controls [29]. Another mechanism connecting OSA to neurodegeneration is mediated by neuroinflammation, triggered by microglial activation and Toll Like Receptor 2 (TLR2) functionality in the murine OSA model [30]. TLR2 is an innate immune receptor widely expressed by microglial cells, which was recently demonstrated to be involved in inflammatory responses' initiation and modulation in the rodent brain under OSA-like conditions [30]. This brain immune response, in turn, influences expression of neuroplasticity markers such as neuroplastin [30]. Neuroplastin has been proposed as a potential biomarker for AD progression, with its involvement in human hippocampal tissue reorganization [31]. In this light, the interplay between TLR2 and neuroplastin is a putative pathway linking OSA

to neurodegeneration [32]. Taken together, these studies on animal models of OSA and AD suggest that OSA may act as either a precipitating or an accelerating factor on AD pathology progression. This evidence is further corroborated by human studies investigating the associations between OSA severity and AD biomarkers. In a longitudinal study of cognitively normal subjects undergoing lumbar puncture twice, at baseline and after two years follow-up, baseline OSA severity correlated with the annual decreases in CSF $A\beta_{42}$ levels [33]. Moreover, a cross-sectional study of patients with SCI showed that SCI patients with OSA present with lower CSF $A\beta_{42}$ levels compared to SCI patients without OSA [34]. Noteworthy, CSF $A\beta_{42}$ levels in the OSA group positively correlated with mean oxygen saturation [34], supporting the role of hypoxia on AD pathogenesis, as shown in animal studies. Consistent results come also by brain nuclear medicine imaging studies. In a cross-sectional study of community-dwelling cognitively normal older adults undergoing a florbetapir-PET scan, individuals diagnosed with OSA presented greater amyloid burden in the left precuneus, posterior cingulate, calcarine, and cuneus regions compared with participants without OSA [35]. Moreover, the authors showed that amyloid burden is significantly associated with severity of nocturnal hypoxia.

A recent meta-analysis summarized the evidence regarding the association between AD biomarkers and OSA, arising from 11 included studies, all evaluating OSA by nocturnal PSG recordings in patients with normal cognition, or MCI [36]. Results from the meta-analysis reinforce the hypothesis of neurodegeneration triggered or worsened by OSA. Indeed, it revealed that decreased CSF $A\beta_{42}$ levels, increased CSF t-tau levels, and an increased Aβ burden, as assessed by PET imaging, was associated with moderate/severe OSA assessed with PSG [36].

In recent times, dysfunction of the glymphatic system has been proposed as a possible pathogenetic mechanism connecting OSA to AD. The glymphatic system is supposed to remove brain extracellular waste products, including tau and β amyloid, through the perivascular and interstitial spaces [37, 38]. However, the anatomical substrates and the clearance mechanisms are still a matter of debate [39]. In particular, the glymphatic system is hypothesized to maximally function during Slow Wave Sleep (SWS), due to reduced noradrenergic projections that allow dilation of interstitial spaces [38]. Moreover, Slow Wave Activity (SWA), being expression of reduced neuronal activity, is associated with decreased production of amyloid-β, which release is in turn positively correlated to neuronal synaptic activity [40]. In this regard, recent studies in healthy volunteers have shown that one night of SWA disruption leads to increased CSF amyloid-β levels the following morning [41]. Therefore, the disruption of SWS operated by OSA [42] could lead to increased release of amyloid-β on the one hand, and to decreased clearance of amyloid-β and tau on the other hand, through impairment of the glymphatic system functionality. Besides having a negative impact on SWA expression, another hypothesized mechanism by which OSA impairs the glymphatic system is a mechanical one, namely the repetitive increases of intrathoracic and intracranial venous pressure, due to prolonged Valsalva maneuvers associated with obstructive events, may reduce the glymphatic flow and thus the clearance of CSF metabolic waste products [43]. However, the hypothesis of a hydrostatic, pressure-driven waste clearance by means of bulk flow is still a matter of controversy. Indeed, pre-clinical experimental studies simulating flow through the brain interstitial space have challenged the existence of convective transport of solutes, thus doubting the possibility of an active clearance of toxins operated by the glymphatic system [44–46]. Conversely, solute diffusion (without convection) in the extracellular space seems adequate to explain experimental transport observed in models of brain parenchyma [45]. Furthermore, the glymphatic theory has been additionally questioned by a recent study reporting the reduction of brain clearance during sleep and anesthesia [47], unlike previously described [38]. However, the results of this experiment, as stated by the Authors [47], are valid for a small dye that can freely move in the extracellular space of a mouse brain model, but how molecules of larger molecular weights behave in the human brain interstitial space is still uncertain.

Actually, several studies have tried to measure the glymphatic system activity 'in vivo' by means of neuroimaging and nuclear medicine imaging. A proposed method is an indirect evaluation by means of diffusion tensor imaging analysis along the perivascular space (DTI-ALPS), with lower diffusivity reflecting impairment of the glymphatic system[48]. Using this technique, an observational study reported decreased diffusivity values in patients with OSA compared to controls [49]. Moreover, several studies investigating glymphatic system activity by means of DTI-ALPS showed a significantly reduced diffusivity in patients with AD dementia compared to controls [50–53]. Also PET studies showed a reduction in CSF clearance of Aβ and tau tracers in patients with AD compared to healthy controls [54].

Finally, the effect of aging on the lymphatic vessels is itself a major risk factor for dysfunction of the glymphatic system [55]. Arterial stiffness due to accumulation of amyloid-β [56] may further worsen glymphatic function. Notably, aging is associated with reduced sleep quality, with lower expression of SWS and reduced total sleep time [57]. In this light, the combined effect of aging, and OSA on sleep quality, continuity, and SWS expression, may concur together to impairment of the glymphatic system, aggravating or exacerbating AD neuropathology (Fig. 1).

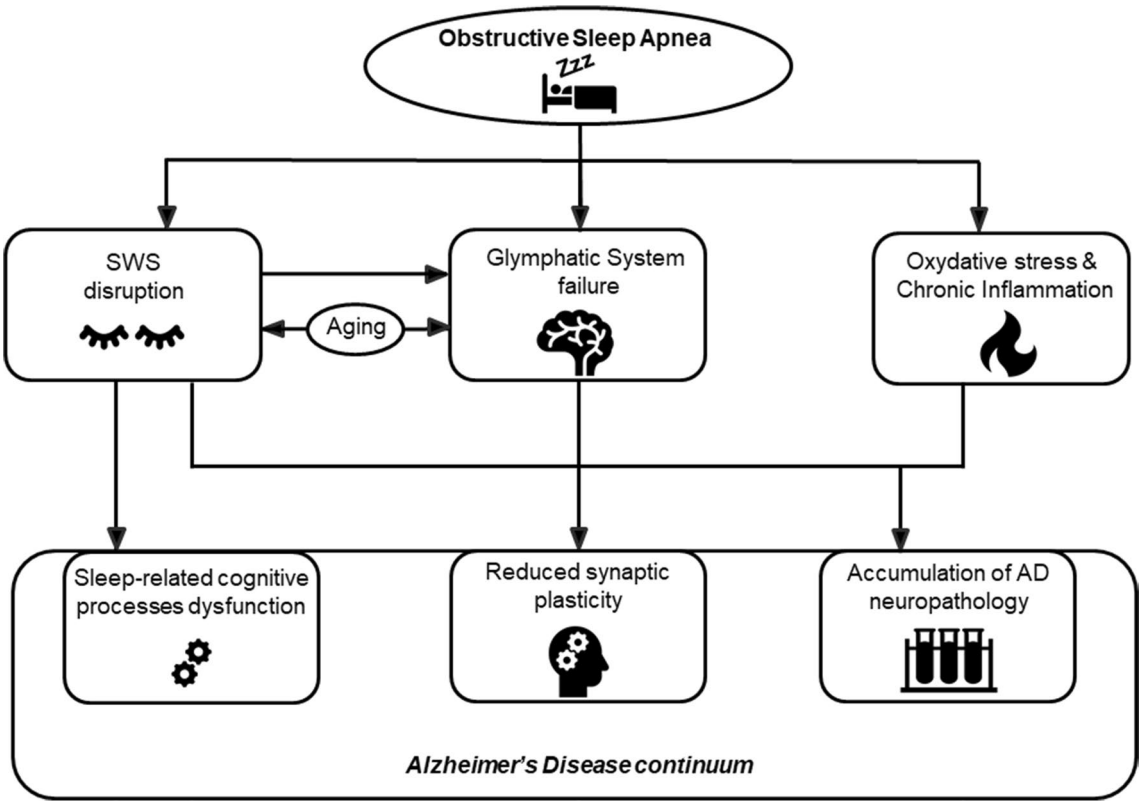

Fig. 1 Pathogenetic mechanisms connecting OSA to AD. AD = Alzheimer's Disease; SWS = Slow Wave Sleep

OSA Treatment in Patients with MCI and Dementia Due to AD: Rationale and Evidence from Studies

Continuous Positive Airway Pressure (CPAP) is the gold-standard treatment for moderate-severe OSAS. It provides constant airway pressure throughout the entire respiratory cycle, avoiding sleep-related upper airways collapse. OSA treatment with CPAP results in effective reduction of daytime sleepiness, and in mild improvement of executive functions [58] and attention [59]. This is particularly relevant, given that the cognitive domains affected the most by OSA are sustained attention, vigilance, executive functions, and perceptual-motor functions [60].

The evidence arising from a heavy volume of experimental and observational studies points towards a connection between OSA and accumulation of AD pathology, via the multiple mechanisms discussed above (Fig. 1). In the context of the intricated, multifactorial process of neurodegeneration in AD, OSA could act as a factor for disease progression, accelerating the cascade of amyloidogenesis and tau phosphorylation. Hence, treating this comorbid disorder may potentially slow AD disease progression. These effects could be manifested at multiple levels. First, CPAP is associated with effective blood pressure reduction in patients with hypertension, especially resistant hypertension [61, 62]. Thus, action on the vascular component of Alzheimer's pathophysiology is an important putative beneficial mechanism of CPAP. Midlife hypertension is a recognized modifiable risk factor for AD [63], and its effective treatment is regarded as a primary prevention measure for AD [64]. Moreover, optimal control of hypertension is recommended to slow progression of mixed AD and vascular dementia [65]. Another possible beneficial effect of CPAP is stimulating clearance of beta amyloid and tau. This hypothesized effect is mediated by the enhancement of the glymphatic system activity, possibly through the modification of intrathoracic and intracranial pressures, improvement of the fluid dynamics [66] and through increase in SWA [67].

Nonetheless, the few studies that investigated the effect of CPAP treatment on amyloid and tau biomarkers provided conflicting results. Liguori et al. evaluated CSF biomarkers in patients with SCI categorized into three subgroups: OSA treated with CPAP, untreated OSA patients and controls without OSA [34]. Untreated OSA patients

showed lower CSF $A\beta_{42}$ levels with respect to controls and OSA-CPAP patients [34]. On the other hand, a cross-sectional study of Vietnam Veterans found no difference in 18F-florbetaben PET scans between subjects with OSA treated with CPAP and CPAP non-users [68]. Another study found that OSA treatment was associated with SWA increase, and that after CPAP treatment there was a negative association between SWA and AD pathology [67]. Thus, the available evidence does not allow to draw firm conclusion on the possible reversible effect of CPAP on AD pathology accumulation in AD patients with comorbid OSA. However, data arising from longitudinal observations of patients with OSA suggest a potential modifiable mechanism operated by CPAP. Indeed, a retrospective study analyzing data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, in which patients had a follow-up ranging between two and three years, showed that use of CPAP is associated with a significant delay in MCI onset [22]. Another element of debate is whether CPAP may have an impact on cognition in patients already diagnosed with AD dementia. Few randomized controlled trials (RCT) have specifically investigated the effect of OSA treatment with CPAP in patients with AD dementia. The studies are summarized in Table 1. In a double-blind placebo controlled RCT, the primary outcome measure was improvement in cognitive functioning in patients with mild-moderate AD dementia and OSA. While comparison between treatment and sham group failed to demonstrate an improvement, in the paired analyses (i.e., three weeks of therapeutic CPAP in both the treatment and the sham group) there was a modest significant improvement in the mean composite neuropsychological score [69]. Even with the limitations of a small, underpowered study, these results imply that OSA may aggravate cognitive dysfunction in patients with AD dementia, and that patients may show some cognitive benefits from OSA treatment with CPAP, particularly in episodic memory and executive functions [69]. Polysomnographic evaluation of the same cohort revealed a significant improvement of sleep quality after one night of therapeutic CPAP, as reflected by an increase of SWS, and an improvement of several macrostructural sleep parameters after three weeks of treatment, including wake after sleep onset, arousals frequency, and increased time spent in SWS compared to pre-CPAP treatment [70]. In a pilot study, patients with mild-moderate AD dementia and OSA treated with CPAP for up to 13 months showed improvement in executive functions, and stabilization or improvement of sleep quality and mood, while patients who withdrew CPAP continued to deteriorate over time [71]. Moreover, also caregivers seemed to benefit from the patients' sustained treatment with CPAP, as expressed by improvement of their own mood [71]. Treatment with CPAP seems to have an impact also on cognitive trajectories of patients over time. In a proof-of-concept study, patients with mild to moderate AD dementia and OSA treated with CPAP showed a significantly slower cognitive decline, as expressed by MMSE annual scores change, at three years follow-up compared to patients who refused CPAP treatment [72]. In another pilot study, amnestic MCI patients with OSA, who were treatment-adherent to CPAP, showed improvement on psychomotor/cognitive processing speed and stability in global cognition at one year follow-up [73]. Conversely, patients who were not adherent to treatment experienced a significant decline in MMSE scores after one year [73]. A recent meta-analysis of studies investigating CPAP treatment in patients with MCI or AD dementia and OSA confirmed that cognitive functions, as expressed by MMSE, were mildly but significantly improved after CPAP use, particularly after long-term treatment [74]. Besides this, treatment with CPAP results in effective reduction of subjective daytime sleepiness in patients with AD dementia and OSA [75].

Overall, these findings suggest that CPAP in patients with MCI and dementia due to AD displays the same beneficial effects on sleep occurring in the general population. These benefits include: improvement of daytime vigilance, improving mood, and cognition, especially executive functions, and consolidating sleep. Moreover, even if supported by low-quality evidence, CPAP treatment seems to slow cognitive decline over time. In this light, treatment with CPAP may modify dementia risk intervening on sleep health promotion and interacting with the reduction of other acknowledged risk factors for dementia such as obesity, hypertension, and diabetes [63], which are important counterparts of the OSA-associated morbidity. Sleep health is indeed enlisted as one of brain health determinants by the World Health Organization (WHO), and acts synergically with other interlinked factors in dementia risk modification [76]. Henceforth, the fifth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia recommends treatment of sleep apnea with CPAP, to improve cognition and decrease the risk of dementia [77].

OSA Management in Patients with MCI and Dementia Due to AD

The proper management of patients with MCI and dementia due to AD should include the routine assessment for OSA symptoms. Simple questions to screen

Table 1 Studies of CPAP treatment in patients with AD dementia and MCI

Chong et al. (2006) [75]	double blind RCT	78.0 ± 7.04	mild-moderate AD dementia with OSA (AHI > 10)	t-CPAP (n = 19) for 6 weeks	s-CPAP (n = 20) for 3 weeks followed by t-CPAP for 3 weeks	ESS	t-CPAP: 3w ESS = -2.33 ($p < 0.05$); 6w ESS = -3.36 ($p < 0.01$) s-CPAP: 3w ESS = -0.7(n.s.); 6w ESS = -1.21 ($p < 0.05$)
Ancoli-Israel et al. (2008) [69]	double blind RCT	t-group: 78.6 ± 6.8 s-group: 77.7 ± 7.7	mild-moderate AD dementia with OSA (AHI > 10)	t-CPAP (n = 27) for 6 weeks	s-CPAP (n = 25) for 3 weeks followed by t-CPAP for 3 weeks	Composite Neuropsychological Score	3 w t-CPAP vs s-CPAP: no difference 3w t-CPAP (paired analysis): improvement ($p < 0.05$)
Cooke et al. (2009) [70]	double blind RCT	77.8 ± 7.3	mild-moderate AD dementia with OSA (AHI > 10)	t-CPAP (n = 27) for 6 weeks	s-CPAP (n = 25) for 3 weeks followed by t-CPAP for 3 weeks	PSG macrostructural parameters at 1st night and after 3 weeks	1st night: tCPAP ↓N1% ($p < 0.05$) and ↑ N2% ($p < 0.05$) compared to s-CPAP 3w (paired analysis): ↓in WASO ($p < 0.01$), TIB ($p < 0.01$), SP ($p < 0.001$), TST (n.s.), ArI ($p < 0.01$) and N1% ($p < 0.01$), and ↑N3%($p < 0.01$)
Cooke et al. (2009) [71]	pilot study	75.7 ± 5.9	mild-moderate AD dementia with OSA (AHI > 10)	CPAP sustained use (n = 5)	CPAP withdrawal (n = 5)	PSQI ESS FOSQ CSD caregivers NPI Neuropsychological battery test	CPAP + group showed less deterioration or improvement compared to CPAP-; caregivers of CPAP + reported patients' NPI stabilization, and improvement in their own mood
Troussiere et al. (2014) [72]	pilot study	n.a	mild-moderate AD dementia with severe OSA	CPAP group (n = 14)	non-CPAP group (n = 9)	median annual decline in MMSE score	CPAP group: − 0.7 points per year non-CPAP group: − 2.2 points per year ($p < 0.05$)

Table 1 (continued)

Chong et al. (2006) [75]	double blind RCT	78.0 ± 7.04	mild-moderate AD dementia with OSA (AHI > 10)	t-CPAP (n = 19) for 6 weeks	s-CPAP (n = 20) for 3 weeks followed by t-CPAP for 3 weeks	ESS	t-CPAP: 3w ESS = -2.33 ($p < 0.05$); 6w ESS = -3.36 ($p < 0.01$) s-CPAP: 3w ESS = -0.7(n.s.); 6w ESS = -1.21 ($p < 0.05$)
Richards et al. (2019) [73]	quasi-experimental pilot clinical trial	70.1 ± 8.3	amnestic MCI and OSA (AHI > 10)	CPAP adherent group (n = 29)	CPAP non-adherent group (n = 25)	HVLT-R DS subtest MMSE SCW PVT ESS	CPAP adherent: ↑in DS and ↓in ESS from baseline to 6 months and baseline to 1 year CPAP non adherent: significant↓in MMSE from baseline to 1-year
Skiba et al. (2020) [93]	retrospective study	70.4	MCI and OSA	CPAP adherent (n = 42)	CPAP non-users (n = 24) CPAP non-adherent (n = 30)	progression to dementia (mean time)	no difference
Liguori et al. (2021) [86]	multicentre retrospective study	74.8 ± 5.9	MCI due to AD or AD dementia and OSA	CPAP adherent group (n = 12)	CPAP non adherent group (n = 12)	MMSE CDR (change from baseline to follow-up)	No difference in MMSE change (n.s.) CPAP non-adherent higher mean CDR change ($p < 0.01$)
Hoyos et al. (2021) [94]	pilot randomized crossover trial	68.1 ± 7.6	MCI and moderate OSA (n = 40)	cross-over 12 week treatment period (CPAP vs no-treatment)	cross-over 12 week treatment period (CPAP vs no-treatment)	executive functioning, memory, subjective sleep, depressive symptoms	medium effect size improvements in verbal learning and memory retention compared with no treatment
Costa et al. (2023) [87]	retrospective study	69.8 ± 10.6	AD dementia, VD, MCI and moderate OSA	CPAP adherent (n = 61)	CPAP non-adherent/ non-users (n = 110)	Mean MoCA score change from baseline to follow-up (2–12 months)	MCI adherent vs MCI non adherent: + 2.7 (n.s.) AD adherent vs AD non adherent: -0.49 (n.s.)

AD = Alzheimer's Disease, *AHI* = Apnea Hypopnea Index, *ArI* = Arousal Index, *CDR* = Clinical Dementia Rating scale, *CPAP* = Continuous Positive Airway Pressure, *CSD* = Cornell Scale for Depression in Dementia, *DS* = Digit Symbol, *ESS* = Epworth Sleepiness Scale, *FOSQ* = Functional Outcome of Sleep Questionnaire, *HVLT* = Hopkins Verbal Learning Test, *MCI* = Mild Cognitive Impairment, *MMSE* = Mini Mental State Examination, *MoCA* = Montreal Cognitive Assessment, *N1%* = Percentage of time spent in NREM1 over total sleep time, *N2%* = Percentage of time spent in NREM2 over total sleep time, *N3%* = Percentage of time spent in NREM3 over total sleep time, *NPI* = Neuropsichiatric Inventory, *n.s.* = not significant, *OSA* = Obstructive Sleep Apnea, *PSG* = polysomnography, *PSQI* = Pittsburgh Sleep Quality Index, *PVT* = Psychomotor Vigilance Task, *sCPAP* = sham CPAP, *SCW* = Stroop Color Word test, *VD* = vascular dementia, *tCPAP* = treatment CPAP, *TIB* = Time in Bed, *WASO* = Wake After Sleep Onset

for the presence of OSA are assessing the presence of snoring, witnessed apneas, sense of choking or dyspnea during sleep, dry mouth, nocturia, and EDS. EDS can be measured by the Epworth Sleepiness Scale (ESS), which is the most widely used questionnaire to assess EDS [78]. Moreover, several questionnaires are available to screen for OSA risk, namely the Berlin Questionnaire (BQ) [79], the STOP-BANG questionnaire (SBG) [80], the NOSAS score [81]. Even if they are not recommended for OSA diagnosis, they can be helpful to screen for increased OSA risk in non-sleep clinic settings [82]. After a positive screening for OSA, the patient should be referred to a Sleep Medicine Center for proper diagnosis and management. The diagnosis is established on clinical examination and confirmed by objective testing, either with a home sleep apnea test or in-laboratory PSG [83] (Fig. 2).

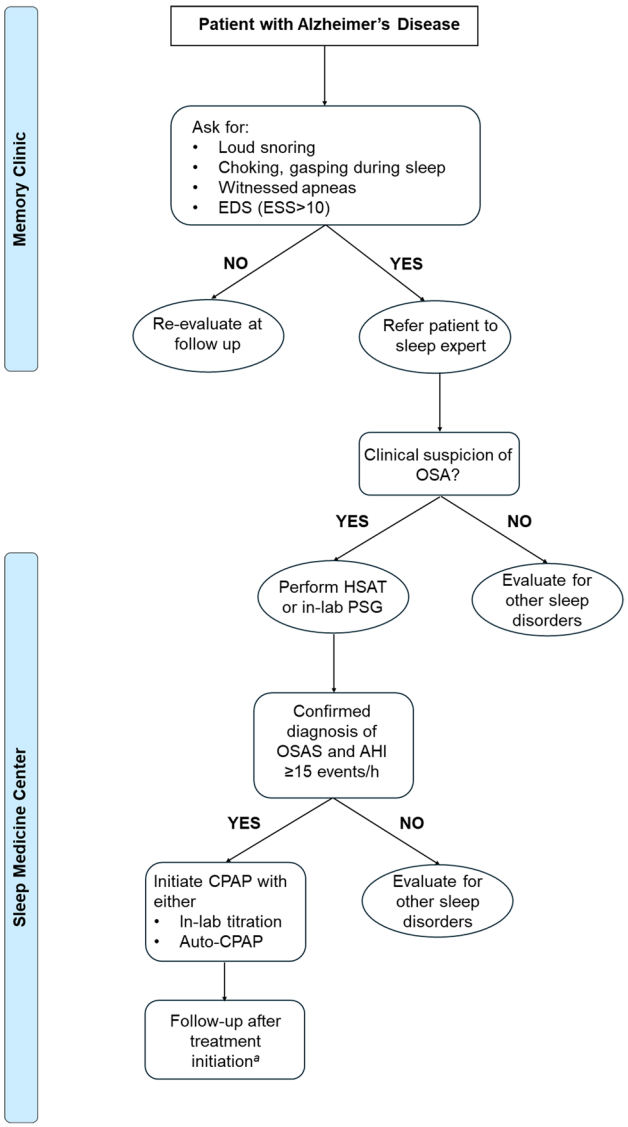

Fig. 2 Management of OSA in patients with MCI or dementia due to AD. [a] = follow-up evaluation should include adherence to treatment, residual AHI, residual EDS. Abbreviations: AHI = Apnea Hypopnea Index; CPAP = Continuous Positive Airway Pressure; EDS = Excessive Daytime Sleepiness; ESS = Epworth Sleepiness Scale; HSAT = Home Sleep Apnea Test; OSA = Obstructive Sleep Apnea; OSAS = Obstructive Sleep Apnea Syndrome; PSG = Polysomnography

Treatment with CPAP is recommended in adult patients with moderate-severe OSA associated with increased daytime sleepiness, reduced quality of life and hypertension [83]. Specific recommendations for patients with comorbid MCI or AD dementia are not available to date. However, given the multiple known beneficial effects of CPAP on cardiovascular health, the multiple possible mechanisms impacting AD progression, and the proven feasibility of the treatment in patients with MCI and AD dementia, there is no reason to prevent this population from accessing a recognized beneficial treatment. Moreover, treatment with CPAP could also help ameliorate neuropsychiatric symptoms of dementia, such as anxiety, apathy and depression, thanks to its benefits on mood disorders affecting patients with OSA [84], and as shown by experimental studies on AD patients [71].

Treatment with CPAP can be initiated either using auto-CPAP or in-laboratory titration. However, to ensure a proper implementation of PAP therapy in the specific population of AD patients, it is reasonable to prefer in-lab titration in order to ensure education of the patients and caregivers on its use, to address any technical issues and to avoid early discontinuation of treatment due to initiation failure. Important variables when setting the CPAP are the patient tolerance to pressure, which is generally comprised between 4 and 15 cmH_2O, a low residual (AHI < 10 events/hr), and acceptable leakage levels (< 24 L/min).

Further important recommendations pertain to lifestyle interventions: sleep hygiene, adequate physical exercise, Mediterranean diet, weight loss in the presence of obesity. These recommendations, that are generally provided to OSA patients, are valid for a comorbid OSA and MCI or dementia patient as well, since they address acknowledged modifiable risk factors for dementia [63].

Finally, it is key to recommend avoidance of hypnotics such as benzodiazepines, and opioids, the former known for their myorelaxant effect, the latter for their respiratory depressant effect, both having a detrimental effect on cognition.

Compliance to CPAP in AD Patients

An important aspect when issuing OSA treatment with CPAP is recommending adherence to treatment. Good compliance is generally defined as use of the CPAP device

for more than four hours per night and for more than five nights per week, on average. This is of paramount importance to ensure the therapeutic benefits from CPAP. Not surprisingly, early evidence arising from the experimental and observational studies supports the impact of good CPAP adherence in AD and MCI population as well. Indeed, successful CPAP adherence results in improvement in attention and processing speed, and is associated with a trend for delaying progression of cognitive decline in MCI patients [73, 85] and in patients with AD dementia [86]. In a recently published retrospective study, good CPAP adherence was even associated with improvement in MoCA scores in patients with MCI and OSA, relative to those who were not adherent or not users [87].

One of the pitfalls encountered in clinical practice is hesitance in prescribing CPAP in patients with cognitive impairment due to uncertainty in patients' compliance to treatment. However, experimental studies of CPAP in patients with AD dementia and MCI have shown an overall good adherence to treatment in this population. A recent meta-analysis of experimental and observational studies of CPAP in AD dementia/MCI reported adherence rates ranging from 35.6 to 73% [88]. Even with the limitations of a treatment period restricted to the duration of the clinical studies, such adherence rates are encouraging since they do not substantially differ from those reported in the general adult population (30–60%) [89]. As a matter of fact, a retrospective study of MCI patients reported a sustained long-term compliance to CPAP of 62% at 12 months [90]. Hence, compliance issues should not limit the correct prescription of CPAP in comorbid OSA and AD dementia or MCI, where indicated.

Clinicians' efforts should be oriented towards warranting correct treatment adherence by providing educational interventions to patients and caregivers. Indeed, participation to a tailored CPAP adherence intervention, delivered through telemedicine, was a significant predictor of good CPAP adherence at three months in a prospective study of amnestic MCI patients [91]. In this study, educational intervention consisted in weekly and then monthly scheduled support phone calls, during which patients and caregivers were assisted in CPAP use, and motivational enhancement was provided. A similar strategy was applied by Richards et al., including phone and face-to-face contacts to provide support for participants, discuss CPAP hygiene and share their experience [73].

Therefore, as recommended by the American Academy of Sleep Medicine, educational interventions should be given with initiation of CPAP therapy, including if possible behavioral and troubleshooting interventions [83]. Useful methods of improving compliance are telemonitoring-guided interventions during the initial phases of CPAP therapy, modified pressure profiles, humidification and appropriate mask selection [83].

Follow-up

Finally, it is important to establish a proper follow-up of patients, especially after initiation of therapy. It is recommended to re-evaluate patients few weeks after treatment start to assess any problematics with CPAP use, tolerability issues and to value therapeutic benefit. A cardiorespiratory polygraphy performed during CPAP nocturnal use is sufficient to measure residual AHI, and to eventually prompt adjustment of pressures. Alternatively, automatic event detection by CPAP device can be used to estimate residual AHI. The ESS is useful to investigate residual EDS. Presence of residual EDS warrants evaluation of possible treatable causes of EDS, such as inadequate CPAP use (insufficient usage, excessive mask leak, suboptimal pressure, treatment-emergent central sleep apnea), as well as insufficient sleep, and medications with somnogenic effects [92]. Where indicated, wake-promoting medications currently available for residual EDS are Solriamfetol (dual-acting dopamine and norepinephrine reuptake inhibitor) and, in European Union, Pitolisant (selective histamine H3 receptor antagonist). However, they have not been tested in patients with comorbid OSA and cognitive impairment due to AD, therefore their use in this population is off-label.

Conclusions and Future Directions

OSA is a frequent comorbidity in patients with MCI and AD dementia, and multiple mechanisms suggest their possible pathogenetic link. Screening of OSA symptoms in patients with cognitive impairment should be part of the standard clinical assessment in memory clinics, and a positive screening should prompt referral to sleep medicine experts for proper OSA diagnosis and management. OSA treatment with CPAP is feasible in patients with MCI or dementia due to AD, since evidence arising from the literature reports similar adherence rates as for the general adult population. Because of its known beneficial results on cardiovascular health, and its possible benefits on mood and cognitive functions, CPAP therapy should be prescribed in comorbid MCI and AD dementia patients with moderate-severe OSA showing increased daytime sleepiness, hypertension and impaired quality of life.

Future studies should focus on the specific characteristics of individuals who would benefit the most from CPAP treatment in the context of cognitive impairment to provide tailored recommendations in this population. Longitudinal studies are needed to clarify the temporal relationship between the two conditions and eventually prove causality, and to investigate the role of CPAP as a disease modifying therapeutic agent in the context of AD.

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Declarations

Competing Interests The authors declare no competing interests.

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