

Published: February 28, 2023

**Citation:** Seda G., Shrivastava S, 2023. Effects of Obstructive Sleep Apnea and Insomnia on Cognitive Function, Medical Research Archives, [online] 11(2).

<https://doi.org/10.18103/mra.v11i2.3578>

**Copyright:** © 2023 European Society of Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**DOI:**

<https://doi.org/10.18103/mra.v11i2.3578>

ISSN: 2375-1924

## REVIEW ARTICLE

# Effects of Obstructive Sleep Apnea and Insomnia on Cognitive Function

\*Gilbert Seda<sup>1</sup>, Sharonya Shrivastava<sup>2</sup>

<sup>1</sup>Division of Pulmonary and Critical Care Medicine, Scripps Mercy Chula Vista, 435 H. Street, CV 31, Chula Vista, CA 91910, United States

<sup>2</sup>Internal Medicine Program, 1601 Precision Park Ln, San Diego, CA 92173-1345, United States

\*[gilbert.seda@gmail.com](mailto:gilbert.seda@gmail.com)

### Abstract

*Purpose of Review.* Obstructive sleep apnea and chronic insomnia are the most common sleep disorders in adults. Both sleep disorders can adversely affect physical and mental well-being. Cognitive function has been extensively studied in relation to chronic insomnia and obstructive sleep apnea. This paper reviews the recent studies investigating the cognitive effects of insomnia and obstructive sleep apnea as well as the potential benefits of treatment.

*Recent Findings.* Recent studies indicate that insomnia is associated with impairments in attention, memory, and executive function. Chronic insomnia may have a moderating role in mild cognitive impairment and Alzheimer's dementia. Mood and anxiety disorders may moderate the effects of insomnia on cognitive function. Hyperarousal and short sleep time associated with insomnia are risk factors for cognitive impairment. Cognitive behavior therapy for insomnia may improve cognitive function but more studies are needed. Nonbenzodiazepine receptor agonists improve insomnia without causing cognitive impairment. Benzodiazepine use is associated with cognitive impairment.

Obstructive sleep apnea is associated with impairments in attention, concentration, memory, and executive function with apnea severity as measured by the apnea hypopnea index and severity of nocturnal hypoxemia being the largest risk factors. Untreated obstructive sleep apnea may have a significant impact on the progression of mild cognitive impairment and Alzheimer's dementia. The impact of obstructive sleep apnea treatment, particularly with continuous positive airway pressure, appears to mitigate and slow the rate of cognitive decline but more randomized controlled studies are needed.

*Summary.* Standardized cognitive assessments and larger, long-term controlled prospective studies with diverse populations are needed to further elucidate the cognitive impairments associated with chronic insomnia and obstructive sleep apnea. More studies are needed on the benefits of various treatments for obstructive sleep apnea and insomnia.

**Keywords:** Obstructive sleep apnea, insomnia, cognition, attention, concentration, executive function, memory, continuous positive airway pressure (CPAP), and cognitive behavior therapy-insomnia, mild cognitive impairment, Alzheimer's dementia.

## Introduction

Obstructive sleep apnea (OSA) is the most prevalent sleep-related breathing disorder. It is characterized by repetitive episodes of upper airway obstruction during sleep resulting in intermittent nocturnal hypoxemia, transient sympathetic surges, and fragmented sleep due to repetitive respiratory related arousals. The upper airway obstructions are either complete (apnea) or partial (hypopnea) and last a minimum of 10 seconds. Risk factors for OSA include obesity (BMI > 35 kg per m<sup>2</sup>), male sex, age 40-70 years, postmenopausal women not on hormonal replacement therapy, family history of OSA, craniofacial abnormalities, and tobacco use. Clinically, patients present with one or more of the following symptoms: excessive daytime sleepiness, episodes of choking or gasping when sleeping, loud snoring, sleep maintenance insomnia, nocturia, nonrestorative sleep, morning headache and/or fatigue. Common physical exam findings are elevated body mass index (BMI), neck circumference greater than 17 inches in men and 16 inches in women, large waist circumference, and a crowded oropharyngeal airway (e.g., elongated uvula, macroglossia, tonsillar hypertrophy, high arched or narrow palate, retrognathia, deviated nasal septum or nasal polyps). There is substantial epidemiologic and clinical evidence associating systemic hypertension as the most common medical consequence of OSA. Furthermore, OSA is also an independent risk factor for stroke, coronary artery disease, type 2 diabetes, and atrial fibrillation. Treatments for OSA include weight loss, positional

therapy, oral appliances, positive upper airway pressure, oro-maxillo-facial surgery, hypoglossal nerve stimulation, and bariatric surgery. Of these, continuous positive airway pressure (CPAP) is the most prescribed treatment.<sup>1</sup>

Chronic insomnia disorder is defined as a frequent or persistent difficulty initiating or maintaining sleep that results in general sleep dissatisfaction.<sup>2</sup> It occurs in 10% of the population in contrast to transient insomnia which has a prevalence of 30-35%. Symptoms include difficulty falling asleep and/or staying asleep. Individuals complain of nonrestorative sleep, poor sleep quality, waking up from sleep earlier than anticipated, and/or trouble maintaining or initiating sleep. The distress associated with poor sleep quality results in impairment of social, vocational, or academic functioning. Daytime impairment related to the sleep disturbance include one or more of the following: fatigue, cognitive impairment, daytime sleepiness, behavioral problems, reduced motivation, proneness to errors/accidents, and distress related to poor sleep. For chronic insomnia, the sleep disturbance and daytime impairment occur at least three times a week and must be present for at least 3 months. The primary treatment for chronic insomnia is cognitive behavior therapy for insomnia (CBT-I). CBT-I is a multimodal treatment that helps change the maladaptive behaviors and thought processes that promote insomnia and learn healthy strategies to improve sleep.<sup>3</sup> Despite the efficacy of CBT-I, many patients with insomnia use medications for improving sleep.

Multiple studies have investigated the association of insomnia and OSA in cognitive impairment. The purpose of this paper is to review the recent studies over the past 5 years investigating the relationship between insomnia or obstructive sleep apnea, and cognitive impairment and whether treatments for these sleep disorders improve cognitive function. Studies have also investigated the role of insomnia and OSA in moderating the risk factors for mild cognitive impairment (MCI) and Alzheimer's dementia (AD).

### **Insomnia and Cognitive Impairment**

Recent studies investigating the effects of insomnia on cognitive impairment indicate that insomnia can impair attention, memory, and/or executive function and may even moderate the effects of MCI and AD. Studies vary on the instruments used to assess cognitive function, study design, and participant characteristics. Furthermore, advancing age, medical comorbidities, and psychiatric disorders may moderate the effects of insomnia on cognition.

One of the challenges evaluating the relationship between chronic insomnia and cognitive function is the role of mediating factors such as gender, depression, or age-related vascular disease. In a longitudinal study, Zaheed and colleagues investigated the role of insomnia on cognitive functions and the moderating effects of gender, and mental or physical health over a period of 14 years.<sup>4</sup> They found that difficulty initiating sleep was associated with poorer episodic memory, executive function, language, visuoconstruction, and processing speed.

Furthermore, the presence of depressive symptoms accounted for 12.3%-19.5% of these associations and vascular disease accounted for 6.3%-14.6% of non-memory associations. Their study found no other insomnia symptoms that were associated with cognition, and there were no associations modified by gender.

Several studies evaluated the relationship between insomnia and MCI and AD. Using data from the Health and Retirement Study (HRS), Resciniti and colleagues evaluated the relationship between insomnia and the subsequent development of MCI and AD.<sup>5</sup> Insomnia symptoms were identified by the Brief Insomnia Questionnaire which was compiled into an insomnia severity index. Dementia was assessed using the HRS global cognitive assessment tool and participants were classified as having either dementia, mild cognitive impairment, or cognitively healthy. Using a nationally representative sample of adults ages 51 and older, this study found that time-varying insomnia symptoms were associated with an increased risk of MCI and AD. In another study using the 9,518 elderly participants from the HRS, Beydoun and colleagues conducted a longitudinal study investigating the relationship between physician-diagnosed memory problems and insomnia.<sup>6</sup> Their findings indicated that elderly participants who experienced an increase in the severity of insomnia symptoms over an 8-year period exhibited a 41-72% increased risk of physician-diagnosed memory problems and a 45-58% increased risk of dementia diagnosis based on HRS criteria.

Two additional studies investigated the moderating effects of insomnia on AD progression. In a study using the Alzheimer's Disease Neuroimaging Initiative, Xu and colleagues studied whether insomnia moderated amyloid-beta and longitudinal cognitive performance in non-demented elders (N = 385).<sup>7</sup> They found that although amyloid-beta-positive status independently predicted faster cognitive decline over an 8-year period, those individuals who had insomnia and were amyloid-beta-positive experienced faster cognitive decline. In another study, Baril and colleagues investigated whether insomnia had an effect on cognitive function and APOE E4 allele carriers.<sup>8</sup> Using 511 dementia-free Framingham Heart Study participants (N = 511) over 3.4 years, they found that severe insomnia symptoms combined with short sleep duration was associated with lower performance on global cognition, and immediate and delayed logical memory recall especially in participants with APOE E4 allele carriers. Their findings suggest that chronic insomnia may have a moderating role in AD.

Recognizing that patients with insomnia are heterogeneous, Olaithe and colleagues studied the effects of two insomnia phenotypes on cognitive performance.<sup>9</sup> They compared 124 adults with insomnia to 124 healthy sleepers. In addition, the insomnia group was subdivided into normal sleep duration with insomnia and short sleep duration with insomnia. The insomnia group with normal sleep duration had more inconsistency with normal working memory while the group with short sleep duration

insomnia had more inconsistency with attention and executive functioning compared to healthy sleepers and those with normal sleep duration insomnia. The hyperarousal associated with insomnia may also have a role in cognitive impairment. Khassawneh and colleagues examined the association between hyperarousal and short sleep duration in patients with insomnia.<sup>10</sup> Subjects with insomnia who scored high on a Hyperarousal Scale were compared to controls with no sleep disorders and scored low on the Hyperarousal Scale. Both groups completed home polysomnograms and four daytime trials of neurocognitive tests: simple reaction time, choice reaction time, big circle-little circle, rapid visual information processing, attention switching task, and spatial working memory tests. Subjects with insomnia disorder with hyperarousal and short sleep duration were associated with daytime cognitive deficits in complex attentional and spatial working memory tasks.

Insomnia symptoms in middle-age can later increase the risk for cognitive impairment. In a prospective study using survey data from the Helsinki Health Study, Etholén and colleagues investigated the relationship between insomnia and self-reported cognitive function (i.e., memory, learning, and concentration).<sup>11</sup> Their study showed that insomnia symptoms already in working age adults can increase the risk of cognitive decline in retirement age. Furthermore, adults with increased insomnia complaints were related to more severe problems in subjective cognitive function compared to adults with minimal insomnia symptoms.

The emotional significance of the cognitive learning may also be a contributory factor. In an observational study, Chunhua and colleagues investigated emotional memory and decision making in adults with primary insomnia.<sup>12</sup> Twenty-five adults with primary insomnia and 20 healthy controls completed an emotional picture memory task and the Iowa Gambling Task. Primary insomnia had different effects on memory, depending on the emotional significance of the memory. Specifically, memory performance was impaired for positive and neutral items, but the recognition of negative stimuli seemed to be more resistant to the detrimental effects of insomnia.

The moderator effects of psychiatric disorders can also influence the effect of insomnia on cognitive impairment. In the Army Study to Assess Risk and Resilience in Service Members, Brownlow and colleagues examined the moderator effects of psychiatric disorders on insomnia and cognitive impairment.<sup>13</sup> Military soldiers completed a Brief Insomnia Questionnaire and the Composite International Diagnostic Interview Screening Scales to assess for psychiatric disorders and cognitive impairment. Insomnia had an adverse effect on memory and concentration problems which was moderated by psychiatric disorders such as major depression, posttraumatic stress disorder, or generalized anxiety disorder. In another study, Dagher and colleagues conducted a cross-sectional study to evaluate the mediating effects of anxiety, depression, stress and insomnia on social media use and memory performance.<sup>14</sup> Memory was

assessed in 466 Lebanese participants using the Memory Awareness Rating Scale (MARS). Although they found a correlation between social media use and lower memory performance, the multivariable analysis found no independent association with depression, stress and insomnia to lower memory performance. Finally, Asavik and colleagues conducted a cross-sectional study of 76 subjects to examine the effect of insomnia on cognitive functioning, spatial and verbal working memory, and inhibitory control. Participants had concurrent symptoms of pain, fatigue, and mood disorders.<sup>15</sup> They found that insomnia severity correlated with deficiencies in spatial and verbal-numeric working memory.

There were two studies which used a large dataset from the Canadian Longitudinal Study on Aging. Cross and colleagues examined the cognitive differences in middle-age and older adults with probable insomnia disorder, insomnia symptoms, or no insomnia symptoms.<sup>16</sup> Neuropsychological testing assessed processing speed, memory, and executive functions. The study identified 1,068 participants with probable insomnia disorder and 7,813 with insomnia symptoms. Using linear regression and adjusting for confounding variables such as anxiety, depression, diabetes, smoking, daytime sleepiness, and obstructive sleep apnea, and BMI, only performance on a test of declarative memory was worse in participants with probable insomnia disorder. Zhao and colleagues conducted a similar study examining the longitudinal association between probable insomnia and subjective

---

and objective memory decline in middle-aged and older adults.<sup>17</sup> Participants were greater than 45 years old (N = 26,363) and completed baseline and 3-year follow-up testing on memory, executive functions, and psychomotor speed. Participants who initially had no insomnia symptoms at baseline and developed probable insomnia disorder at a 3-year follow-up had worsening subjective memory decline compared to participants who remained insomnia-free or improved their sleep. However, there were no significant differences on performance of neuropsychological tests.

Impairments in executive function have been associated with insomnia. Unsal and colleagues conducted a study on the relationship between insomnia and falls in the elderly.<sup>18</sup> They postulated that falls were associated with impaired executive function. Study participants were 122 adults (i.e., 47 with insomnia and 75 controls). Executive function was evaluated using the Mini-Mental State Examination (MMSE), Quick Mild Cognitive Impairment Screen, Trail Making Test A, clock-drawing test, and digit span test. Falls were assessed using fall history and the Falls Efficacy Scale. Fall history and fear of falling were more frequent in the insomnia group. Their study showed that dual tasking and executive function were associated with falls in patients with insomnia and suggested that treating insomnia may reduce the risk of falls. Using actigraphy to assess insomnia, A Finnish retirement and aging study of 289 healthy participants in their 60's using a wrist worn accelerometer found that early morning awakening was associated with poorer

executive functioning and nonrestorative sleep was associated with lower spatial working memory and poorer executive functioning.<sup>19</sup>

There is mounting evidence that chronic insomnia may be a risk factor late-life dementia. A cross-sectional study of 1683 adults middle to late middle-aged adults without cognitive impairment from the ALFA (ALzheimer and FAMILies) study underwent neuropsychological assessment, T1-weighted structural imaging (n = 366), and diffusion-weighted imaging (n = 334).<sup>20</sup> The study aimed to characterize the cognitive performance and brain structural pattern of cognitively unimpaired adults at increased risk for AD with insomnia. Individuals with insomnia (n = 615) performed worse in executive function tests than non-insomniacs and displayed lower gray matter volume in left orbitofrontal and right middle temporal cortex, bilateral precuneus, posterior cingulate cortex and thalamus, higher gray matter volume in the left caudate nucleus, and widespread reduction of mean and axial diffusivity in right hemisphere white matter tracts. Insomnia interacted with the APOE genotype, with APOE E4 carriers displaying lower gray matter volumes when insomnia was present, but higher volumes when insomnia was not present, in several gray matter regions, including the left angular gyrus, the bilateral superior frontal gyri, the thalami, and the right hippocampus.

### Obstructive Sleep Apnea and Cognitive Impairment

A number of studies have evaluated the neurocognitive consequences of OSA. Gosselin and colleagues conducted a review on the recent findings related to the neurocognitive effects of OSA.<sup>21</sup> In terms of the mechanisms underlying cognitive impairment, OSA is associated with intermittent hypoxemia and altered sleep macro- and micro-architecture (slow wave sleep, spindles, sleep fragmentation, REM sleep) resulting in systemic and brain responses to hypoxemia such as metabolic disturbances, diabetes, oxidative stress, inflammation, hypertension, blood-brain barrier dysfunction, and brain edema. The physiologic detrimental effects on the central nervous system are reduced neurogenesis, synaptic plasticity, small vessel disease and microinfarcts, changes in grey and white matter and cerebral networks, and accumulation of amyloid plaques and hyperphosphorylated tau proteins. Clinically, these changes result in cognitive decline and dementia.

Impaired attention and memory have been associated with OSA. Angelelli and colleagues studied patients with OSA for attentional impairment.<sup>22</sup> They investigated 32 untreated patients with OSA and 34 matched controlled volunteers. OSA was confirmed with polysomnogram, and attention was assessed using 4 subtests from the Test of Attentional Performance (i.e., alertness, vigilance, Go/No Go, and divided attention). Patients with severe OSA and severe hypoxemia underperformed on

alertness and vigilance attention subtests. Using non-demented elderly patients, Pan and colleagues studied the association of OSA and age on cognitive decline.<sup>23</sup> Using 1422 participants from the Alzheimer's Disease Neuroimaging Initiative cohort (493 normal cognition and 929 amnesic mild cognitive impairment), they assessed the effects of self-reported OSA, age, APOE E4 carriers/noncarriers and cognitive function using the MMSE, Alzheimer's Disease Assessment Scale (ADAS) and the Rey Auditory Verbal Learning Test (RAVLT). The OSA group demonstrated significant cognitive decline versus the non-OSA group. In addition, in APOE E4 negative group, there was a significant OSA and age interaction for ADAS-cog11 and RAVLT immediate recall, but not on the MMSE.

Severity of nocturnal hypoxemia may be one of the main mechanisms for cognitive impairment associated with OSA. Khu and colleagues studied the role of OSA in cognitive impairment in patients with minor ischemic stroke.<sup>24</sup> Using a sample size of 94 patients with no OSA, mild OSA, and moderate-to-severe OSA based on the apnea hypopnea index (AHI) from polysomnogram, cognitive assessment was performed with the Auditory Verbal Learning Test, Digital Span Test (DST)-Backward, MoCA, and Stroop Color and Word Test (SCWT)-Interference. Participants with moderate-to-severe OSA performed worse on all the cognitive measures. Furthermore, the severity of the cognitive impairment on the MoCA was negatively related to AHI and lowest SpO<sub>2</sub>. Their findings suggest that hypoxemia is a

---

significant contributor to OSA-induced cognitive impairment. McCloy and colleagues investigated polysomnographic risk factors for cognitive decline in patients with OSA.<sup>25</sup> Cognitive function was assessed using the psychomotor vigilance task (PVT). Polysomnographic measures included excessive daytime sleepiness using the Epworth Sleepiness Score, overnight change of systolic blood pressure, change of oxygen desaturation, and sleep arousals. OSA severity, change in oxygen saturation, and change in oxygen desaturation with sleep arousals were associated with cognitive decline as measured by the PVT. Ji and colleagues conducted a retrospective analysis of adults 18-70 years old investigating OSA and cognitive impairment.<sup>26</sup> All participants underwent a polysomnogram and MoCA questionnaire. They found that 68% of OSA patients showed cognitive impairment, and patients with moderate to severe OSA were more likely to develop cognitive impairment than those with mild OSA. Cognitive dysfunction in OSA patients was associated with age, obesity, education, and intermittent nocturnal hypoxia or hypoventilation.

Studies have shown impairments in memory and executive functioning. Qui and colleagues investigated the gender specific association between OSA and cognitive impairment.<sup>27</sup> In a large population based cross-sectional study, they compared three groups: OSA, self-reported snoring without OSA, and healthy controls. Cognitive function was assessed by a brief computerized task with five cognitive domains: visual-spatial memory, prospective memory, fluid

intelligence, short numeric memory, and reaction time. The study included 267,889 participants and demonstrated that the snoring without OSA and OSA groups shows significant cognitive impairment in prospective memory fluid intelligence and short numeric memory in female participants. In regards to executive functioning, Macchitella and colleagues investigated the cognitive and socio-cognitive profiles of patients with severe obstructive sleep apnea.<sup>28</sup> They assessed 29 previously untreated severe OSA patient's and compared them to a control group of 34 healthy participants. Study participants completed an extensive neuropsychological battery that included social cognition. In OSA patient's, nonverbal reasoning, the theory of mind skills, and mental shifting ability were impaired. Furthermore, patients with severe nocturnal hypoxemia performed worse compared to patients with OSA without significant nocturnal hypoxemia. Their study suggests a key role of hypoxemia in cognitive impairment with executive functioning and social cognition particularly affected.

One study investigated the dual effects of COPD and obstructive sleep apnea on cognitive function. Zhang and colleagues investigated the combined effects of OSA and COPD on cognitive function.<sup>29</sup> They performed polysomnograms on 65 stable patients with COPD and gave them the MMSE. Compared to patients with COPD alone, patients with both COPD and OSA performed worse on the MMSE and were more likely to be at risk for developing dementia based on the MMSE score. The



severity of the OSA is a critical factor as COPD patients with an apnea hypopnea index (AHI) of  $\geq 30$  events/h had lower MMSE scores than those with an AHI of  $< 15$  events/h. In addition to age and education level, they also found that the severity of nocturnal intermittent hypoxia was an independent predictor of the risk of dementia in patients with COPD. Thus, patients with COPD with comorbid OSA may be at greater risk for global cognitive impairment relative to patients with COPD alone. The mechanisms underlying the exaggerated cognitive dysfunction seem to be related to intermittent hypoxia.

Bilukov and colleagues investigated the cognitive functioning and affective disorders among patients with obstructive sleep apnea syndrome to examine their frequency and severity in comparison with the scores of healthy volunteer controls.<sup>30</sup> Cognitive function was assessed with the word memory test, MMSE, and trail making test. The OSA group demonstrated deficiencies in domains of attention, memory, and executive function in comparison to the control group. The MMSE did not demonstrate a statistically significant relation between OSA and cognitive impairment. On the Trail Making Test Part B severity of OSA did correlate with impairment in attention, psychomotor speed, executive functions and general cognitive functioning increases as well.

Patients with OSA and mild cognitive impairment may not be aware of their cognitive deficits. Gagnon and colleagues conducted a study to determine whether self-reported cognitive complaints predict

objective cognitive deficits in late middle-age and older adults with OSA.<sup>31</sup> They compared 58 patients with moderate to severe OSA (AHI  $\geq 15$  events/h) to 54 patients with mild/non-OSA on their ability to evaluate their objective cognitive function. They then recruited a similar proportion of participants with OSA and non-OSA with MCI. All participants completed polysomnography and a comprehensive neuropsychological assessment. Participants with OSA and MCI were less aware of their cognitive deficits compared to those in the mild/non-OSA group. Participants without MCI in the moderate to severe OSA group reported more subjective cognitive complaints than the mild/non-OSA group. They found the reverse association among participants with MCI. The OSA group had less subjective cognitive complaints than the mild/non-OSA group.

Olaithe and colleagues studied the relationship of cognitive profiles in sleep clinic and community samples in patients with moderate-to-severe OSA.<sup>32</sup> The Cognitive Drug Research System, a computerized battery of cognitive assessments measured attention, short-term memory, and episodic long-term memory. Sleep was assessed using polysomnography in the clinic sample and dual channel (flow, oximetry) portable monitoring in the community sample. Their study identified three cognitive profiles: (1) strong thinkers (performed well across most domains and showed greater cognitive reserve); (2) inattentive fast thinkers (strong processing speed but poor ability to maintain attention); and (3) accurate slow thinkers (strengths in maintaining attention but poor

processing speed). Their study supports the notion that resilience factors (e.g., cognitive reserve), risk factors (e.g., number of comorbidities and age), and nocturnal features (e.g., nocturnal SaO<sub>2</sub>) contribute to the cognitive dysfunction seen in OSA.

One of the challenging issues with studying cognitive impairment and obstructive sleep apnea is identifying which cognitive tests are optimal to identify cognitive impairments. Gagnon and colleagues studied the association between OSA and the risk of mild cognitive impairment and dementia.<sup>33</sup> Their study focused on using two cognitive screening tests to determine their ability to screen for mild cognitive impairment: the MMSE and the MoCA. Using 42 adults with mild OSA, 67 adults with moderate-to-severe OSA, and 22 controls to detect mild cognitive impairment in adults aged 55-85 years with and without OSA, their findings showed that the MoCA was able to correctly identify 81% of participants with mild OSA and 72% of participants with moderate-to-severe OSA who had mild cognitive impairment, whereas 86% of control subjects were correctly identified as having MCI. They concluded that the MMSE should not be used to screen for cognitive impairment in patients with OSA. The MoCA could be used in clinical settings. However, they recommended clinicians should refer patients for neuropsychological assessment when neurodegenerative processes are suspected.

The American Thoracic Society (ATS) conducted a workshop summarizing the state of knowledge in the field, identifying

important research gaps, and identifying potential directions for future research on OSA, cognition, and dementia.<sup>34</sup> They concluded that studies investigating cognitive impairment and obstructive sleep apnea demonstrated considerable heterogeneity across studies. OSA negatively increases risk and may possibly lead to progression of MCI and AD as well as other forms of dementia. Cognitive testing with emphasis on memory needs to be incorporated into OSA evaluations. Furthermore, more studies are needed to delineate the role of sleep fragmentation versus intermittent hypoxemia. Engaging, recruiting, and retaining diverse populations in health care and research may help to reduce the racial and ethnic disparities in OSA and AD. Key recommendations from the ATS workshop include research aimed at underlying mechanisms; longer-term longitudinal studies with objective assessment of OSA, sensitive cognitive markers, and sleep-dependent cognitive tasks. They also recommended pragmatic study designs for interventional studies that control for other factors that may impact cognitive outcomes and use novel biomarkers.

### **Effect of Insomnia Treatment on Cognitive Impairment**

With respect to treatment of cognitive impairment in patients with insomnia, studies have investigated pharmacologic and nonpharmacologic treatments. Blackman and colleagues conducted a systemic review of pharmacologic and nonpharmacologic treatments to enhance sleep in mild cognitive

impairment and Alzheimer's disease.<sup>35</sup> They reviewed a total of 18 articles from 1998 to 2020. Interventions reviewed included Cognitive Behavior Therapy - Insomnia (CBT-I), a Multi-Component Group Based Therapy, a Structured Limbs Exercise Program, Aromatherapy, Phase Locked Loop Acoustic Stimulation, Transcranial Stimulation, Suvorexant, Melatonin, Donepezil, Galantamine, Rivastigmine, Tetrahydroaminoacridine and CPAP. Both pharmacologic and nonpharmacologic treatments demonstrated improvement in sleep quality. There was a paucity of data on sleep interventions for patients with MCI and mild AD. Their review identified a significant need to investigate multiple, alternative sleep interventions through high quality, comparison experimental studies utilizing validated sleep outcome measures.

The recommended treatment for chronic insomnia is CBT-I. Several studies have investigated the cognitive benefit of CBT-I. The findings were mixed with some studies showing benefit while other studies showing no significant benefit in cognitive function. In a small study, Roninger and colleagues analyzed the effect of a CBT-I on 10 adults with chronic insomnia using a battery of pre and post neuropsychological tests.<sup>36</sup> They found that CBT-I was associated with significant improvements in scores of attention, executive function, and memory. Cassidy-Eagle and colleagues evaluated a six-session cognitive behavioral therapy for insomnia (CBT-I) in 28 adults with mild cognitive impairment.<sup>37</sup> The CBT-I group had improvements in a measure of executive

functioning but no change in a measure of verbal memory. McCrae and colleagues studied the efficacy of a brief behavioral treatment for insomnia on cognitive outcomes in 62 adults with chronic insomnia.<sup>38</sup> Although the behavioral treatment improved sleep onset latency, wake after sleep onset, sleep efficiency, and sleep quality, there were no significant changes in cognitive outcomes. Perrault and colleagues conducted a randomized control trial of CBT-I vs. a wait-list control on subjective and objective measures of sleep, sleep-state misperception, and cognitive performance.<sup>39</sup> Although insomnia severity decreased and self-reported sleep satisfaction improved with CBT-I, there was no effect on cognitive performance. Finally, a small internet-based CBT-I program using 12 participants demonstrated improvement in insomnia such as insomnia severity as measured by the Insomnia Severity Index, sleep efficiency, sleep onset latency and wake after sleep onset but there were no improvements in any cognitive measures.<sup>40</sup>

Although CBT-I is the primary treatment recommended for chronic insomnia by the American Academy of Sleep Medicine<sup>41</sup> and the American College of Physicians<sup>42</sup>, many patients receive pharmacologic treatments for insomnia. Medications to enhance sleep include benzodiazepines (BZDs), the non-BZD hypnotic Z-drugs (i.e., zolpidem, zopiclone and zaleplon), melatonin receptor agonists, selective histamine H1 antagonists, orexin antagonists, antidepressants, antipsychotics, anticonvulsants and non-selective antihistamines.<sup>43</sup> Opioids, herbal preparations, barbiturates, alcohol and pain

medications have been used historically in treatment of insomnia or sleep disturbance management.<sup>44</sup> Pharmacologic agents approved by the US Food and Drug Administration (FDA) for insomnia treatment include BZDs, the Z-drugs, the dual orexin receptor antagonist (DORA) suvorexant, the melatonin receptor agonist ramelteon, the first-generation histamine antagonist doxepin and off-label use of alternate agents.

Benzodiazepines and nonbenzodiazepines have been used for chronic insomnia. Non-benzodiazepines which act at the GABA-A receptor complex include eszopiclone, zopiclone, zolpidem, and zaleplon. Studies have shown that benzodiazepines have greater risk of cognitive impairment. In a review of benzodiazepine use, Picton and colleagues found that a greater association of cognitive decline in geriatric participants with long acting benzodiazepines, earlier rather than later exposure, and longer rather than shorter duration of use.<sup>45</sup> An outpatient neurology clinic in a Beijing hospital compared patients with chronic insomnia taking benzodiazepines to patients taking nonbenzodiazepines (i.e., the Z-drugs) on cognitive performance.<sup>46</sup> Benzodiazepine exposure was an independent risk factor for cognitive impairment in middle age and older adults with chronic insomnia, but no correlation was found with nonbenzodiazepines indicating these medications may have a lower risk of cognitive impairment.

In a systemic review, Sumsuzzman and colleagues examined cognitive outcomes

from randomized controlled trials of melatonin for AD, insomnia, and healthy subjects.<sup>47</sup> They found one study that reported that chronic melatonin use improved memory in patients with insomnia.<sup>48</sup> A second study showed that daytime cognitive performance was not impaired by melatonin.<sup>49</sup> Karsten and colleagues conducted a randomized double-blind crossover placebo controlled trial investigating mirtazapine or quetiapine for transient insomnia. Cognitive functioning was assessed using the Leeds Sleep Evaluation Questionnaire, Karolinska Sleepiness Scale, Digit Symbol Substitution Task, Psychomotor Vigilance Task, and an addition task. Both mirtazapine and quetiapine improved total sleep time and reduced awakenings. In terms of cognitive function, both mirtazapine and quetiapine caused daytime sleepiness and lessened sustain attention.

#### **Effect of Continuous Positive Airway Pressure on Cognitive Impairment**

The predominant treatment for obstructive sleep apnea is CPAP. CPAP treatment is effective for reducing apneas and hypopneas and treating sleep fragmentation due to respiratory related arousals. Because CPAP is the most common treatment for OSA, most studies evaluating treatments for obstructive sleep apnea and cognitive function investigate the use of CPAP. Jiang and colleagues conducted a meta-analysis of the effectiveness of CPAP on cognitive function.<sup>50</sup> They identified published studies from 1970 to 2020. They identified 288 patients from 7 articles which revealed cognitive functions of

OSA patients with MCI or AD were mildly but significantly improved after CPAP treatment especially long-term CPAP treatment as measured by MMSE. However, no significant cognitive benefits were detected by the MoCA. Specifically, cognitive improvements by CPAP were detectable on OSA patients either at a younger age or over longer periods of CPAP treatment. In summary, their findings highlight the partial efficiency of CPAP treatment on cognition improvement in OSA patients with MCI or AD.

In a systemic review, Wang and colleagues investigated the therapeutic effects of CPAP on cognitive function.<sup>51</sup> They identified 40 studies dating back to 1985. Cognitive impairments associated with OSA included attention, executive function, intelligence, memory, and psychomotor speed. Moreover, impaired memory and executive function were shown to be associated with the severity of oxygen desaturation or severity of OSA. Respiratory events negatively impacted memory function in older adults with an apolipoprotein epsilon 4 carrier status but not in those non-carriers. Improvements in executive functions, intelligence, and memory have been seen in patients with OSA receiving CPAP treatment. Interestingly, CPAP treatment may delay cognitive deteriorations in patients with OSA. In their review, the duration of CPAP use was critical. Studies showing benefit of CPAP on cognitive function ranged anywhere from 3 to 12 months.

Given the possible association with OSA, MCI, and AD, studies have investigated the use of

CPAP and its role in slowing the progression of MCI and AD. Liguori and colleagues conducted a retrospective study to identify the long-term effects of CPAP treatment in patients with OSA and MCI or Dementia due to Alzheimer's disease.<sup>52</sup> Using a sample of 24 patients (i.e., 8 with MCI and 16 with AD) over a 1-year period, cognitive function was assessed using the MMSE and clinical dementia rating scale (CDR). A significant difference was found for the mean score change of the CDR since CPAP non-adherent patients showed a higher mean change of CDR compared to CPAP adherent patients. There were no significant differences for the mean change of MMSE. Their study highlights the need to treat OSA in patients with MCI and AD.

In summary, the duration of CPAP treatment increases the likelihood of cognitive benefit in patients with OSA and may mitigate the effects of MCI and AD. More studies are needed to investigate the cognitive benefits of other treatments for obstructive sleep apnea such as hypoglossal nerve stimulation, oral appliances, bariatric surgery, and mandibular advancement surgery.

### Conclusion

Studies investigating the association of OSA and insomnia in relation to cognitive impairment indicate that both sleep disorders can impair cognitive functioning. Studies are heterogenous and use different tests for assessing cognitive function. The cognitive domains affected by both sleep disorders include attention, memory and executive function. Inadequate sleep duration and lack

of adequate sleep with hyperarousal may be the mechanisms underlying insomnia while OSA severity as defined by AHI and severity nocturnal hypoxemia severity appear to be the main mechanism for cognitive impairment associated with OSA. Both sleep disorders may influence the effects of aging and cognitive decline in MCI and AD. Treating insomnia with CBT-I may reduce the risk of cognitive impairment but more studies are needed. Non-BZD hypnotic Z-drugs are

preferred to benzodiazepines which are associated with cognitive impairment. CPAP is the most common treatment for OSA and prolonged use of CPAP may reduce the long-term risk of cognitive impairment. Treat of insomnia and OSA may slow the progression of cognitive decline; however, more studies are needed. There is minimal data on the cognitive benefits of alternative treatments for OSA and insomnia.

**Corresponding Author:**

Gilbert Seda, MD, PhD,  
Division of Pulmonary and Critical Care  
Medicine, Scripps Mercy Chula Vista,  
435 H. Street, CV 31, Chula Vista,  
CA 91910, United States;  
Email: [gilbert.seda@gmail.com](mailto:gilbert.seda@gmail.com)

**Funding Statement:**

There was no funding for this manuscript.

**Acknowledgements:**

Not applicable

**Funding Statement:**

None

**Conflicts of Interest:**

The Authors have nothing to disclose.

References:

- <sup>1</sup> Veasey SC, Rosen IM. Obstructive Sleep Apnea in Adults. *N Engl J Med*. 2019 Apr 11;380(15):1442-1449. doi: 10.1056/NEJMcp1816152. PMID: 30970189.
- <sup>2</sup> American Academy of Sleep Medicine. International classification of sleep disorders, 3<sup>rd</sup> ed. Darien, IL: American Academy of Sleep Medicine 2014.
- <sup>3</sup> Sutton EL. Insomnia. *Ann Intern Med*. 2021 Mar;174(3):ITC33-ITC48. doi: 10.7326/AITC202103160. Epub 2021 Mar 9. PMID: 33683929.
- <sup>4</sup> Zaheed AB, Chervin RD, Spira AP, Zahodne LB. Mental and Physical Health Pathways Linking Insomnia Symptoms to Cognitive Performance 14 Years Later. *Sleep*. 2022 Oct 30;zsac262. doi: 10.1093/sleep/zsac262. Epub ahead of print. PMID: 36309871.
- <sup>5</sup> Resciniti NV, Yelverton V, Kase BE, Zhang J, Lohman MC. Time-Varying Insomnia Symptoms and Incidence of Cognitive Impairment and Dementia among Older US Adults. *Int J Environ Res Public Health*. 2021 Jan 5;18(1):351. doi: 10.3390/ijerph18010351. PMID: 33466468; PMCID: PMC7796486.
- <sup>6</sup> Beydoun HA, Beydoun MA, Weiss J, Hossain S, Huang S, Alemu BT, Zonderman AB. Insomnia as a predictor of diagnosed memory problems: 2006-2016 Health and Retirement Study. *Sleep Med*. 2021 Apr;80:158-166. doi: 10.1016/j.sleep.2021.01.038. Epub 2021 Feb 2. PMID: 33601227.
- <sup>7</sup> Xu W, Tan CC, Zou JJ, Cao XP, Tan L; Alzheimer's Disease Neuroimaging Initiative. Insomnia Moderates the Relationship Between Amyloid- $\beta$  and Cognitive Decline in Late-Life Adults without Dementia. *J Alzheimers Dis*. 2021;81(4):1701-1710. doi: 10.3233/JAD-201582. PMID: 33967043.
- <sup>8</sup> Baril AA, Beiser AS, Sanchez E, Mysliwiec V, Redline S, Gottlieb DJ, O'Connor GT, Gonzales MM, Himali D, Seshadri S, Himali JJ, Pase MP. Insomnia symptom severity and cognitive performance: Moderating role of APOE genotype. *Alzheimers Dement*. 2022 Mar;18(3):408-421. doi: 10.1002/alz.12405. Epub 2021 Jul 26. PMID: 34310026; PMCID: PMC8802306.
- <sup>9</sup> Olaithe M, Ree M, McArdle N, Donaldson S, Pushpanathan M, Eastwood PR, Bucks RS. Cognitive Dysfunction in Insomnia Phenotypes: Further Evidence for Different Disorders. *Front Psychiatry*. 2021 Jul 19;12:688672. doi: 10.3389/fpsyt.2021.688672. PMID: 34349682; PMCID: PMC8326515.
- <sup>10</sup> Khassawneh BY, Bathgate CJ, Tsai SC, Edinger JD. Neurocognitive performance in insomnia disorder: The impact of hyperarousal and short sleep duration. *J Sleep Res*. 2018 Dec;27(6):e12747. doi: 10.1111/jsr.12747. Epub 2018 Aug 1. PMID: 30069961.
- <sup>11</sup> Etholén A, Pietiläinen O, Kouvonen A, Hänninen M, Rahkonen O, Lallukka T. Trajectories of Insomnia Symptoms Among



Aging Employees and Their Associations With Memory, Learning Ability, and Concentration After Retirement - A Prospective Cohort Study (2000-2017). *J Aging Health*. 2022 Oct;34(6-8):916-928. doi: 10.1177/08982643221078740. Epub 2022 Apr 28. PMID: 35482013; PMCID: PMC9483690.

<sup>12</sup> Chunhua X, Jiacui D, Xue L, Kai W. Impaired emotional memory and decision-making following primary insomnia. *Medicine (Baltimore)*. 2019 Jul;98(29):e16512. doi: 10.1097/MD.00000000000016512. PMID: 31335727; PMCID: PMC6709269.

<sup>13</sup> Brownlow JA, Klingaman EA, Boland EM, Brewster GS, Gehrman PR. Psychiatric disorders moderate the relationship between insomnia and cognitive problems in military soldiers. *J Affect Disord*. 2017 Oct 15;221:25-30. doi: 10.1016/j.jad.2017.06.023. Epub 2017 Jun 13. PMID: 28628764.

<sup>14</sup> Dagher M, Farchakh Y, Barbar S, Haddad C, Akel M, Hallit S, Obeid S. Association between problematic social media use and memory performance in a sample of Lebanese adults: the mediating effect of anxiety, depression, stress and insomnia. *Head Face Med*. 2021 Feb 23;17(1):6. doi: 10.1186/s13005-021-00260-8. PMID: 33622360; PMCID: PMC7901207.

<sup>15</sup> Borchgrevink P, Inge Landrø N. The Effect of Insomnia on Neuropsychological Functioning in Patients with Comorbid Symptoms of Pain, Fatigue, and Mood Disorders. *Arch Clin Neuropsychol*. 2018 Feb 1;33(1):14-23. doi: 10.1093/arclin/acx040. PMID: 28453603; PMCID: PMC5860517.

<sup>16</sup> Cross NE, Carrier J, Postuma RB, Gosselin N, Kakinami L, Thompson C, Chouchou F, Dang-Vu TT. Association between insomnia disorder and cognitive function in middle-aged and older adults: a cross-sectional analysis of the Canadian Longitudinal Study on Aging. *Sleep*. 2019 Aug 1;42(8):zsz114. doi: 10.1093/sleep/zsz114. PMID: 31089710; PMCID: PMC6685318.

<sup>17</sup> Zhao JL, Cross N, Yao CW, Carrier J, Postuma RB, Gosselin N, Kakinami L, Dang-Vu TT. Insomnia disorder increases the risk of subjective memory decline in middle-aged and older adults: a longitudinal analysis of the Canadian Longitudinal Study on Aging. *Sleep*. 2022 Nov 9;45(11):zsac176. doi: 10.1093/sleep/zsac176. PMID: 35877203; PMCID: PMC9644124.

<sup>18</sup> Unsal P, Sengul Aycicek G, Deniz O, Esme M, Dikmeer A, Balci C, Koca M, Ucar Y, Boga I, Burkuk S, Halil MG, Cankurtaran M, Dogu BB. Insomnia and falls in older adults: are they linked to executive dysfunction? *Psychogeriatrics*. 2021 May;21(3):359-367. doi: 10.1111/psyg.12677. Epub 2021 Mar 8. PMID: 33684960.

<sup>19</sup> Teräs T, Rovio S, Spira AP, Myllyntausta S, Pulakka A, Vahtera J, Stenholm S. Associations of accelerometer-based sleep duration and self-reported sleep difficulties with cognitive function in late mid-life: the Finnish Retirement and Aging Study. *Sleep Med*. 2020 Apr;68:42-49. doi: 10.1016/j.sleep.2019.08.024. Epub 2019 Sep 20. PMID: 32028225.

- <sup>20</sup> Grau-Rivera O, Operto G, Falcón C, Sánchez-Benavides G, Cacciaglia R, Brugulat-Serrat A, Gramunt N, Salvadó G, Suárez-Calvet M, Minguillon C, Iranzo Á, Gispert JD, Molinuevo JL; ALFA Study. Association between insomnia and cognitive performance, gray matter volume, and white matter microstructure in cognitively unimpaired adults. *Alzheimers Res Ther.* 2020 Jan 7;12(1):4. doi: 10.1186/s13195-019-0547-3. PMID: 31907066; PMCID: PMC6945611.
- <sup>21</sup> Gosselin N, Baril AA, Osorio RS, Kaminska M, Carrier J. Obstructive Sleep Apnea and the Risk of Cognitive Decline in Older Adults. *Am J Respir Crit Care Med.* 2019 Jan 15;199(2):142-148. doi: 10.1164/rccm.201801-0204PP. PMID: 30113864; PMCID: PMC6943882.
- <sup>22</sup> Angelelli P, Macchitella L, Toraldo DM, Abbate E, Marinelli CV, Arigliani M, De Benedetto M. The Neuropsychological Profile of Attention Deficits of Patients with Obstructive Sleep Apnea: An Update on the Daytime Attentional Impairment. *Brain Sci.* 2020 May 27;10(6):325. doi: 10.3390/brainsci10060325. PMID: 32471112; PMCID: PMC7349097.
- <sup>23</sup> Pan T, Liu S, Ke S, Wang E, Jiang Y, Wang S; on the behalf of Alzheimer's Disease Neuroimaging Initiative. Association of obstructive sleep apnea with cognitive decline and age among non-demented older adults. *Neurosci Lett.* 2021 Jun 21;756:135955. doi: 10.1016/j.neulet.2021.135955. Epub 2021 May 9. PMID: 33979700.
- <sup>24</sup> Zhu RL, Ouyang C, Ma RL, Wang K. Obstructive sleep apnea is associated with cognitive impairment in minor ischemic stroke. *Sleep Breath.* 2022 Dec;26(4):1907-1914. doi: 10.1007/s11325-022-02575-5. Epub 2022 Mar 19. PMID: 35305233; PMCID: PMC9663369.
- <sup>25</sup> McCloy K, Duce B, Swarnkar V, Hukins C, Abeyratne U. Polysomnographic risk factors for vigilance-related cognitive decline and obstructive sleep apnea. *Sleep Breath.* 2021 Mar;25(1):75-83. doi: 10.1007/s11325-020-02050-z. Epub 2020 Mar 25. PMID: 32215832.
- <sup>26</sup> Ji P, Kou Q, Qu X, Sun G, Liu S, Zhang J. Effects of Obstructive Sleep Apnea-Hypopnea Syndrome and Cognitive Function in Ischemic Stroke Based on Linear Regression Equation. *Scanning.* 2022 Jun 22;2022:4105169. doi: 10.1155/2022/4105169. PMID: 35844265; PMCID: PMC9242756.
- <sup>27</sup> Qiu K, Mao M, Hu Y, Yi X, Zheng Y, Ying Z, Cheng D, Rao Y, Zhang J, Mu X, Ren C, Xu Y, Zhang W, Xu W, Zhao Y, Ren J. Gender-specific association between obstructive sleep apnea and cognitive impairment among adults. *Sleep Med.* 2022 Oct;98:158-166. doi: 10.1016/j.sleep.2022.07.004. Epub 2022 Jul 11. PMID: 35870305.
- <sup>28</sup> Macchitella L, Romano DL, Marinelli CV, Toraldo DM, Arigliani M, De Benedetto M, Angelelli P. Neuropsychological and socio-cognitive deficits in patients with obstructive sleep apnea. *J Clin Exp Neuropsychol.* 2021 Jul;43(5):514-533.

- <sup>29</sup> Zhang XL, Gao B, Han T, Xiang BY, Liu X. Moderate-to-Severe Obstructive Sleep Apnea and Cognitive Function Impairment in Patients with COPD. *Int J Chron Obstruct Pulmon Dis*. 2020 Jul 27;15:1813-1822. doi: 10.2147/COPD.S257796. PMID: 32801679; PMCID: PMC7396955.
- <sup>30</sup> Bilyukov RG, Nikolov MS, Pencheva VP, Petrova DS, Georgiev OB, Mondeshki TL, Milanova VK. Cognitive Impairment and Affective Disorders in Patients With Obstructive Sleep Apnea Syndrome. *Front Psychiatry*. 2018 Aug 7;9:357. doi: 10.3389/fpsy.2018.00357. PMID: 30131730; PMCID: PMC6091233.
- <sup>31</sup> Gagnon K, Baril AA, Montplaisir J, Carrier J, De Beaumont L, D'Aragnon C, Chami S, Pelleieux S, Poirier J, Gauthier S, Lafond C, Gagnon JF, Gosselin N. Disconnection Between Self-Reported and Objective Cognitive Impairment in Obstructive Sleep Apnea. *J Clin Sleep Med*. 2019 Mar 15; 15(3):409-415. doi: 10.5664/jcsm.7664. PMID: 30853044; PMCID: PMC6411171.
- <sup>32</sup> Olaithe M, Pushpanathan M, Hillman D, Eastwood PR, Hunter M, Skinner T, James A, Wesnes KA, Bucks RS. Cognitive profiles in obstructive sleep apnea: a cluster analysis in sleep clinic and community samples. *J Clin Sleep Med*. 2020 Sep 15;16(9):1493-1505. doi: 10.5664/jcsm.8564. PMID: 32400387; PMCID: PMC7970596.
- <sup>33</sup> Gagnon K, Baril AA, Montplaisir J, Carrier J, Chami S, Gauthier S, Lafond C, Gagnon JF, Gosselin N. Detection of mild cognitive impairment in middle-aged and older adults with obstructive sleep apnoea. *Eur Respir J*. 2018 Nov 1;52(5):1801137. doi: 10.1183/13993003.01137-2018. PMID: 30190270.
- <sup>34</sup> Lal C, Ayappa I, Ayas N, Beaudin AE, Hoyos C, Kushida CA, Kaminska M, Mullins A, Naismith SL, Osorio RS, Phillips CL, Parekh A, Stone KL, Turner AD, Varga AW. The Link between Obstructive Sleep Apnea and Neurocognitive Impairment: An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc*. 2022 Aug;19(8):1245-1256. doi: 10.1513/AnnalsATS.202205-380ST. PMID: 35913462; PMCID: PMC9353960.
- <sup>35</sup> Blackman J, Swirski M, Clynes J, Harding S, Leng Y, Coulthard E. Pharmacological and non-pharmacological interventions to enhance sleep in mild cognitive impairment and mild Alzheimer's disease: A systematic review. *J Sleep Res*. 2021 Aug;30(4):e13229. doi: 10.1111/jsr.13229. Epub 2020 Dec 2. PMID: 33289311; PMCID: PMC8365694.
- <sup>36</sup> Roniger DDG, Lechuga YA, León EE, Robles ROG, Escandón ÓS, Pérez GJT, Moctezuma JV. Cognitive behavioral therapy for insomnia helps to reverse cognitive impairment in insomnia patients. *Sleep Sci*. 2022 Apr-Jun;15(Spec 2):355-360. doi: 10.5935/1984-0063.20210026. PMID: 35371411; PMCID: PMC8906373.
- <sup>37</sup> Cassidy-Eagle E, Siebern A, Unti L, Glassman J, O'Hara R. Neuropsychological Functioning in Older Adults with Mild Cognitive Impairment and Insomnia Randomized to CBT-I or Control Group. *Clin Gerontol*. 2018 Mar-Apr;41(2):136-144.

doi: 10.1080/07317115.2017.1384777.

Epub 2017 Dec 8. PMID: 29220627.

<sup>38</sup> McCrae CS, Curtis AF, Williams JM, Dautovich ND, McNamara JPH, Stripling A, Dzierzewski JM, Chan WS, Berry RB, McCoy KJM, Marsiske M. Efficacy of brief behavioral treatment for insomnia in older adults: examination of sleep, mood, and cognitive outcomes. *Sleep Med.* 2018 Nov;51:153-166. doi: 10.1016/j.sleep.2018.05.018. Epub 2018 Jun 2. PMID: 30195661; PMCID: PMC6513321.

<sup>39</sup> Perrault AA, Pomares FB, Smith D, Cross NE, Gong K, Maltezos A, McCarthy M, Madigan E, Tarelli L, McGrath JJ, Savard J, Schwartz S, Gouin JP, Dang-Vu TT. Effects of cognitive behavioral therapy for insomnia on subjective and objective measures of sleep and cognition. *Sleep Med.* 2022 Sep;97:13-26. doi: 10.1016/j.sleep.2022.05.010. Epub 2022 May 23. PMID: 35691208.

<sup>40</sup> Mattos MK, Manning CA, Quigg M, Davis EM, Barnes L, Sollinger A, Eckstein M, Ritterband LM. Feasibility and Preliminary Efficacy of an Internet-Delivered Intervention for Insomnia in Individuals with Mild Cognitive Impairment. *J Alzheimers Dis.* 2021;84(4):1539-1550. doi: 10.3233/JAD-210657. PMID: 34690141.

<sup>41</sup> Edinger JD, Arnedt JT, Bertisch SM, Carney CE, Harrington JJ, Lichstein KL, Sateia MJ, Troxel WM, Zhou ES, Kazmi U, Heald JL, Martin JL. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep

Medicine clinical practice guideline. *J Clin Sleep Med.* 2021 Feb 1;17(2):255-262.

doi: 10.5664/jcsm.8986.

PMID: 33164742; PMCID: PMC7853203.

<sup>42</sup> Qaseem A, Holty JE, Owens DK, Dallas P, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2013 Oct 1;159(7):471-83. doi: 10.7326/0003-4819-159-7-201310010-00704. PMID: 24061345.

<sup>43</sup> Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update. *World Psychiatry.* 2019 Oct;18(3):337-352. doi: 10.1002/wps.20674. PMID: 31496087; PMCID: PMC6732697.

<sup>44</sup> Rosenberg R, Citrome L, Drake CL. Advances in the Treatment of Chronic Insomnia: A Narrative Review of New Nonpharmacologic and Pharmacologic Therapies. *Neuropsychiatr Dis Treat.* 2021 Aug 6;17:2549-2566. doi: 10.2147/NDT.S297504. PMID: 34393484; PMCID: PMC8354724.

<sup>45</sup> Picton JD, Marino AB, Nealy KL. Benzodiazepine use and cognitive decline in the elderly. *Am J Health Syst Pharm.* 2018 Jan 1;75(1):e6-e12. doi: 10.2146/ajhp160381. PMID: 29273607.

<sup>46</sup> Guo F, Yi L, Zhang W, Bian ZJ, Zhang YB. Association Between Z Drugs Use and Risk of Cognitive Impairment in Middle-Aged and Older Patients With Chronic Insomnia. *Front Hum Neurosci.* 2021 Dec 9;15:775144.

---

doi: 10.3389/fnhum.2021.775144.

PMID: 34955792; PMCID: PMC8696350.

<sup>47</sup> Sumsuzzman DM, Choi J, Jin Y, Hong Y. Neurocognitive effects of melatonin treatment in healthy adults and individuals with Alzheimer's disease and insomnia: A systematic review and meta-analysis of randomized controlled trials. *Neurosci Biobehav Rev.* 2021 Aug;127:459-473. doi: 10.1016/j.neubiorev.2021.04.034. Epub 2021 May 3. PMID: 33957167.

<sup>48</sup> Jean-Louis, G., von Gizycki, H., Zizi, F., 1998. Melatonin effects on sleep, mood, and cognition in elderly with mild cognitive impairment. *J. Pineal Res.* 25, 177–183. doi: 10.1111/j.1600-079x.1998.tb00557.x. PMID: 9745987.

<sup>49</sup> Luthringer, R., Muzet, M., Zisapel, N., Staner, L., 2009. The effect of prolonged-release melatonin on sleep measures and psychomotor performance in elderly patients with insomnia. *Int. Clin. Psychopharmacol.* 24, 239–249.

<https://doi.org/10.1097/YIC.0b013e32832e9b08>.

<sup>50</sup> Jiang X, Wang Z, Hu N, Yang Y, Xiong R, Fu Z. Cognition effectiveness of continuous positive airway pressure treatment in obstructive sleep apnea syndrome patients with cognitive impairment: a meta-analysis. *Exp Brain Res.* 2021 Dec;239(12):3537-3552. doi: 10.1007/s00221-021-06225-2. Epub 2021 Sep 21. PMID: 34546386.

<sup>51</sup> Wang G, Goebel JR, Li C, Hallman HG, Gilford TM, Li W. Therapeutic effects of CPAP on cognitive impairments associated with OSA. *J Neurol.* 2020 Oct;267(10):2823-2828. doi: 10.1007/s00415-019-09381-2. Epub 2019 May 20. PMID: 31111204.

<sup>52</sup> Liguori C, Cremascoli R, Maestri M, Fernandes M, Izzi F, Tognoni G, Scarpina F, Siciliano G, Mercuri NB, Priano L, Bonanni E, Placidi F. Obstructive sleep apnea syndrome and Alzheimer's disease pathology: may continuous positive airway pressure treatment delay cognitive deterioration? *Sleep Breath.* 2021 Dec;25(4):2135-2139. doi: 10.1007/s11325-021-02320-4. Epub 2021 Feb 22. PMID: 33619666.