

## Implication of Physical Activity in Older Alzheimer Patients with Sleep Impairments

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### Abstract

Sleep problems are common in institutionalized elders and are associated with increased mortality and morbidity. Recent research has proved that sleep disturbances and circadian rhythm have been related to the pathophysiology of Alzheimer's disease (AD) and would influence the progression of the pathology and lead to both cognitive and non-cognitive disabilities. The last decade has observed increasing recognition of the beneficial role of exercise in brain diseases, and neurodegenerative disorders in particular.

In this review, we will focus on the therapeutic role of physical exercise for sleep disorders in older patients with Alzheimer disease. We integrated multitude possible mechanisms of sleep deprivation leading to Alzheimer's disease and cognitive decline. The role of neuroinflammation, circadian rhythm and sleep disturbances play a basic role in tau generation and A $\beta$  deposition. Available data suggest that physical exercise may have the potential to improve sleep quality and delay the progression of cognitive impairments. However, additional research is required in order to examine and understand the most effective exercise therapy for this disease; the best way to monitor the response to interventions; the beneficial influence of physical exercise on sleep dysfunction in Alzheimer disease; and the mechanisms underlying exercise-induced sleep improvements.

**Keywords:** Alzheimer's Disease; Sleep Disorders; Physical Activity; Cognitive Function; Aged Patients

### Abbreviations

AD: Alzheimer's Disease; A $\beta$ : Amyloid Beta; MAP: Microtubule Associated Proteins; DNA: Deoxyribonucleic Acid; SCN: Suprachiasmatic Nucleus; PA: Physical Activity; BLT: Bright Light Therapy

### Introduction

Alzheimer's disease (AD) is an age-related and irreversible neurodegenerative brain disease [1]. According to a recent study, 24.4 million individuals currently suffer from Alzheimer's disease, and 4.6 million new cases are reported worldwide every year. The number

of patients suffering from this disease is expected to double every 20 years, to reach 43.2 million by 2020 and 81.1 million by 2040 [2]. Alzheimer disease characterized by acquired impairments in cognitive function, with a gradual impact on the patient's professional and social activities.

It is generally known that the majority of Alzheimer's patients have sleep problems, which affect the quality of life and well-being [3]. The physiological disorders in Alzheimer disease affect various tissues, organ systems, and bodily functions, one of them is sleep-wake cycle [4]. In the night sleep, a normal young adult will be awakened 2 to 4 times, however, the older person will be awakened more times, their sleep-awake circadian rhythms is affected [5]. Older people have increased prevalence of sleep disorders secondary to physiological decline in their circadian sleep rhythm [6]. This reflects the importance of sleep control for those elderly patients whose living in chronic care hospitalization and characterized by frailty, cognitive impairment decreased physical activity and increased prevalence of specific sleep disorders compared to normal population [7]. Initially, there is a great evidence relationship between sleep problems and neurodegenerative disease, recent studies suggest that sleep problems can show up years before cognitive disorders and thus become a plausible biomarker for early prevention and diagnostic intervention [8]. The term "sleep quality" refers to how well you sleep. Sleep quality defined as a person's contentment with their sleep experience, which includes factors such as sleep initiation, sleep maintenance, sleep quantity, and wakefulness. Chronic sleep impairments are common and they are related with the disease level [9]. These problems are frequently manifested at night, excessive daytime sleepiness, and an increase in sun-downing behaviour. Patients in the late stages of Alzheimer disease spend more than 40% of their time in bed awake at night [10]. Previous studies has shown the beneficial impacts of physical exercise on sleep quality in older patients. Most of published data on this field describes observational studies evaluating the relationship between physical exercise and sleep in patients with Alzheimer disease. In 58 patients with dementia evaluated with the Mini-Sleep Questionnaire, those who participated in regular physical exercise had lower impairments of sleep compared to those who had fewer participation in physical exercise [11]. Shih and al have examined the influence of physical exercise (based on the total number of walking hours per week) on sleep quality and sundowning.

Results showed a decrease in sleep disorders in patients who walked more hours per week [12]. In this review, we discuss the available evidence supporting the use of exercise for the treatment of sleep disorders in older patients with dementia.

### Theories of sleep

**Restorative theory:** According to the restorative idea, sleep permits the body to revitalize and restore the physiological process required to rejuvenate the body and mind. Numerous biological functions, such as muscle repair, clearing waste toxins from the brain regions [14], protein synthesis, repairing tissues throughout the body [15], and the release of many important growth hormones, are shown to occur largely during and the release of many important growth hormones, are shown to occur largely during sleep [16].

**Adaptive theory:** Also called the evolution theory or preservation theory is also known as the inactivity theory of sleep. A flaw in this theory, scientific studies showed that sleeping limits productivity, such as finding food and reproducing, so staying awake longer would be an evolutionary benefit [17]. Sleepiness, like hunger and thirst, may indicate an underlying physiological need that can only be met by sleeping and is critical to an individual's survival [18].

### Sleep and mental health

Sleep and mental health are closely connected. Sleep disorders affects psychological state and mental well-being. Sleep deprivation has been found to be one of the important causes of a range of negative health outcomes, including: Alzheimer disease, heart disease, type 2 diabetes, and depression. At the same time, sleep disorders can be caused by psychiatric ailments, and abnormalities in sleep can increase the symptoms of many mental illnesses, including depression, anxiety, and bipolar disorder. Sleep has long been recognized as a symptom of many psychiatric and neuropsychological disorders, newer theories imply that sleep can also play a causative role in the development and maintenance of mental illnesses [19].

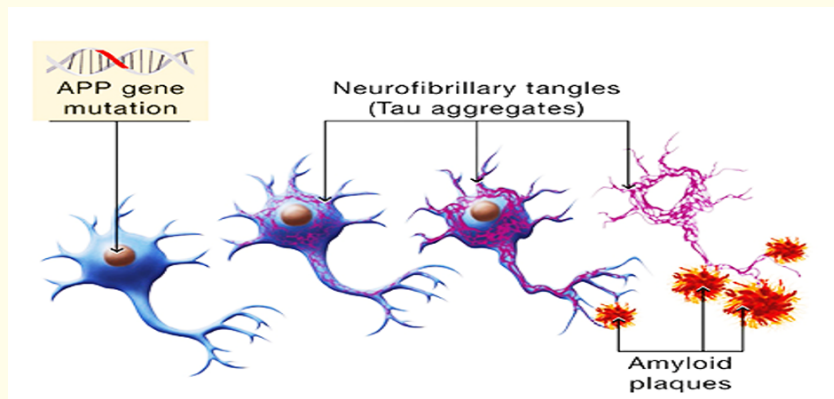
**Sleep deprivation and amyloid beta (Aβ) protein**

Assuming that AD pathophysiology occurs quietly many years before the manifestation of cognitive disorders, recent scientific data show that research in neuroscience is focusing on the preclinical stage of AD. The pathophysiology process of AD is based on the presence and the accumulation of extracellular beta-amyloid (Aβ) deposits. Beta-amyloid molecules play an important role in AD, which is triggered by both genetic and environmental factors, and there is an increasing accumulation of Aβ in all brain regions in patients with Alzheimer disease. Increasing Aβ mass causes neuronal cell death, loss of synapses, and leads to a progressive decreasing of brain volume, which affect most of cognitive and functional parameters [20]. Scientific studies in both academic and pharmaceutical industry have strongly verified the link between the amyloid cascade protein and the presence of Alzheimer disease [21].

Recently, it has been confirmed that the progression of the cognitive functions is relatively due to a high levels of inflammatory response in the brain in AD and high immune gene activation increases the susceptibility to neurodegeneration [22]. Many researchers' studies have verified the relationship between sleep measurements, Aβ protein levels, and cognitive dysfunction in older patients, however, those studies has indicated that poor quality of sleep is related to a poor cognitive parameters. The abnormal accumulation of Aβ and tau proteins is a significant source of synaptic dysfunction, neurotransmission deterioration, and sleep problems, both of them playing a critical part in the development of Alzheimer's disease [23]. Changes in sleep seem to precede the onset of cognitive symptoms in patients with AD, and sleep quality decline further in parallel with both cognitive disorders and the progression of the chronic disease.

**Tau protein homeostasis**

Tau is one of the most important Microtubule Associated Proteins (MAP) in the neurons. The balanced tau phosphorylation binds it to the microtubules, assembles the microtubules, and maintains the structure and stability of the neurons [24]. However, the hyperphosphorylation state of tau facilitates the formation of intracellular tangles, which directly disrupts neuronal homeostasis and contribute to the cell death [25] (Figure 1). Evidence from animal models illustrates that changes in the sleep-wake cycle may increase hyperphosphorylated Tau protein in the brain [26]. Scientific studies have showed that two months of abnormal sleep, causes more than 50% elevation of the insoluble Tau in the brain and lead to increase the dysfunctional process of tau metabolism [27].



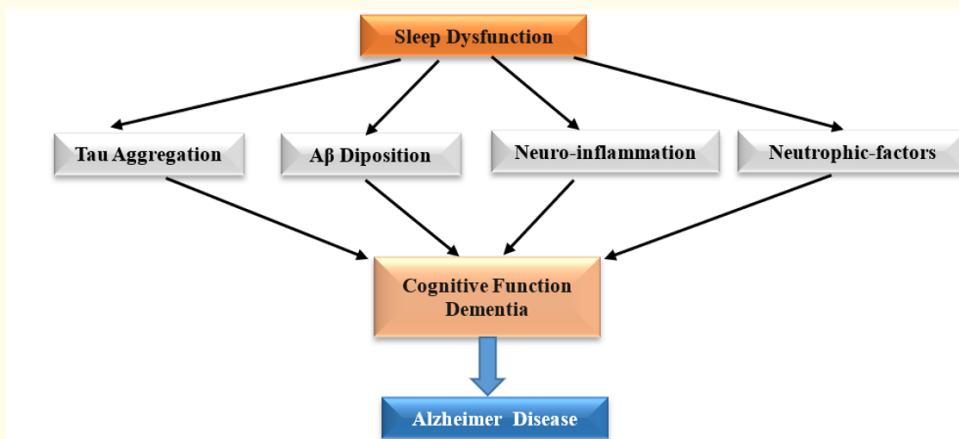
**Figure 1:** Representation of how neurofibrillary tangles and amyloid plaques attacks the neuron.

**Epigenetic factors in Alzheimer's disease**

Epigenetics is the study of how cells control gene activity without changing the DNA sequence. The progression of AD occur with the interaction of various and different factors, such aging, genetic mutations, metabolic activity, and nutritional problems, as well as environ-

mental and social interactions [28]. Recent advances in sequencing technologies have allowed for a large pool of studies investigating DNA methylation in Alzheimer pathology, However, DNA methylation is crucial in maintaining basic cellular mechanism and synaptic plasticity in central nervous system, affecting cognitive parameters [29]. Decreased DNA methylation in brain regions can affect neural plasticity, prevents memory formation, and leads to memory loss with aging in AD patients [30].

In addition to aging factor, cardiovascular diseases, which are other epigenetic risk factors, are the most frequently reported precursor factors of AD. In addition to all of these, the progression of AD is further enhanced by various variables including smoking, diabetes, hypertension, obesity, dyslipidemia (increasing blood cholesterol level), accidents brain injury, marital status, and psychological functions [31].



**Figure 2:** Possible mechanisms of Alzheimer’s disease. Sleep deprivation causes Aβ and tau deposition and can cause neuroinflammation along with disruption in levels of neurotrophic factors.

**Circadian rhythm and Alzheimer disease**

Circadian alterations occur both during healthy aging and in age-related diseases such as Alzheimer disease. There is a progressive deterioration of circadian rhythms with aging. These include various modifications in the sleep wake cycle influenced by an important decreasing in sleep quality and cognitive impairment [32], and involve nocturnal sleep fragmentation, increased wakefulness, and decreased levels of daytime activity [33].

These sleep disturbances have a significant impact on patients and their caregivers, and present a major risk factor for early institutionalization. There is good reason to detect problems in circadian rhythms in patients with dementia, especially those with Alzheimer’s disease.

The principal reason for the fluctuation in sleep-wake cycle can be explained with the alterations in the superchiasmatic nucleus (SCN) and melatonin secretion [34]. At the cellular level, there is a decrease in the activity of neurons within the SCN in Alzheimer’s patients [35]. It would be surprising not to find alterations in circadian rhythms for these patients, but one might expect problems to develop only at advanced stages of neurodegeneration. Nevertheless, contradictions results concerning the nature of circadian rhythms have been reported. Research’s about Alzheimer patients have showed worse [36], similar [37], and better circadian temperature rhythms [38] when compared with non-demented older patients.

### Body clock disruptions

People with Alzheimer's disease are known to have disturbances in their internal body clocks that affect the sleep/wake cycle and may increase the risk of developing the disorder. The biological clock is regulated and synchronized by the suprachiasmatic nucleus (SCN) of the hypothalamus [39]. It resets on a daily basis via light inputs from the retina during the day and melatonin secretion during the night. The SCN regulates and controlling the timing of humoral controls including sleep-wake, temperature, and cognitive function by sending signals to numerous hypothalamic nuclei [40]. The SCN regulates output pathways that affect different physiological parameters using two types' neuronal and humoral signals. These output pathways [41] determine the proper timing of hormone release, feeding behavior, and body temperature changes.

### Nonpharmacological treatment

#### Potential therapeutic and treatments strategies

The aim of the treatment is to improve the quality of life of patients and caregivers. Because these conditions can have a major impact on quality of life, it seems logical to think that the treatment would also improve some cognitive domains. Authors have suggested a possible preventive effect for controlling the progression of Alzheimer disease [42]. More research is needed to generate evidence-based guidelines backed up by strong scientific evidence, but currently, the available therapeutic information's offers some potential strategies discussed in the following paragraphs.

### Physical activity and cognition

The beneficial impacts of physical activity on healthy aged people have been widely demonstrated, especially regarding cognitive parameters [43]. Previous studies have demonstrated the protection role of physical activity in physically active patients [44]. Currently, we know that physical activity decreases the progression of cognitive disorders in elderly patients with Alzheimer's disease [45], and has various beneficial effects, improving functional capacity, increasing autonomy and improving life quality in older patients with neurodegenerative disease [46]. Furthermore, physical exercise at midlife appears to exert a neuroprotective effect later in life. For example, practicing physical exercise two times a week decreases the prevalence of Alzheimer's disease by half, two decades later [47]. It is very important that patients maintain a regular physical training program for a maximum prolonged period to obtain effects that are more beneficial [48], even a minimal level of exercise (e.g. walking, balance) generates some health benefits, as opposed to being sedentary [49].

### Physical activity and sleep

Exercise has shown potential for improving sleep dysfunction in AD as well. Given the possibility that exercise can be used to potentiate other circadian resynchronization methods [50], confirmed with potential evidence that leisure-time physical activity is protective against AD [51]. Most published research studies describe observational studies evaluating the relationship between physical activity and sleep in AD.

In cross-sectional study, 59 patients with dementia evaluated with the Mini-Sleep Questionnaire, participants who following a regular physical training had fewer sleep disorders compared to those who had lower levels of physical training [52]. In another observational study, 183 patients with dementia examined the effects of physical activity based on walking hours per week on sleep quality. Results showed a significant improvement in sleep quality in patients with Alzheimer disease who practiced more walking hours [53]. In summary, several studies suggest that exercise has the potential to improve sleep in persons with AD (Figure 3). Physical activity recommendations should be settled for controlling the progression of the disease for patients in all different stages of this chronic pathology and to determine the potential mechanisms underlying exercise-induced changes in sleep.

Currently, faced with this public problem, it is necessary to adopt methods that are more beneficial and techniques to improve AD patients' quality of life and well-being healthy. Nevertheless, there are no specific and compelling drugs for treating definitively Alzheimer

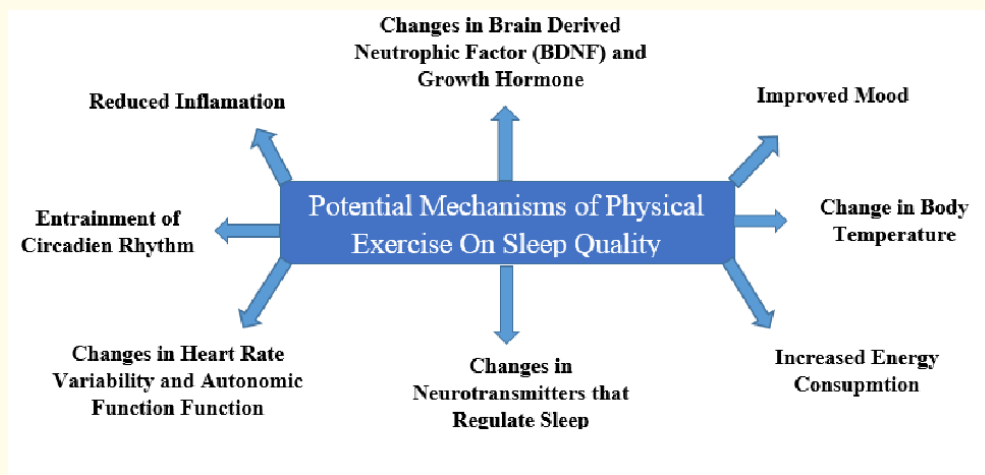


Figure 3: Effects of physical exercise on sleep quality.

disease, so researchers have a strong awareness of the shift from pharmacotherapy to physical activity (PA) and expect to find a cure approach for AD.

**Other non-pharmacological treatments**

**Sleep hygiene and environmental measures**

The term ‘sleep hygiene’ refers to a set of behavioral and environmental recommendations intended to improve sleep quality. The basic advices of sleep hygiene include maintaining a regular sleep schedule, engaging in adapted daily exercises, minimizing daytime naps, minimizing and decreasing the use of caffeine, tobacco and alcohol, keeping the sleep environment dark, quiet, try to stay out from noise, and generally restricting light close to bedtime [54]. Environmental factors contribute in change of sleep disorders that occur with age, that affect daily activities specially after retirement, mealtimes become irregular, pain and other comorbidities lead to increases the level of physical inactivity, while loneliness become more prevalent and that can also contribute to increase psychologic problems in patients with Alzheimer disease such as depression and anxiety [55].

**Meal timing**

It has been shown that eating timing, can prevent circadian disruption and even induce circadian resynchronization, however, research studies indicates that food timing can be a powerful synchronizing [56], or desynchronizing factor [57] and affect circadian system through complex interplay of central and peripheral oscillators [58].

**Bright-light therapy**

Bright light therapy (BLT) is a therapy used to treat sleep disorders. Research study have confirmed that 2h of bright-light therapy during 4 weeks improve the circadian rhythm in patients with Alzheimer dementia, most specifically it helps to decreased daytime sleep and increase nighttime sleep [59]. These measures showed a reduction in daytime sleepiness, a decrease in average duration and frequency

of nocturnal awakenings, although one study found no significant change [60]. The impacts of bright light therapy have been well studied, however, this technique applied at an intensity of greater than 2500 Lux for half an hour or more in the morning or all day shows a various improvement in sleep quality [61].

### Musical therapy

Music interventions have also been shown to have other positive physiological effects on AD persons that may affect cognition and behavior, such as improving sleep by increasing melatonin levels [62].

The musical therapy has gained an important increasing amount of interest in scientific studies, it's a very accepted method and therapeutic technique, inexpensive, easily implemented, and highly enjoyable means of treatment for persons with Alzheimer disease. Behavioral studies concerning musical therapy intervention in AD indicate a good motivation level and high engagement in those with the disease and for the caregivers [62].

### Conclusion

Sleep disturbances occur frequently in persons with Alzheimer disease, oftentimes increasing as the progression of severity of this disease increases. Changes in the brain region, in addition to normal changes in sleep because of aging as principal factor, add to the sleep disorders that are experienced by older patients with dementia. Evidence supports a strong relationship between sleep problems and A $\beta$  and tau burden, meaning that sleep disruption might be both a cause and a consequence of neurodegenerative disease such as Alzheimer. Practice of Sleep hygiene which encourages habits conducive to restorative sleep and avoidance of substances or behaviors that can affect sleep can help in resolving the problems associated with sleep disturbances to a very great extent. Understanding the sleep cycle of the individual, factors that significantly affect sleep and using a customized intervention model of psychological therapies can also help improving the sleep- Nevertheless, much needs still to be learned about these links, and subsequently improve treatment outcomes, decrease health distress experienced by both patients and caregiver's providers and increase overall level of function. In individuals, there by alleviating the distress experienced because of it. This can also help in preventing the secondary effect on mental health issues such as anxiety and depression.

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### Conflict of Interest

The authors declare no conflict of interest.

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