Advances in Research and Treatment on Patients with Alzheimer's disease Induced by Sleep disorders

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Abstract. Alzheimer's disease (AD) is a disease characterized by memory impairment, loss of words and inability in emotional control that occurs in the early and intermediate stage of the end of our lives. A number of studies have shown that the incidence and severity of AD is higher in patients with sleep disorders than in healthy people. The pathogenic mechanism of AD is still inconclusive, while several hypotheses have been proposed according to its etiological characteristics: Some studies suggest that the β-amyloid protein hypothesis and the mechanism of abnormal phosphorylation of protein tau induced by sleep disorders may be the key factors leading to AD. This paper will summarize the mechanisms of AD induced by sleep disorders and discuss the current therapies approaches to it, which included pharmacological therapy, using Trazodone, Midazolam Maleate tablets, Gardenia Citrusaurantium capsules as well as non-pharmacological therapy, which use aerobic exercise and light therapy, promoting the idea of relieving sleep disorders as an adjunctive treatment for AD. The contents summarized in this paper have some significance of reference to the direction of treatment of AD sleep disorders.

Keywords: AD(Alzheimer's disease), Sleep disorders, insomnia, β-amyloid, Abnormal phosphorylation of protein tau, Pharmacological therapy, Non-pharmacological therapy.

1. Introduction

Alzheimer's disease is a progressive developmental neurodegenerative disorder that occurs to the early and intermediate stage of the end of our lives, involves loss of words and inability in emotional control. According to the WHO report on AD of 2018, dementia has become a global crisis, with an average of one new case per 3 seconds. At then approximately 50 million patients were discovered worldwide, while it is expected to increase to 82 million by 2030 and to 152 million by 2050. By then, they, AD patients, will be accounted for more than half of the dementia population [1]. However, Pathogenic mechanism of AD is still inconclusive, and several hypotheses of pathogenesis have been proposed based on its etiological features, such as the β-amyloid hypothesis [2] and the abnormal phosphorylation of Protein tau hypothesis [3].

Sleep disorders are clinically manifested by abnormal sleep pattern and behavior during sleep, as well as disorders of normal rhythmical alternation of sleep and wakefulness. It can be caused by a variety of factors, often related to physical illness. A study had been conducted to point out that sleep disorders may induce AD [4], while other reports indicated that sleep disorders may be a leading factor of causing AD to strike individuals [5]. Another study released on March 4, 19 by the Mayo Clinic, showed that sleep disorders may accumulate more toxic Protein tau and that abnormal phosphorylation of Protein tau is a mechanism relevant to the pathogenesis of AD [6] Therefore, it is concluded that there is a positive correlation between sleep disorders and AD.

This paper aims to review the development and research progress on AD induced by sleep disorders, and will first introduce the mechanisms involved in AD caused by sleep disorders such as the β-amyloid hypothesis and the abnormal protein tau phosphorylation hypothesis that disrupts sleep and circadian patterns. Then comes to the therapies which relieve AD sleep disorders through addressing sleep disorder. The latter part is divided into two categories: pharmacological and non-pharmacological therapies, and finally summarize the future prospects for the treatment of AD sleep disorders.
2. Characteristics of different levels of dementia and sleep disorders

The common geriatric syndromes that afflict the elderly are usually dementia and sleep disorders. It has been shown that more than 60% of AD patients present with sleep disorders, and even some of them have started to change their sleeping pattern before the clinical stage before AD [7]. As individual start to age, further changes in sleeping pattern occur, mainly in the form of increased arousals, fragmentation of sleeping pattern and reduced slow-wave sleep (SWS) [8-9]. An experiment investigated the characteristics of sleep disturbances in patients with different degrees of dementia, and 752 patients with different degrees of AD were divided into four groups to compare their Pittsburgh Sleep Quality Index (PSQI) total score and each factor score. The results showed that the scores of sleep efficiency, sleep latency, and daytime dysfunction in various behavior were higher in the severe dementia group than in the mild and moderate dementia groups. Thus, it could be concluded that patients with cognitive impairment had severer sleep disturbances and the sleep disturbances were proportional to degree of dementia. Furthermore, the effect of the degree of dementia on sleep disturbance characteristics was dominated by daytime dysfunction in behavior first. Then, within time it gradually progressed to the involvement of both sleep efficiency and sleep latency [10].

3. Factors contributing to sleep disorders and AD as well as the causal cycle between them

3.1. Factors that induce sleep disorders

A recent report pointed out that sleep delay is also one of the factors leading to sleep disorders, and in 2021, the average daily sleep duration of Chinese is 7.06 hours, while 64.75% of respondents actually sleep less than 8 hours per day, and the proportion of respondents with more than 8 hours was a mere 7.97%. The report also concluded that sleep duration was affected by reduced time in bed or spending much time on smartphones. The young with low self-control ability could spend more than 2 hours of daily on using smartphones, thus leading to sleep disorders [11]. In addition, caffeine, nicotine and alcohol in the diet are the three main contributors to sleep disruption. Studies have shown that caffeine is a stimulant [12], and intaking it in the afternoon or evening prolongs sleep latency, reduces sleep quality and even may induce anxiety [12], and high intakes of caffeine produces toxic compound in the body, which may further trigger insomnia and other side effects [13]. While nicotine is another stimulant, smoking near bedtime not only causes difficulty in falling asleep and affects sleep quality. Alcohol is a sedative that has a hypnotic effect, but it can disrupt the sleep cycle and make us get broken sleep, thus causing sleep disorders [12]. There is also an experiment, examined the psychological effects on sleep, where excessive demands for sleep, sleep control, external attributions of insomnia and poor perceptions of dependence on sleep also lead to sleep disorders [14]. In addition, sleep inequality, home bedding choices and well-being are also among the factors that influence sleep [11].

3.2. AD caused by Sleep disorder

For the part of how sleep disorder induces AD, it has been experimentally demonstrated that sleep disorders accelerate the deposition of Protein Aβ and Tau in the brain, leading to severer symptoms of AD [15]. Meanwhile, experiments have been conducted to analyze the sleep of patients with different degrees of AD. Results showed that sleep alterations are already present in the preclinical phase of AD, leading to the conclusion that sleep disturbance is both an early sign of AD pathology and a marker for early AD [16]. Thus, this further concluding that sleep disturbance can lead to AD.

3.3. Factors that induce AD

It is commonly believed that AD is associated with both congenital genetic and acquired iatrogenic factors. Evidence suggests that former family members with dementia might cause decedents to get
AD [17], and 60%–80% of that risk of AD comes from congenital inheritance, most commonly caused by the APOEε4 allele [18]. Similarly, another study showed that family history of dementia increases the risk of AD. By analyzing four prospective data on AD and family history of dementia, it came across to this fact [19]. Recent evidence has shown that a high-fat diet may contribute to the pathogenesis of AD by increasing the plasma levels of saturated free fatty acids, while accelerating the pathological process of AD. After that, such development would subsequently promote the development of AD by affecting blood lipid levels. As a result, this leads to the production of large amounts of fat and causing chronic inflammation, with the production of inflammatory factors that cross the blood-brain barrier. Thus neuroinflammatory cells would be stimulated. The high-fat food affects the intestinal flora, which in turn affects the microbiota-brain-gut axis, leading to the development of AD [20]. In contrast, severe head trauma has also been reported for having greater risk for AD, especially within 6–24 months after sustaining a traumatic brain injury (TBI) when the risk may have peaked [21]. Gender may also be a risk factor for AD, as follicle-stimulating hormone is no longer suppressed after menopause in aged women, increasing dramatically to ten- to ten-fold. In contrast, an increase in men of the same age group would only suffer an increase of two- to three-fold. The dramatic increase in follicle stimulating hormone binds to receptors on the surface of neurons in the brain and activates the C/EBPβ/AEP pathway in the brain, leading to the development of AD. This in turn leads to a conclusion that women are being more at risk for AD [22].

3.4. Sleep disorders exacerbated by AD

The research on how sleep disorders exacerbated by AD had already started long ago. For instance, a report from Spain 08’ came to a fact that about 35.1% AD patients had sleep disorders [23]. Another study set an observation group of 40 patients with AD and compare to control group consist of 40 healthy counterparts for the assessment of sleep status. Results showed that the former has a higher PSQI, concluding that patients with AD have poorer sleep quality and have diverse clinical features [24]. This proved the fact that AD do cause sleep disorder.

3.5. Summary

A large number of experiments have been conducted to discover the causal relationship between AD and sleep disorders. Sleep disorders would be exacerbated by AD, while AD would affect sleep disorder as well. Therefore, it is reasonable to assume that AD and sleep disorders has the causality relation between them. Due to the limitations of current uncertainty of experimental studies and various other factors, it is still unclear whether healthy people develop Alzheimer’s disease or sleep disorders first. However, as it’s evidenced by the various experiments mentioned above, multiple causes can lead to both sleep disorders or AD in healthy people, and thus may enter a vicious circle between the two.

**Figure 1.** Factors contributing to sleep disorders and AD as well as the causal cycle between them
4. Mechanisms associated with AD induced by sleep disorders

4.1. β-amyloid hypothesis

The β-amyloid hypothesis, an important hypothesis supported by experimental results, states that the pathogenesis of AD is influenced by the interaction between β-amyloid (Aβ) and amyloid precursors [25]. Experiments have come to a conclusion that, Aβ can result in decreases in neuron cells in human brain as it shown in Fig. 2[26]. A certain amount of reports has shown that sleep disorders can affect Aβ levels in the brain to some extent. One study has confirmed for the first time a U-shaped relationship between nighttime sleep duration and AD pathogenesis at the biomarker level, which is, both insufficient or excessive sleep promote abnormal Aβ deposition in vivo. Furthermore, this experiment found that daytime dysfunction also promotes abnormal amyloid deposition in the body, and further increases in dose led to the conclusion that the optimal nighttime sleep duration was between 5.6 and 7 hours, and that the risk of AD is significantly higher if the nighttime sleep duration is less than 4 hours or more than 10 hours [27]. A more recent study had found that there is a specific microglia in the brain that are regulated by a circadian rhythm to dissolve Aβ, but the rate of dissolve is affected when the biological clock is disrupted [28].

4.2. Abnormal Phosphorylation of Protein Tau

The hypothesis of abnormal phosphorylation of protein tau is another hypothesis that has been extensively demonstrated experimentally, mainly due to the formation of intracellular Neuronal Fiber Tangles (NFT) due to hyper-phosphorylation of protein tau affecting the AD pathology [29]. It has been suggested that phosphorylation and total amount of Protein tau in human cerebrospinal fluid (CSF) are essential to distinguish AD patients from those with mild cognitive decline [30-31], and it has been reported that the toxic effects of Aβ need to be mediated by Protein tau [32]. Multiple experiments proved that sleep disorders were associated with this mechanism, one was conducted using rats as experimental subjects, founding that the amount of Tau protein in their cerebrospinal fluid fluctuated with sleep pattern, decreasing when asleep and multiple by two when awake. As such, in the following experiment, rats were kept awake for one night, and the experimental results revealed an increase of more than 50% in Protein tau level of their cerebrospinal fluid and a significant increase in Aβ [33]. It has also been reported that Protein tau levels in sleep-deprived rats were twice as high as in well-rested rats, suggesting a correlation with sleep duration as well [34].

4.3. Summary

Although the pathological mechanism of AD is not yet clear, the mainstream theories include the β-amyloid hypothesis and the tau protein abnormal phosphorylation hypothesis. From the two parts above, it can be seen that both Aβ and tau proteins can affect the course of AD to some extent, and sleep disorders can promote the abnormal deposition of both, thus greatly increasing the risk of AD pathogenesis.
5. Therapies for sleep disorders induced by AD

5.1. New Pharmacological Therapy

5.1.1. Trazodone

In a general sense, Trazodone is considered a multifunctional drug with dose-dependent pharmacological effects [35]. Although trazodone is internationally defined as an antidepressant, it is often used to improve sleep. Fig. 3 shows the difference of certain receptors of 5-hydroxytryptamine on the postsynaptic nerve membrane status between before and after the use of trazodone. A trial was conducted to study the efficacy of a dose if 50mg Trazadone by applying to 30 subjects diagnosed with AD and sleep disorders, and the results showed that two-thirds of patients perceived sounder sleep during the trial, thus providing preliminary evidence that AD patients with sleep disorders can benefit from Trazodone [36], and because Trazodone is well tolerated [37], none of the subjects showed cognitive impairment in or after two weeks [36]. Another trial also compared Hamilton Anxiety Scale (HAMA), Hamilton Rating Scale for Depression (HAMD) and PSQI scores and patients’ internal satisfaction with treatment, as well as the incidence of adverse effects, between 76 subjects with sleep disorders induced by AD before and after treatment in both groups. After three months, the former was better than the control group and the latter was lower than the control group, concluding that Trazodone has a good improvement effect on patients with sleep disorders induced by AD [38]. As such, Trazodone can be used to address AD through relieving sleep disorder.

Figure 3. The difference of certain 5-hydroxytryptamine receptors’ on the postsynaptic nerve membrane status between before and after the use of trazodone[39]

A. Stage 1: When the presynaptic nerve sends a signal, 5-hydroxytryptamine molecules enter the synapse and flow to receptors on the surface of the postsynaptic nerve. Upon contact, the nerve is stimulated, thus sending a nerve signal.

Stage 2: The 5-hydroxytryptamine molecules flow back to the presynaptic nerve where they will be drawn into the nerve by the reuptake pump.

Stage3: Upon entering the nerve, MAO will destroy them one by one.

B. Trazodone inhibits the 5-hydroxytryptamine receptors on the postsynaptic nerve. After the presynaptic nerve sends a signal, the 5-hydroxytryptamine molecule is unable to stimulate the postsynaptic nerve.
5.1.2. Midazolam Maleate Tablets

Midazolam maleate tablets, as a drug for the treatment of sleep disorders and insomnia, have been widely reported to improve the self-care ability and mental status of patients with AD with sleep disorders, to enhance their sleep quality, and also to treat the inflammatory response of the body. The drug is a short-acting maleate salt benzodiazepine sedative-hypnotic midazolam, and the mechanism is shown in Fig. 4. In one of the studies, 40 patients with AD with sleep disorders were treated with Donepezil Hydrochloride tablets, and the observation group was treated with Midazolam Maleate tablets, and the results were better than the control group in terms of Activities Daily Living (ADL) and PSQI scores [44]. The results showed that the PSQI, HAMA and HAMD scores were significantly lower in the observation group than in the control group (P<0.05), while the ADL scores were significantly higher than in the control group (P<0.05). In conclusion, Midazolam Maleate tablets do have some efficacy in the treatment of patients with this disorder.

![Figure 4](image)

**Figure 4.** Mechanism of how maleate salt benzodiazepine sedative-hypnotic midazolam affect

Midazolam maleate tablets are a benzodiazepine (BZ) drug, which interacting mechanism is, first binding to the BZ receptor of the α subunit, then changes the conformation of the receptor protein and promotes the binding of GABA to the GABAA receptor on the β subunit, increasing the frequency of Cl-channel opening, resulting increases in Cl- inward flow and cell hyperpolarization, thus producing postsynaptic inhibition.

5.1.3. Gardenia Jasminoides and Gardenia Citrusaurantium Capsules

Gardenia Jasminoides and Gardenia Citrusaurantium can be made into medicines which improve digestion system, strengthen the spleen, liver, inner cycle, respiratory system and relieve depression. They are considered to have great value in the dietary treatment of patients with sleep disorders induced by AD and clinical application. A recent study was to construct a pathological model of patients with sleep disorders induced by AD and mild anxiety. The experimental results confirmed that the three capsule made from Gardenia Jasminoides and Gardenia Citrusaurantium improved the learning and memory function, mental status and pharmacological efficacy in the treatment of the disease [43]. Previous experiments on mice [44] and fraction on the raw material of Gardenia Citrusaurantium [45] have also confirmed that it helps improve memory loss and sleep disorders, and has good preventive and curative effects on the development of AD disorders.

5.2. Non-pharmacological Therapy

5.2.1. Acupuncture Therapy

Traditional Chinese Medical (TCM) treatment includes not only bitter herbs, but also an acupuncture therapy and moxibustion therapy. One study reported that acupuncture therapy in TCM can improve dementia and improve sleep quality in patients with sleep disorders induced by AD. In this experiment, 90 patients with sleep disorders induced by AD admitted as subjects were randomly divided into two groups, and the experimental observations showed that patients treated with acupuncture were less likely to have sleep disorders than the control group, thus providing some valid evidence that acupuncture treatment is effective for this group of patients [46]. There are also
experiments done by comparing acupuncture combining with western medicine therapy with pure western medicine therapy, and it was concluded that acupuncture combining with western medicine is indeed effective in the treatment of Alzheimer's disease [47]

5.2.2. Phototherapy

Numerous studies have suggested that light therapy may be effective on patients with sleep disorders induced by AD, and it has been suggested that effective improvement in community-dwelling AD patients may consist of a combination of both walking and light [48]. Experiments have also been conducted to observe the clinical efficacy and safety of full-spectrum therapy with different light durations in certain groups of patients. 127 patients with AD with sleep disorders were treated with 10,000 lux full-spectrum light therapy for 1 month. After that, they scored with the Pittsburgh Sleep Quality Index Scale (PQSI), the Simple Mental Status Scale (MMSE), the General Decline Scale (GDS) Epworth Sleepiness Scale (ESS), and the Neuropsychiatric Questionnaire (NPI). Later it was concluded that light therapy was effective in improving sleep quality, excessive daytime sleepiness, neuropsychiatric symptoms in AD patients with an optimal light duration of 120 min. No adverse effects were observed [49].

5.3. Prospects and effectiveness of therapies

A recent study has shown that the risk of getting a dementia is more than twice as high in people who sleep less than 5 hours a day, and it had also suggested that treating sleep disorders might be a potential treatment for AD and reduce the risk of death [50]. Several experiments cited above in this paper suggest a correlation between sleep disorders and AD. Therefore, the development of such therapies can both treat sleep disorders and alleviate AD, which is a win-win.

In addition, the biomarkers for the development of AD are not yet clear, but the clinical features of sleep disorders, such as insomnia and dreaminess, are well known and can be effectively prevented if treated in a timely manner, it can be predicted that the future of these therapies is promising and effective.

6. Conclusion

AD patients worldwide generally have sleep disorders, but drug development is particularly difficult. From 1998 to 2017, drug development for the disorder has failed 146 times, with a mere 2.7% success rate, which is, 4 drugs were approved [51]. The major problem is that the causative mechanism of AD is still not fully understood. A large number of studies mentioned above have shown that AD and sleep disorders are inextricably linked, and people can start from this point and to further clarify the causal relationship between two and find a better angle for drug development aiming to alleviate the symptoms of AD patients in the future.

Firstly, it is crucial to find accurate biomarkers. Currently, drug treatment is limited to the early and middle stages and is difficult to cure. If accurate biomarkers are found, early stage intervention and remission of the disease can be achieved.

Secondly, it is important to understand how individual can improve one’s sleeping quality. Efficient sleep can minimize the deposition of Aβ and Protein tau in the body, decreasing the risk of getting caught by AD.

Finally, the need for discovering new pathogenic mechanisms is urgent, and the 2.7% success rate of AD drug development over 20 years reflects the difficulty of research, and some of them still cause serious side effects, while the clinical trial results of drugs targeting β-amyloid show that their clinical efficacy is not obvious. GV-971 is a pioneer in the development of drugs that use neuro-inflammation induced by intestinal flora disorders as an important pathogenesis of AD as an entry point [52]. Thus, it is clear that by turning around and exploring new pathogenic mechanisms, more research directions may be opened up, such as for sleep disorders, providing more possibilities for drug development.

With the rapid development of the biomedical industry, the continuous research on the causative mechanism of AD and the failure and success of drug development have provided more points and
entry points for later research, and it can be believed that the future of AD sleep disorders treatment is still very broad.

REFERENCES


