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Melatonin and Sleep Disturbances in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by sleep, behavioral, memory, and cognitive deteriorations. Sleep disturbance (SD) is a major disease burden in AD which has a reciprocal relationship with AD pathophysiology. It aggravates memory, behavioral, and cognitive complications in AD. Different studies found that melatonin hormone levels reduce even in the pre-clinical stages of AD. Melatonin is the primary sleep-regulating hormone and a potent antioxidant with neuroprotective roles. The decrease in melatonin levels can thus promote SD and AD neuropathology. Exogenous melatonin has the potential to alleviate neuropathology and SD in AD by different mechanisms. Various studies have been conducted so far that assessed the efficacy of exogenous melatonin to treat SD in AD. Though most of the studies suggest that melatonin is useful to ameliorate SD in AD, the remaining studies show opposite results. The timing, dosage, and duration of melatonin administration along with disease condition, genetic, environmental, and some other factors can be responsible for the discrepancies between the studies. More extensive trials with longer durations and higher dosage forms and studies including bright light therapy and melatonin agonists (ramelteon, agomelatine, and tasimelteon) should be performed to determine the efficacy of melatonin to treat SD in AD.

Keywords: Melatonin, Alzheimer's disease, sleep disturbances, melatonin receptor agonists

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease which is featured by continuous damage of memory and cognitive performance along with sleep and behavioral disorders [1, 2]. The etiology of AD is mostly unknown; however, senile plaque formed by amyloid beta (AB) peptide deposition and intracellular neurofibrillary tangles formed by abnormally hyperphosphorylated microtubule-associated protein tau are some neuropathological hallmarks of AD [3]. Oxidative damage of neurons and synapses [4], reduced and irregular melatonin secretion [5, 6], genetic susceptibility (*i.e.,* expression levels and sub-forms of apolipoprotein (*Apo*) E, presenilins (*PSEN1* and *PSEN2*), amyloid precursor protein (APP), orexin receptor genes (*Bmal1, Npas2,* and *PER1*) [6-9], reduced ApoE clearance from the brain extracellular space (ECS) [10], circadian metabolic dysfunction [7], impaired insulin signaling [11], cholinergic system insufficiency [6], hippocampal and posterior parietal cortical blood flow reduction [7], regional atrophy [12], mitochondrial loss [13], inflammatory cytokine releasing [6], alteration of neurotrophin function on related tyrosine kinase receptors [13], and exposure to metal ions [14] may be some pathophysiological causes of AD. AD is the most common neurodegenerative disease with women being highly prevalent [12, 15]. Based on the updated data, there are more than 44 million dementia patients currently, and the number is projected to be more than triple by 2050 [16].

Melatonin is a chronobiotic and cytoprotective hormone, reduced level and diurnal rhythm of which have been found even in primary stages of AD [6]. It has been suggested that the loss of melatonin and its circadian rhythmicity is primarily responsible for SDs in AD and thus exacerbation of various AD complications [6]. Sleep is critical for brain

functioning and neuroprotection [17]. Thus, disruption of sleep can hamper memory, behavior, and cognitive function which are observed in patients with AD [18]. SDs include both sleep architecture alterations and circadian rhythm sleep disorders (CRSDs) [19]. Other AD symptoms and pathologies worsen with the increment of SDs [20]. SDs are also related to cardiovascular and respiratory problems, reduced immune activity, and physical and mental disabilities [21]. SDs are the primary reasons behind the institutionalization of AD patients [21, 22]. So, treating SDs may be a prime concern to reduce AD complications [5]. As SDs are apparently correlated with melatonin insufficiencies in AD [20], it is hypothesized that treating AD patients with exogenous melatonin might reduce sleep complications of the patients [23]. Different studies have been done so far to determine whether exogenous melatonin can reduce SDs in AD.

This paper aims to critically review the outcomes of the studies on exogenous melatonin treatments on SDs in patients with AD and the possible reasons behind the discrepancies between the findings. Besides, we have critically discussed the properties and mechanisms of melatonin, its insufficiency in AD, SDs in AD, and possible mechanisms through which melatonin can reduce SDs in patients with AD.

METHODS

We searched PubMed, Scopus, and Google Scholar databases in a systematic way using appropriate keywords associated with melatonin, Alzheimer's disease, and sleep disturbances. The last search was performed on 30 June 2020.

MELATONIN AND ITS SLEEP-PROMOTING EFFECTS

Melatonin (5-methoxy-N-acetyltryptamine) is a sleep regulatory hormone that is mainly synthesized in the parenchymatous pinealocytes of the pineal gland (PG) from tryptophan through serotonin in response to photic sensation obtained through the retino-hypothalamic pathway [24-26]. It can also be synthesized in other areas than PG in the brain and other organs and found in some foods as well [26, 27]. But extrapineal melatonin cannot substitute the activities of pineal melatonin [20]. Melatonin has both chronobiotic and cytoprotective effects [28]. Melatonin can exert its effects either as a hormone by binding with specific receptors in cell membrane and nucleus or binding with intracellular proteins (*i.e.*, calmodulin, dihydronicotinamide riboside:quinone reductase 2, and tubulin-associated proteins) or as a powerful antioxidant by activating the intracellular antioxidant system and chelating reactive oxygen species (ROS) and reactive nitrogen species (RNS) [24, 26]. It indirectly enhances gene expression of antioxidant enzymes and suppresses gene expression of prooxidant enzymes [29]. It has a broad diversity of physiological roles in the regulation of sleep-wake rhythm [11], mood [30], body temperature [31], cortisol secretion [31], immune activity [30], mitochondrial function [7], energy homeostasis [31], sexual maturation [30], cytoprotection [7], blood-brain barrier (BBB) protection [11], antioxidant activity [30], biogenesis [7], epigenetics [31], cardiovascular functions [30], prevention of insulin resistance [11], and neurodegenerative disorders [31].

Circadian rhythm adjustment, sleep initiation, and sleep maintenance are the primary roles of melatonin and it is used to treat different chronobiological disorders like insomnia, desynchronized sleep-wake rhythm, SDs because of blindness, jet lag, and shift work [32]. The circadian rhythm is regulated by the suprachiasmatic nucleus (SCN)

of the anterior hypothalamus via the retino-hypothalamic pathway [30, 33]. The pathway is shown in Fig. 1. Photic and time-related information is transduced to the PG from the retina via SCN and the superior cervical ganglion (SCG) of the sympathetic nervous system [9, 25]. The SCN remains activated because of light input in the retina during the light phase (day) and inhibits melatonin secretion by PG as the SCG activity is suppressed by light stimulation [25, 30]. At the dark phase (night), SCN becomes inactivated [30]. The superior cervical region nerve terminals secrete noradrenaline, which activates β receptors on the PG and promotes the secretion of melatonin. Arylalkylamine N-acetyltransferase converts serotonin to N-acetylserotonin, and then Hydroxyindole-O-methyltransferase converts N-acetylserotonin to melatonin [25]. Melatonin production can be inhibited mainly by night-time light exposure through pineal N-acetyl transferase degeneration [7]. The secretion of melatonin also follows a circadian rhythm in the absence of light both in normal and blind individuals [10].

Melatonin is secreted into the third ventricle and then in the circulation [18]. The night-time melatonin secretion initiates about 2 hours before a person's habitual bedtime and it can be measured by dim light melatonin onset test [9, 30]. Generally, the secretion starts at around 9 – 10 PM, plasma melatonin level peaks at around 12 PM and 3 AM (80-120 pg/ml), and falls to the minimum at around 7 – 9 AM (10-20 pg/ml) [27]. The melatonin levels in CSF and hypothalamus are about 30 times and 50 times higher respectively than the melatonin level in the blood [5].

Melatonin induces sleep by different complex mechanisms. It is proposed that melatonin induces sleep by suppressing circadian wakefulness producing mechanisms [24]. Apart from its effect on circadian regulation, it has a direct sleep-promoting effect.

Human melatonin binding receptors MT1 and MT2 (both G protein-coupled receptors) work differently to induce sleep [30]. MT1 decreases neuronal firing rate and MT2 exerts a phase-shifting effect [34]. The receptors are expressed in SCN, hippocampus, hypothalamus (particularly in the paraventricular and supraoptic nucleus), occipital cortex, substantia nigra, and ventral tegmental area [25, 35]. The areas are shown in Fig. 1. MT1 prevents firing in SCN slices and MT2 (also MT1) contributes to phase shifting in the slices [35]. These findings suggest that SCN is the primary target of the phase-shifting effects of melatonin [24, 35]. Moreover, MT1 receptors were found co-localized with the part of the vasopressin expressing neurons in the SCN, suggesting that these neurons are involved in the effect of melatonin in the SCN [21].

Both MT1 receptors and mRNA and only MT2 mRNA had been found in the dopaminergic system [25, 35]. Melatonin can also act in adjunction with gamma-aminobutyric acid (GABA) receptors in the cerebral cortex. Both MT1 and MT2 receptors differentially regulate the retino-hypothalamic signaling via modulation of dopaminergic and GABAergic transmission [24, 35]. The phase-shifting effect of melatonin is exerted by its direct effect on the metabolic and electrical function of the SCN, apparently including mechanisms related to aminobutyric acid [36]. Melatonin induces fatigue by inhibiting default mode network (DMN) connectivity and promotes sleep-related changes by attenuating activation of the precuneus [18]. Melatonin mainly promotes non-rapid eye movement (NREM) sleep in the elderly [13]. It also induces slow-wave sleep (SWS) [10].

Melatonin administration was found to induce sleep in healthy individuals in different studies. Its administration during the day promotes daytime sleepiness [24]. The administration of melatonin was found to synchronize sleep-wake cycles in both sighted

and blind individuals. Circadian sleep disorders like jet lag, delayed phase sleep syndrome, or shift-work are also treated successfully by melatonin [24, 34, 36]. Melatonin was found to improve sleep outcomes and sundowning in elderly patients with insomnia, dementia, depression, and mild cognitive impairments in different studies [5, 13, 34]. Sundowning syndrome is characterized by a night-time exacerbation of disruptive behavior such as aggressiveness, anxiety, agitation, hallucinations, confusion, wandering, and mood swings in the evening, and it is associated with CRSD, phase-delay of body temperature, and night-time SD of AD patients [9, 21, 30].

Two common oral dosage forms of melatonin are available: the immediate-release (also called fast-release) form and the prolonged-release (also called extended-release, slow-release, sustained-release, and controlled-release) form. Sometimes different combinations of the two are also used. When treated with prolonged-release melatonin (PRM), the melatonin level remains elevated in blood for a more extended period than treated with immediate-release melatonin (IRM). For the same dose of melatonin, the C_{max} (highest concentration in blood) value is higher and the T_{max} (time to reach C_{max}) value is lower for IRM than PRM [37, 38].

In various studies, 2 mg PRM was found effective in improving sleep quality (SQ) in insomnia patients [27]. Melatonin receptor agonists ramelteon (which has a high affinity for MT1 receptors) and tasimelteon were also found to be effective drugs to treat different types of sleep disorders and improve various sleep outcomes in different studies, though they exhibit hepatotoxic activity [5, 27]. Another high-affinity melatonin agonist, agomelatine was found effective in treating insomnia and improving other sleep outcomes in patients with depression [25]. Inhibition of melatonin synthesis (*i.e.,* treatment with β-

blockers) can induce insomnia. Conversely, enhancement of plasma melatonin levels by inhibiting liver melatonin metabolizing enzymes can induce sleepiness [24].

ENDOGENOUS MELATONIN IN ALZHEIMER'S DISEASE

Reduced melatonin production along with SD is frequently pronounced in patients with AD [18]. In many studies, reduced night-time melatonin levels in CSF, PG, serum, saliva, and urine and impairment of diurnal rhythm of melatonin have been found to be correlated in patients with AD when compared to age-matched controls [6, 12, 20, 21, 39]. On the other hand, increased daytime melatonin level was found in AD patients [40]. AD patients may contain only 20% of normal melatonin levels in their brain CSF [41]. Melatonin levels are negatively correlated with the acuteness of AD and reciprocally the reduction of melatonin exacerbates the disease [12, 28]. Decreased CSF melatonin levels are found in preclinical stages of AD when patients don't exhibit any cognitive symptom (at Braak stages I-II of AD) indicating that lowered melatonin levels in CSF can be a primary marker and trigger for AD [39]. The melatonin precursor serotonin is also found decreased in the preclinical stages of AD [30].

In AD, the calcification of PG occurs when calcareous deposits (hydroxyapatite) are formed within the connective tissue of PG stroma due to environmental factors like sunlight exposure. This results in decreased PG activity and size and decreased melatonin production which leads to SD [42]. Dysfunction of PG suppresses melatonin production, promotes SD, induces neuroinflammation and unusual immune response, and interrupts vascular homeostasis. It was found that AB associates with toll-like receptors in PG of AD patients and inhibits melatonin production [20]. Senile plaque and

neurofibrillary tangle formation, increased astrocyte/neuron ratio due to astrogliosis, and neurodegeneration due to increased oxidative and inflammatory stress in SCN can deteriorate this area [9, 19]. A reduced number of neurons were found in the SCN of AD patients [39]. With the degeneration of SCN cells, desynchronization in oscillation occurs between brain regions such as the cingulate cortex, the bed nucleus of stria terminalis, and the PG [8]. The SCN innervation to the PG and the signaling mechanism between them were also found disrupted in patients with AD [30, 40]. As a result, the diurnal expression of clock genes and their interrelations are lost [30]. The superior cervical ganglia and the noradrenergic fibers in the PG were found to have swollen axons in AD patients [40]. As the disease progresses, the circadian rhythm of melatonin secretion drops out and becomes extremely irregular [8, 30, 40]. Though extrapineal secretion of melatonin is greater than pineal secretion of melatonin, it cannot replace the neuroprotective functions of pineal melatonin [20].

In the clinical and pre-clinical stages of AD, the daily rhythm of β1-adrenergic receptor mRNA in the pinealocytes was found died out indicating a disordered noradrenergic regulation of SCN melatonin production [21]. Also, upregulated expression and activity of monoamine oxidase A was found in the PG of AD patients which might diminish melatonin precursor serotonin. In addition, a higher 5-hydroxyindole acetic acid/serotonin ratio is found in PG of AD patients [43]. These changes might be responsible for decreased melatonin production and disturbed melatonin rhythm [21, 43].

In AD patients, the expression of MT2 melatonin receptors was found downregulated in the hippocampal, pineal, and cortical regions [18, 20]. The expression of MT1 receptors was found reduced in SCN, pineal, and cortical areas, parallelly with

the reduction of melatonin, exacerbating the severity of SD in AD patients. MT1 mRNA was found increased in the hippocampus and neocortex of advanced AD patients likely to compensate for reduced melatonin levels [18, 27]. The number of MT1 expressing neurons was found greatly reduced in the last neuropathological stages of AD (Braak stages V-VI) however, not in the primary stages (Braak stages I-II) [21]. Alterations of MT1 and MT2 receptors' expressions were found in postmortems of AD brains [12].

The ApoE-Ɛ4/4 allele is the greatest known genetic risk factor for early-onset and late-onset AD and 15-20% of AD events are related with this allele [7, 24, 30]. The allele is linked with an increased AB toxicity and quicker disease advancement [13]. Homozygous patients for the allele are found to have the lowest levels of melatonin [30]. A risk variant of melatonin receptor type-1A (MTNR1A) gene (*i.e.*, rs12506228A) located downstream of MTNR1A can be responsible for intolerance to shift work and development of AD at old age. The polymorphism is responsible for reduced MTNR1A expression and thus decreased MT1 receptor amounts in the brain. This subsequently leads to CRSD and AD pathology and shift work increases the risks of these disorders [44].

SLEEP DISTURBANCE IN ALZHEIMER'S DISEASE

Description of sleep disturbance in AD

Various studies indicate that SD and AD pathology have a bidirectional relationship [8]. Disruption in both the sleep-wake cycle and sleep architecture is seen in AD [45]. Sleep disturbances usually increase with age because of CRSD, in addition to reduced and irregular melatonin secretion [28]. Around 50-80% of people over 65 years of age

experience some form of SD [21]. The prevalence of SD in AD patients was estimated to be 25-66% [20].

Conversely, a systematic review and meta-analysis demonstrated that people with SD have 1.49 – folds high risk of developing AD compared to people without SD [46]. CRSD and delayed acrophase are considered as the risk factors for developing AD in elderly individuals [47]. AD patients exhibit a higher level of disturbance in the sleep-wake (circadian) rhythm compared to age-matched controls [48]. A number of overt rhythms such as body temperature, concentrations of various hormones (*i.e.*, melatonin, cortisol, glucocorticoids, vasopressin, testosterone, β-endorphine, dehydroepiandrosterone, and pulsatile luteinizing hormone) are disrupted in AD [21, 39]. Serum cortisol levels are found significantly higher at night in AD patients which can be associated with sleep-wake cycle disturbance and cognitive dysfunction [21]. The SDs in AD are sometimes so serious that they can be categorized as chronic insomnia or primary comorbid sleep disorder [49]. SD exacerbates AD pathology [20] as it is correlated with memory, behavioral, and cognitive disorders in AD [18]. The most noticeable sleep disorders are correlated with more acute dementia and cognitive impairment [8, 50]. The Combination of dementia and depression can exhibit more severe SD than dementia alone. AD patients exhibited a higher percentage of night-time sleep when their depression level was low [33].

Yesavage *et al.* [51] proposed criteria to distinguish SD in AD. According to the criteria AD sleep disorders are characterized by insomnia and/or exceeding daytime drowsiness that are later ascertained by actigraphy, polysomnography (PSG), or sleep record. Sleep disorders should involve at least two of these: decreased total sleep time

(TST), increased wake after sleep onset (WASO), bad daytime wake continuation, and desynchronization of sleep-wake rhythm.

Both primary SDs and circadian rhythm disruptions are seen in AD. Primary SDs include insomnia, increased sleep latency, decreased TST, nocturnal sleep fragmentation with frequent awakenings and prolonged awake time, reduced rapid eye movement (REM) sleep, early morning awakenings, and too much daytime sleepiness with augmented napping and unintended sleep periods. Circadian rhythm disruptions include phase delay of night-time sleep, reversed circadian pattern, and sundowning behavior [30]. Sleep fragmentation is the most common sleep problem in AD which is found in 30-50% of the patients [52]. Complete reversal of day/night sleep pattern can be seen in extreme cases of AD [49]. Reduced sleep efficiency (SE, the ratio of TST to total time in bed) and TST, increased sleep latency and WASO time, and a higher number of awakenings is detected in AD patients by actigraphy and PSG [53]. Increased number of awakenings results in reduced REM and deep sleep [33]. Increased sleep latency and WASO time can cause TST reduction, night-time agitation, and daytime somnolence. Daytime napping was found correlated with the intensity of cognitive dysfunction and dementia [19, 33]. Actigraphy results also showed decreased inter-daily stability, higher intra-daily inconstancy, and reduced comparative magnitude of the rest-activity rhythm in AD dementia patients. A reduction of cyclic alternating pattern rate, a scale of sleep resilience, was found connected with cognitive degeneration of AD patients. It was found that moderately demented AD patients exhibit more disturbed sleep than advanced level patients [8].

Disturbance of SWS (third stage of NREM sleep, deep sleep) is observed in AD which is correlated with higher AB levels and deposition of AB might disrupt the SWS generation [7, 53]. During sleep, especially during SWS, the connectivity within the DMN is diminished. Poor SQ increases DMN connectivity and activation of precuneus, leading to increased AB production and accumulation in these areas which induce neurodegeneration in AD [18]. AD patients sometimes also show REM sleep behavior disorder (RBD) in conditions of mixed neurodegenerative processes [50]. According to some studies, REM sleep remains unhampered during primary stages of AD but begins to deteriorate at advanced stages [7]. Sleep-related breathing disorders (SRBDs) are common in AD and can be a causative factor of AD [49]. These disorders can be caused by obstructive sleep apnea (upper airway obstruction), central apnea (temporary ventilatory effort loss), or aggregation of both [33]. 40-70% of AD patients experience different levels of obstructive sleep apnea syndrome (OSAS). AD may damage the respiratory center of the brain to cause OSAS and reciprocally OSAS may induce neuron damage because of hypoxia and sleep fragmentation [50]. Sleep architecture is disrupted by apneas which leads to decreased SWS and REM sleep and increased awakenings [49]. Sleep apnea is frequently correlated with daytime drowsiness and restless sleep because of increased night-time awakenings [33]. SRBDs can be associated with cognitive and memory dysfunctions in AD patients. 6-24% of the AD patients suffer from restless leg syndrome (RLS) and RLS can be correlated with cognitive impairment [19]. RLS can also worsen sundowning [47]. 80% of the AD patients with RLS experience

periodic limb movement disorder [19]. Different types of SDs observed in AD are depicted in Fig. 2.

Diurnal motor activity and temperature were found higher during the night in AD patients. In AD patients, delayed sleep-wake phase dysfunction can be found in most cases [9]. In AD patients with phase delay, sleep onset occurs later than most people and waking up in the morning becomes harder for them. AD patients with both phase delay and frequent night-time awakenings can experience extreme daytime sleepiness [33]. In advanced stages of AD, the core body temperature cycles are significantly delayed. The phase difference between core body temperature cycles and rest-activity is a CRSD seen in advanced stages of AD [13].

The delta frequency power as measured by electroencephalogram (EEG) does not reduce dynamically across NREM/REM sleep cycles in AD dementia patients. The patients showed decreased slow delta waves and increased fast delta waves compared to controls [8]. During post-learning sleep, in both SWS and REM sleep, faster mean theta frequency has been observed in AD patients compared to age-matched controls [19]. A selective reduction of fast spindle number and density was also found in AD patients in different studies that interrelated with cognitive status. A progressive slowing of EEG in both REM sleep and wake was detected in AD dementia patients which increased with disease advancement [8]. Significant reduction of K-complex density, which is a distinctive feature of NREM sleep, was also seen in fully developed AD [7, 8].

Causes and pathophysiological changes underlying sleep disturbance in AD

AB deposition, tau pathophysiology, oxidative stress, inflammation, dysfunction of insulin system, and circadian neurodegeneration can cause CRSD in patients with AD [7]. Sleep deprivation generates oxidative damage, neurodegenerative inflammation, mitochondrial dysfunction, abnormal enzyme activation, and impaired proteasomal processing [5]. Neurodegeneration is associated with SD due to the loss of magnitude and phase alterations of circadian rhythms such as secretion of melatonin. Neurodegeneration has an impairing effect on sleep and reciprocally SD exacerbates neurodegenerative processes [10].

Sleep quality and duration are correlated with AB concentration in CSF and interstitial fluid (ISF) [54]. Chronic SD significantly increases AB plaque formation in the hippocampus and conversely, AB amount decreases with increased sleep time [55]. Brain metabolites (*i.e.*, lipids and large proteins) accumulated during the day are removed from CSF to ISF via the glymphatic system, mostly active during sleep [50]. In AD, the activity of glymphatic system becomes impaired leading to deposition of α-amyloid, AB, and tau [50, 54]. Conversely, SDs, especially reduced SWS and increased wakefulness inhibit glymphatic activity and aggravate AD complications [18]. AB and tau protein dynamics are also altered because of impairments in the orexinergic (aka hypocretinergic) system and vice versa [54, 56]. Orexins are neurotransmitters that promote wakefulness [56]. In AD patients, reduced CSF orexin levels are found in the daytime which promotes daytime sleepiness and increased orexin signaling is found at night-time which promotes night-time SD [57]. Higher orexin levels are correlated with higher AB and tau in CSF of AD dementia patients [8]. Amyloid plaques and tau tangles are found in the hypothalamus, locus coeruleus, and the regions of the cortical layer of the brain which are critical for

sleep-wake cycle regulation [56]. SD may raise AB and tau levels in ISF also by increased exocytosis and synaptic activity [54]. AB accumulation induces tau hyperphosphorylation and conversely, this toxic tau increases AB toxicity by a feedback loop [8]. So, SD is linked with increased AB and tau deposition by a vicious circle where the two factors intensify and aggravate each other, leading inexorably to a worsening of AD complications. SD also exacerbates neuroinflammation potentially, reduces cAMP signaling by increasing PDE4 activity, and misregulates cofilin signaling. All of these promote AD progression [54, 56]. SD also suppresses apolipoprotein E clearance from brain ECS and promotes AD complications [10]. Decreased glucose uptake in the hypothalamus can also promote SD in AD [20].

The ApoE-Ɛ4/4 allele is found to be a genetic risk factor for SDs like obstructive sleep apnea and hypopnea, and decrease of REM sleep, though some studies detected conflicting results [19, 49]. Altered expression of clock genes can cause CRSD in AD. The rhythmic diurnal expression of clock genes (*hPer1, hCry1,* and *hBmal1*) and positive correlation between *hPer1* and *hb1-ADR* mRNA were found diminished in both pre-clinical and clinical AD stages [21]. Disrupted monoamine oxidase A promoter polymorphism is found in postmortem of AD patients which may contribute to SD in AD patients [19].

Environmental factors like chronic bed rest, physical inactivity, night-time light exposure, overstimulation, community living arrangements, institutionalization, caregiver burden, patient's comorbidities, and lack of assistance, caregiver at night, daytime indoor illumination, and quality of social networks at nursing homes can also induce SD and CRSD in AD patients [8, 9, 19]. AD patients having interrupted endogenous pacemaker

activity may have minimized ability to synchronize rest-activity and temperature [9]. Some AD medications like cholinesterase inhibitors (*i.e.* rivastigmine) can disturb sleep [19]. Also, drugs like antidepressants, antipsychotics, serotonin reuptake inhibitors, benzodiazepines, and nonbenzodiazepine sedative hypnotics can cause SD in AD [33].

Reduction of optic nerve axons, melanopsin retinal ganglion cells, and retinal nerve fiber layer thickness and deposition of AB in the retina can also exacerbate CRSD in AD [8]. Vasopressin expressing neuron levels in SCN can be significantly decreased in AD patients [40]. It is previously discussed that SCN deterioration occurs in AD. SCN and hypothalamic dysfunction can cause CRSD in AD [9]. Disrupted input to and output from SCN can be responsible for CRSD in AD [19]. Decreased external zeitgebers (*i.e.*, light, diurnal activities) because of cognitive dysfunction and neurosensory disruptions (cataract, retinopathy, and glaucoma) can contribute to CRSD in AD [19, 40]. The decrease of vasopressin expressing neurons and vasoactive intestinal polypeptide expressing neurons in SCN can also contribute to CRSD in AD [40, 58]. Three times decreased vasopressin mRNA with unclear diurnal rhythm was found in AD patients. Vasopressin gene expression in SCN was also found reduced in early stages of AD which can be responsible for reduced CSF melatonin levels in early AD stages. Also, the density of neurotensin neurons is reduced and the number of glial fibrillary acidic protein-stained astrocytes is increased in SCN of AD patients indicating decreased SCN activity [21]. These alterations in the SCN are proposed to be accounted for disturbed melatonin synthesis and CRSD in AD [40].

In AD dementia patients, reduced galanin-immunoreactive neurons in the ventrolateral preoptic nucleus (VLPO) have been found involved in sleep fragmentation.

VLPO has a sleep-promoting function, and degeneration of these neurons can be responsible for reduced NREM and frequent awakenings in AD dementia. Early neurodegeneration of the cholinergic system of the basal forebrain, cholinergic neurons of the brainstem, and midpontine cholinergic neurons can hamper sleep regulation including REM sleep in AD patients [8]. Cholinergic signaling is of great importance in sleep regulation and loss of cholinergic neurons can be one of the causative factors of SD in AD. The introduction and maintenance of REM sleep are reliant on the functionality of the cholinergic system [52]. Cholinergic neurons are more prone to AB toxicity. Decreased levels of choline acetyltransferase are seen in the brains of AD patients [52]. Noradrenergic and serotonergic signaling systems are disordered in AD. Noradrenaline (also called norepinephrine) and serotonin monoamines are mainly produced in the neurons of the brainstem locus coeruleus and raphe nucleus, respectively [52]. Also increased monoamine oxidase A in the PG can reduce the levels of these monoamines. The degradation of these systems can contribute to decreased melatonin production, CRSD, and impaired sleep architecture in AD patients [21, 43, 52].

SD is a cause of physical and mental burden for the caregivers of AD patients and is an important reason for the institutionalization of AD patients [8]. For instance – sundowning, nightmares, and repeated arousals at night cause severe caregiver burden in AD [49].

MELATONIN THERAPY FOR SLEEP DISTURBANCE IN ALZHEIMER'S DISEASE

Melatonin is a chronobiotic, it does not primarily work like a sleeping pill. Melatonin, compared to other treatment compounds including antioxidants, has the advantage of

crossing the BBB and entering cellular compartments such as mitochondria [13]. Studies have found that melatonin is a safe drug with low toxicity. Several studies have found that melatonin treatment is effective in treating AD complications like SD, cognitive decline, and emotional performance [28]. Melatonin was also found effective in improving cognitive performance in different studies which might be due to SQ improvement by melatonin [12]. A number of different types of studies have been conducted so far to determine if exogenous melatonin treatments are useful to treat SD in AD. The outcomes of the studies are summarized in Table 1.

Open-label pilot studies

Fainstein *et al.* [59] used three groups of patients (SD alone, SD + depression, and SD + dementia) who were treated with 3 mg of melatonin. The timing and duration of the treatment are given in Table 1. There were five AD-type dementia patients in SD + dementia group. Melatonin was not effective in improving SQ, the number of nocturnal awakenings, and daytime alertness in SD + dementia (including AD type) patients, though it was effective in the other two groups. However, melatonin significantly improved the coefficient of variation of bedtime ($p < 0.03$) and sundowning syndrome in SD + dementia patients. In the study conducted by Mahlberg *et al.* [60], 3 mg melatonin was found effective in treating CRSD and sundowning in probable AD patients. The timing and duration of the treatment are given in Table 1. Five out of seven patients exhibited significant ($p = 0.018$) reduction in nocturnal activity, while diurnal and evening activity was altered differentially. Four patients remitted completely from circadian rhythm disorders or sundowning.

Randomized controlled trials

The efficacy of 6 mg PRM on SQ of AD type dementia patients with SD was measured in the study conducted by Serfaty *et al.* [61]. The duration of the treatment is given in Table 1. Melatonin failed to show any efficiency to improve TST, number of awakenings, or SE in the subjects. In the study of Singer *et al.* [62] which is considered as the largest randomized-controlled trial so far, the efficacy of 2.5 mg PRM and 10 mg IRM on sleep parameters of AD patients was measured by actigraphy and a sleep diary. The timing and duration of the treatment are given in Table 1. No significant change from baseline was observed after treatment from actigraphy data in SE and sleep disorders inventory in any group. Nonsignificant trends for prolonged night-time TST, decreased WASO time, and decline in the day-night sleep ratio was observed in the melatonin groups compared to placebo. SQ according to sleep dairy improved significantly ($p = 0.03$) in the 2.5 mg melatonin group compared to placebo. But overall findings could not detect any efficiency of melatonin in treating SD in AD patients. The authors suspected several reasons behind the negative results such as i) they might have chosen a wrong 12-hour epoch to measure sleep, ii) the subjects might have had improved sleep during one part of the night, and iii) wakefulness in another which ebbed sleep scores. Also, a larger trial might have given better results.

The efficiency of 3 mg melatonin on night-time and daytime sleep and activity of AD type dementia patients was measured in the study of Asayama *et al.* [63]. The timing and duration of the treatment are given in Table 1. Though melatonin treatment did not show any difference in daytime sleep and activity between melatonin and placebo-treated

groups, night-time TST significantly improved (p = 0.017) and activity significantly decreased (p = 0.014) in melatonin treated group compared to placebo. This indicates that melatonin can be an effective night-time sleep-promoting agent for AD-type dementia patients. Melatonin application didn't influence daytime activity in this study. It might be that the influence of melatonin on sleep-wake rhythm is less potent than morning bright light therapy (BLT). In another study [64], it was observed that 3 mg melatonin or 2.5 mg cannabinoid dronabinol can be effective in reducing nocturnal activity in patients with probable dementia of AD type and agitation. The timing and duration of the treatment are given in Table 1. The patients were divided into two groups: the verum group (received melatonin or dronabinol) and the placebo group. There were two control groups: the healthy younger subjects and the healthy elder subjects. The patients were treated for two weeks. Nocturnal activity was significantly decreased (p = 0.001) in the verum group compared to baseline. The treatment-baseline ratio of nocturnal activity was significantly reduced in the verum group compared to all other groups (p = 0.004), especially to placebo (p = 0.021). The treatment-baseline difference for the nocturnal portion of 24 h activity significantly reduced (by 16%) in the verum group (p = 0.007) compared to placebo (p = 0.012). A non-significant trend in differences in 24 h activity was found in verum group.

In the study of Dowling *et al.* [65], it was found that morning BLT (≥2500 lux for 1 hour) + 5 mg melatonin was effective in increasing daytime wake time and activity and strengthening the circadian rhythm in AD patients. The timing and duration of the treatment are given in Table 1. Daytime sleep time decreased significantly in the BLT + melatonin group compared to BLT + placebo (p < 0.001) and control (p < 0.001) groups.

A significant increase in the daytime total activity score in the BLT + melatonin group was observed compared to BLT + placebo ($p < 0.001$) and control ($p = 0.002$) groups. Day-night sleep ratio in the melatonin group improved significantly compared to BLT + placebo ($p = 0.002$) and control ($p < 0.001$) groups. In the BLT + melatonin group, a significant increase in rest-activity rhythm amplitude (parametric: compared to both control and BLT + placebo: $p = 0.002$, non-parametric: compared to BLT + placebo: $p = 0.002$), in Cosinor model goodness of fit (compared to control: $p = 0.008$), and in average activity during 10 most-active hours (compared to control: $p = 0.007$ and compared to BLT + placebo: $p = 0.003$) were also observed. Significant differences were not found in night-time sleep variables between the groups. Light treatment alone was not effective in improving any of the parameters. Some individuals might have received light during a sensitive period of their phase-response curve and others did not.

The efficacy of prolonged use of 2.5 mg medium-fast-release melatonin with day-long BLT to treat SD of elderly dementia patients (mostly AD patients) was measured in the study of Riemersma-van der Lek *et al.* [66]. The timing and duration of the treatment are given in Table 1. Nocturnal restlessness ($p = 0.01$), SE ($p = 0.01$), and duration of awakenings ($p = 0.01$) values all improved significantly in melatonin + BLT group. Melatonin alone improved sleep onset latency ($p = 0.02$), TST ($p = 0.004$), and mean duration of uninterrupted sleep periods ($p = 0.02$) significantly. The results suggested that melatonin with or without BLT has positive effects on sleep improvements of elderly dementia patients with or without AD. The authors inferred that melatonin benefits slowly and/or only in amalgamation with BLT in some individuals and improvement of sleep-wake timing system function had been related to the treatment outcomes. Though

combined treatment improved SE by 3.5%, it was not enough to get over 85% to attain clinically pertinent normal sleep. The authors suggested that to inhibit negative impacts on the mood of aged persons, the prolonged use of melatonin can only be prescribed in addition to bright light. Being cautious about the multiplicity of analyses and outcomes, a practical clinical trial with more participants and longer follow-up might show better results, as suggested by the authors.

In the study of Gehrman *et al.* [67], the effects of 8.5 mg IRM and 1.5 mg PRM on sleep and circadian rhythm parameters of AD patients were measured by actigraphy. The timing and duration of the treatment are given in Table 1. No significant difference was observed between the melatonin and placebo-treated groups suggesting that 10 mg melatonin was ineffective in improving sleep in AD patients. The authors presumed that the subjects in the study might have undergone such extreme neuroanatomical degradation that the pathways needed to influence sleep by melatonin were no longer workable. Additionally, the timing of melatonin administration might not have customized to individuals' rhythms. The study failed to exhibit melatonin's phase-shifting outcome, probably due to the dose being sub-optimal.

The effects of add-on 2 mg PRM to standard therapy (acetylcholinesterase inhibitors with or without memantine) on sleep scores of AD patients were measured by the Pittsburgh Sleep Quality Index (PSQI) and a sleep diary in the study of Wade *et al.* [68]. The timing and duration of the treatment are given in Table 1. The PSQI component 4 score which measures SE, improved significantly in the melatonin-treated group over placebo in full analysis set (FAS) ($p = 0.004$) and insomnia comorbid subpopulation (ICS) ($p = 0.031$). PSQI global ($p = 0.004$ in FAS, $p = 0.031$ in ICS), component 2 ($p = 0.016$ in

FAS), component 3 (p = 0.026 in FAS, p = 0.031 in ICS), sleep latency (p = 0.042 in FAS, p = 0.031 in ICS), and TST (p = 0.004 in FAS, p = 0.031 in ICS) scores improved significantly compared with baseline in FAS and ICS treated with melatonin. The SQ according to sleep diary improved significantly in PRM group compared placebo both in FAS (p = 0.007) and ICS (p = 0.091). The results indicated that add-on PRM to acetylcholinesterase inhibitors has positive outcomes on sleep maintenance of AD patients, especially with insomnia comorbidity.

Non-randomized controlled trials

5 mg IRM was found effective in improving sleep parameters in middle-to-moderate AD patients in the study conducted by Cruz-Aguilar *et al.* [69]. The timing and duration of the treatment are given in Table 1. At the first night of melatonin treatment, phase 2 of NREM sleep 2 (p = 0.044), delta sleep (p = 0.017), and REM sleep (p = 0.032) installation latencies were decreased significantly. A tendency to increase TST and reduction of the total wake time was seen in melatonin treatment, especially on the second night. Non-significant improvements in melatonin treatment were seen in other sleep parameters including SE. In this study, it was demonstrated for the first time that melatonin has the capability to promote REM sleep in AD patients. The authors suggested that, even at middle-to-moderate stages of AD, the sleep generating mechanisms are capable to be induced by melatonin. Melatonin can promote a greater amount of night-time sleep and it has an effect over both circadian rhythm and sleep homeostasis. Melatonin was not found to have an effect on sleep maintenance. The authors suggested that PRM can be effective to improve SE as melatonin has a short half-life.

In another study, the effects of 5 mg IRM on cortical activity in AD patients were investigated during SOP [70]. The timing and duration of the treatment are given in Table 1. The administration of melatonin induced EEG activity in AD patients during SOP as seen in healthy individuals; i.e., the relative power (RP) of delta slow waves increased significantly in the prefrontal cortex. Melatonin administration significantly ($p = 0.04$) reduced SOP in AD patients compared to placebo. The short SOP was related to a higher RP of the delta band at F7-T3, F3-F4, and C3-A1 (especially in the left hemisphere), a lower RP of the alpha 1 band at F7-T3, and a reduced interhemispheric EEG coupling in the alpha1 band at F7-T3 and F8-T4. The intensity of slow-wave activity in the prefrontal cortex of the brain is the most determinative change in SOP in healthy individuals. The intensity of slow waves in the prefrontal cortex is essential for an optimum shift from wakefulness to sleep which can be assisted by applying melatonin to AD patients.

Case reports

Two AD patients with SD were treated with 6 mg of melatonin in the study conducted by Jean-Louis *et al.* [71]. The timing and duration of the treatment are given in Table 1. One patient did not show any improvement on treatment, but the other one showed a significant reduction in daytime sleepiness ($p = 0.05$) as per Stanford Sleepiness Scale, a significant increase for daytime arousal ($p = 0.02$), borderline increase in daytime activity ($p = 0.07$), better organized rest-activity cycle, and non-significant improvement in sleep onset time. The acrophase of rest-activity in both patients was delayed for about one hour. This indicates that melatonin can be effective to treat SD in some patients with AD. One of two monozygotic twins were treated with 6

mg of melatonin and showed improvements in SQ, reduction in sundowning, and less progression of cognitive and behavioral symptoms in the study conducted by Brusco *et al.* [72]. The timing and duration of the treatment are given in Table 1. The other twin showed negative results in these parameters. These outcomes suggested that melatonin can be effective to treat SD in AD patients.

A subject in the study of Singer *et al.* [62] had an unusual free-running sleep-wake rhythm who responded robustly with 2.5 mg melatonin therapy. The duration of the treatment is given in Table 1. The sleep-wake cycle restored to the normal routine, SE increased from 47.2% to 78.2%, and TST improved from 5.4 to 6.6 hours. After the study, the patient was maintained with constant benefit with 3 mg melatonin. This case inferred that melatonin can be considerably helpful to improve sleep in AD patients with free-running sleep-wake rhythm [73]. In a case report of a patient with probable AD having RBD and some sleep apnea (which impeded clonazepam usage), it was found that melatonin was greatly effective against the RBD of the patient. The patient's symptoms included violent dreams that the patient exerted wounding himself and his wife, violent arm or leg movement, shouting, being suffocated, and throwing himself out of bed. After 5 – 10 mg melatonin administration, the symptoms were almost completely resolved. The timing of the treatment is given in Table 1. The authors suggested that exogenous melatonin can stabilize and reinforce REM sleep and thus can reduce the fragmentation of REM sleep in RBD [74].

In a case report, 2 mg melatonin, administered twice a day, was found useful in improving sleep and sundowning behavior in an AD patient. The timing and duration of the treatment are given in Table 1. SQ was improved within 1 week of night-time

melatonin administration. Sundowning behavior was improved significantly within 2 hours of night-time melatonin administration and Neuropsychiatric Inventory score improved subsequently (from 50 to 20) over 2 weeks of treatment. Further behavioral change was not detected over 2 months of follow-up [75].

Only two case studies have been found where the effects of melatonin receptor agonists on SD in AD have been discussed. In the study of Asano *et al.* [76], melatonin receptor agonist ramelteon (8 mg) dramatically improved SD and severe refractory behavioral and psychological symptoms of dementia (BPSD) in an AD patient with CRSD and agitated behavior. The timing and duration of the treatment are given in Table 1. Decreased night-time awakenings and daytime sleepiness were also observed. The patient was able to sleep approx. 7 hours regularly at night. BPSD is considered to be closely associated with CRSD. The patient took various medications such as donepezil, memantine, quetiapine, risperidone, and Yi-gan-san (herbal medicine) before, however had to discontinue those due to different side-effects. Ramelteon did not show any adverse effect on treatment. Melatonin receptor agonist agomelatine (25 mg) was found effective to reduce insomnia, sleep fragmentation, daytime sleepiness, depressive symptoms, and cognition in an AD patient with severe insomnia and depression in the study of Altınyazar *et al.* [77]. The duration of the treatment is given in Table 1. The patient took mianserin and lorazepam before to treat insomnia, but they were not as effective as agomelatine. The authors suggested that an increase in sleep duration and REM period by agomelatine might be responsible for the improvement of insomnia and cognitive functions.

Other clinical studies

In another study [78], AD patients with SD were treated with 9 mg of melatonin for a long time. The timing and duration of the treatment are given in Table 1. As per the sleep log, the SQ range was 2 – 4 before treatment, but after the treatment, the range was observed as 5 – 8. Melatonin significantly improved SQ ($p = 0.001$) indicating that it was highly effective in treating SD in AD patients. In the study of Yin *et al.* [79], sleep disturbed AD patients were treated with 2.55 mg melatonin or atypical antipsychotics (0.5-1.0 mg risperidone) or non-benzodiazepine hypnotic (5-10 mg zolpidem tartrate) or no drug along with 5-10 mg donepezil for 5 years and their sleep scores were measured by Epworth Sleepiness Scale (ESS) and PSQI. The duration of the treatment is given in Table 1. Melatonin treatment was the least effective among the drugs used.

Meta-analyses

In a meta-analysis conducted by McCleery *et al.* [80], no evidence was found that melatonin ameliorated any important sleep result over 8 to 10 weeks at doses up to 10 mg in AD patients with SD. No difference was found for sleep SE, the number of nocturnal awakenings, or time awake after sleep onset between melatonin and placebo groups. A secondary sleep outcome (carer-rated SQ) was analyzed and no evidence of a difference for carer-rated SQ (change from baseline) between melatonin and placebo groups was found. Melatonin receptor agonist ramelteon was also found ineffective to improve sleep in AD dementia patients.

In another meta-analysis by Zhang *et al.* [81], some pieces of evidence were found that melatonin elevates SQ in AD patients. But exogenous melatonin did not generate

significant results on objective sleep outcomes as analyzed from four studies. No significant effect of melatonin was found in night-time TST, SE, wake after sleep onset, number of nocturnal awakenings, and daytime to night-time sleep ratio. The authors gave several explanations for the lack of efficacy of melatonin. Firstly, the AD patients had acute disorders of sleep patterns and diurnal rhythms, and melatonin has little impact on the sleep-wake cycle. Secondly, melatonin might be effective in prolonged usage. Thirdly, the sample sizes were small in the included studies. Lastly, the etiology of SDs in AD is complex which involves compound molecular mechanisms.

However, in the meta-analysis by Wang *et al.* [82], melatonin was found effective in improving SQ in AD patients over 10 days to 24 weeks period at doses ranging from 2 to 10 mg. Six randomized controlled trials were included for TST analysis. Significant enhancement of night-time TST ($p = 0.04$) was detected in melatonin treated subjects compared to placebo, though no difference was observed in daytime TST and sleep efficacy between the two groups. The authors discussed several limitations of the meta-analysis such as a wide range of dosages with no assessment of dose-response relationship and large variation in study periods.

DISCUSSION

Treatment of SD may be a priority to arrest and prevent AD progression. Reduction of sleep disorders is of key importance in the treatment of AD patients because cognitive and memory impairments are aggravated by SDs [5]. Many of the present drugs used in the treatment of AD patients ameliorate symptoms without any notable disease-changing outcome [55]. Melatonin is found to have an antagonizing effect on AD pathogenesis and

therefore can improve the patients' SDs, postpone progression of AD, and reduce family costs [5, 12].

A considerable number of discrepancies are present in the findings of the studies that tried to determine whether exogenous melatonin treatments are useful to treat SD in AD. So, it becomes challenging to come to any conclusion whether melatonin therapy is useful to treat SDs in AD. However, there might be some factors behind the negative results of some studies. Caregiver burden and emotional suffering can negatively influence SQ. It is important to note that most studies that found negative results regarding the efficacy of melatonin on SD in AD used actigraphy for sleep assessment. The use of actigraphy as an alternative to PSG in AD patients is not well-recognized. Actigraphy and subjective sleep evaluation results can differ in sleep assessments [68].

Apart from this, melatonin dosage and formulation along with study design and duration may be responsible for ambiguous findings in different studies [68]. The timing and dosage of melatonin administration and stage, severity, and heterogeneity of the disease can be responsible for the discrepancies in the outcomes of the studies [83]. Slow form of dosage can be a reason behind negative results [12]. Inclusion of participants of different stages of AD and dementia and the brief duration of studies can be possible reasons behind negative results. Long term trials showed positive results in abating SD in AD patients [7].

Whether the patients had reduced melatonin levels or reduced SCN melatonin receptors can also regulate study outcomes [83]. The reduction in number and density of melatonin receptors in SCN at advanced stages of AD can explain the fact that melatonin and melatonin agonist treatments are less effective at that stage [22, 28]. Melatonin

therapy at the early stages of AD can control the formation and metabolism of APP and AB, thus can be more beneficial than administration at later stages [29]. It has been suggested that melatonin is no longer able to prevent amyloid deposition and amyloid-dependent damage after the disease reaches a certain level of severity [13]. Usually, AD is diagnosed relatively later in life when melatonin treatment doesn't exhibit significant improvements [84].

The subjective sleep measures showed more positive results where objective measures showed more negative results. BLT along with melatonin showed more positive results in improving SDs [12, 22]. BLT in the early stages of AD can improve circadian rhythm disruptions [30]. Melatonin, melatonin agonist receptors, and light therapy can be useful against sundowning syndrome in AD [9]. So, the amalgamation of melatonin therapy with BLT can exert more positive results to improve sleep in AD than melatonin alone [85, 86]. It might be more helpful to decide light exposure and melatonin administration time after assessing individual's sleep onset period (SOP) and TST [65]. Genetic predispositions, environmental factors, and patients' comorbidity can also be responsible for negative outcomes.

Sleep is critical for memory and cognitive functioning. Poor SQ is responsible for beta-amyloid deposition in the preclinical stage of AD. Treating sleep disorders in AD patients with traditional hypnotics (*i.e.*, benzodiazepines) may not be effective and may even be detrimental as these drugs can cause damages in cognitive and memory performance. These can exert REM sleep inhibition, delirium at night, muscle reluctance, stumbling, carry-over effects, and daytime sleepiness. It is important to insist on the fact that melatonin is an endogenous molecule, thus not toxic, as it can easily be metabolized

by the body. Exogenous melatonin was also found to be a less toxic drug that improves sleep without doing harm to memory and cognition. So, melatonin can be a safe drug to treat SDs in AD [63, 68, 87].

MELATONIN IN OTHER CENTRAL NERVOUS SYSTEM (CNS) DISORDERS

As melatonin has powerful antioxidant, neurogenerative, anti-inflammatory, anti-fibrillogenic, immune-enhancing, and sleep-regulating abilities, it has a common neuroprotective role against different neurodegenerative, mental, and behavioral disorders of the CNS. Neurodegenerative disorders such as Parkinson's disease, Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis share some common pathophysiological phenomena like increased oxidative damage and mitochondrial dysfunction. Melatonin was found capable of prevention and treatment of these diseases [12, 88]. Melatonin was also found effective in treating epilepsy, different types of headaches, brain ischemia, sleep disorders, paraplegia, and tetraplegia. In various studies, melatonin showed efficacy to treat mental and behavioral disorders like autism spectrum disorders, attention-deficit hyperactivity disorder, and dementias [12]. It is important to note that reduced melatonin levels and CRSDs had been frequently found in the diseases mentioned above. So, melatonin is of high importance in both pathophysiology and treatment of CNS disorders [12].

POSSIBLE MECHANISMS BY WHICH MELATONIN CAN TREAT SLEEP DISTURBANCES IN ALZHEIMER'S DISEASE

Inhibiting AB related effects

With the advancement of aging and AD, the SWS is reduced which leads to AB formation and aggregation, and reduced glymphatic clearance of AB. Small vessel disease, traumatic brain injury, and amyloid plaques induce astrogliosis that leads to reduced AB clearance, AB aggregation, and reduced SWS [10]. AB deposition promotes the flavoenzyme-mediated increase of hydrogen peroxide and lipid peroxides which increase free radical generation and protein, lipid, and DNA oxidation [5]. Toxic oligomers formed by abnormal deposition of AB cause synaptic impairment, change in synaptic plasticity-related signaling pathways, impairments in glutamate receptors, and circuit hyperexcitability [89].

Melatonin abates beta APP soluble derivatives' secretion [30], suppresses AB β-sheet and amyloid fibril formation [6], inhibits AB aggregation [10], removes AB from the brain including hippocampus and frontal cortex by glymphatic clearance [10, 22, 30], and decreases the concentration of cerebral AB [30]. Both AB_{40} and AB_{42} peptides are efficiently suppressed by melatonin [90]. Melatonin attenuates AB mediated oxidative damage [30]. It prevents the death of neuroblastoma and astroglioma cells exposed to AB [88]. Melatonin suppresses neurotoxicity caused by aggregations of ApoE4 or ApoE3 and withdraws the pro-fibrillogenic function of ApoE4. Astrocyte apoptosis contributes to AD pathophysiology. Astrocytes perform tau hyperphosphorylation, activate stress kinases, generate ApoE4 that exacerbate AB effects, interacts with AB, and lose control over glial nitric oxide (NO) production. Melatonin was found to prevent AB induced NO production by C6 astroglioma cells [5].

Inhibiting free radical damage and neurodegeneration

Though the human brain holds only 2% body weight, it utilizes 20% of oxygen intake. As a result, it produces more ROS than any other body part. The brain also generates ascorbic acid and polyunsaturated fatty acids which are susceptible to free radical damage [25]. Melatonin can remove ROS and RNS including hydrogen peroxide (H_2O_2), hydroxyl radical (OH), hypochlorous acid, singlet oxygen, peroxynitrite anion (ONOO-), and/or peroxynitrous acid. Melatonin increases the expression and activity of antioxidant enzymes like catalase, glutathione peroxidase and reductase, and superoxide dismutase [91]. Mitochondria are the production houses of ROS and RNS and the preliminary targets of their attack [92]. Mitochondrial respiratory chain damage can cause mitochondrial permeability transition pore opening, mitochondrial membrane proton potential breakdown, promotion of apoptosis, and more free radical generation [92]. AB deposition induces functional insufficiencies of the mitochondrial respiratory chain complexes leading to mitochondrial dysfunction and increased oxidative stress [5]. Melatonin prevents mitochondrial transition pore opening, intramitochondrial lipid peroxidation, mitochondrial DNA oxidation, intramitochondrial effects of AB, and cell death. Melatonin increases activities of the mitochondrial respiratory enzyme complex and intramitochondrial glutathione pool. Melatonin conserves electron flow through the transport chain and increases ATP synthesis. Thus melatonin prevents mitochondrial dysfunction and AD pathogenesis [92].

Calcium overload, glutamate excitotoxicity, and ROS in the brain cause neurodegeneration in AD [54]. ROS induces lipid peroxidation, DNA damage, and BBB breakdown [26]. During lipid peroxidation, malondialdehyde (MDA) and 4-hydroxy-2-nonenal are generated which damage tissue by enhancing free radical events. Melatonin

directly interacts with MDA and protects neurons from oxidative damage. Melatonin inhibits lipid peroxidation [91], BBB breakdown [7], and DNA damage [41]. AB interacts with transition metals and produces redox-active ions. These ions induce lipid peroxidation and oxidative stress. As a metal-chelating substance, melatonin binds to metals like zinc, iron, copper, and aluminum and reduces metal-induced lipid peroxidation [91]. Melatonin also curtails the absorption and peroxidation of cholesterol and thus lowers AB generation [41]. Melatonin prevents calcium overload by inhibiting voltage-gated calcium channels, suppresses glutamate excitotoxicity by inhibiting N-methyl-D-aspartate glutamate receptors, and reduces oxidative stress by scavenging ROS. It also upregulates superoxide dismutase catalase activity which also scavenges ROS. Melatonin associate with brain-derived neurotrophic factor which enhances neurogenesis and suppresses neuronal apoptosis. SD inhibits melatonin production and neurons and glial cells become more susceptible to oxidative stress and apoptosis [54].

Maintaining neuronal glucose metabolism

Melatonin attenuates type 3 diabetes by reducing insulin resistance, hyperglycemia-mediated BBB breakdown, AB accumulation, and tau hyperphosphorylation and by regulating glucose homeostasis. Insulin resistance in the brain is termed type 3 diabetes and it is a risk factor for AD. Higher insulin levels and disrupted glucose metabolism can induce CRSD in AD. Melatonin reinstates insulin/insulin receptor mechanisms and augments phosphoinositide 3-kinase/Akt signaling activity. Thus, melatonin modulates glycogen synthase kinase 3 which interacts with presenilin-1 (a cofactor for γ secretase) and aids to suppress AB generation from

APP, tau hyperphosphorylation, and AD neurodegeneration. Expression of glucose transporter (GLUT)-1 and GLUT-3 is reduced because of insulin signaling dysfunction. Melatonin repairs neuronal glucose metabolism which increases tau N-acetylglucosamine acylation and thus decreases tau hyperphosphorylation [11, 25, 29]. It also reduces tau hyperphosphorylation by regulating protein kinases and phosphatases [3]. Melatonin prevents tau hyperphosphorylation induced by wortmannin (PI3 kinase inhibitor) and resists lipid peroxidation stimulated by wortmannin [13].

Other mechanisms

Melatonin suppresses cytoskeletal disorganization [13]. It attenuates the generation of protein carbonyl products [93]. Melatonin was found to slow down the degeneration of hippocampal regions, especially CA1 [22]. Melatonin also reduces synaptic dysfunction [11]. It has choline acetyltransferase and acetylcholine esterase inhibitory activity and thus has safeguarding outcomes on the cholinergic system [6]. Melatonin also reduces neuroinflammation by inhibiting nuclear factor κB, AB, and NO and thus inhibiting the synthesis of inflammatory cytokines like TNF-α, IL-1β, and IL-6 [6, 29]. Impairment in the orexinergic system can promote nocturnal wakefulness in AD. Melatonin was found to inhibit orexin neurons acting via MT1 receptors, promote sleep (mainly NREM sleep), and reduce wakefulness at night [8, 94]. Tyrosine kinase receptors and neurotrophins were found to be affected by oxidotoxins including AB. Melatonin has the ability to normalize tyrosine kinase receptors and neurotrophin expression in neuroblastoma cells [13]. Melatonin can increase the secretion of growth hormones and neurotrophins and inhibit astrogliosis. It increases the restorative phases of sleep and

promotes SWS in AD [10, 34]. Melatonin also suppresses sundowning by ameliorating CRSD in AD [10]. Melatonin can be metabolized to cyclic 3-hydroxymelatonin in different tissues and kynuramines like N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and N^1-acetyl-5-methoxykynuramine (AMK) in brain which also have neuroprotective roles [5, 13].

As AD pathophysiology and SD have a bidirectional relationship, the best way to improve SD in AD is to treat both SD and AD pathophysiology. Melatonin has both chronobiotic and neuroprotective role, and so it can inhibit different pathophysiological causes of AD and SD. The possible mechanisms through which melatonin can promote sleep, prevent AD pathology, and treat SDs in AD are depicted in Fig. 3.

FUTURE DIRECTIONS

We suggest that melatonin treatment at the early stages of AD may be more effective as the action of melatonin needs a functional sleep-promoting system which is more severely disordered in the advanced stages of AD. As melatonin levels are diminished at preclinical stages of AD, melatonin treatment should be started early when its level begins to reduce. The timing of melatonin administration is also important. As melatonin opens the gates of sleep and its level begins to rise about 2 hours before sleep, the timing of its administration should be set based on an individual's habitual bedtime. Also, the dosage quantity of melatonin is important in sleep promotion. As melatonin is not toxic and is a safe drug, larger doses can be administered to sleep-deprived AD patients to see possible outcomes. The measurements of expression levels of melatonin receptors before melatonin therapy can be an effective way to set dosage quantity. AD Patients with reduced expressions of melatonin receptors might need higher levels of

dosage. Also, PRM can be beneficial, as it can keep melatonin levels high for a longer duration which can keep sleep macro-architecture undisturbed. Sleep disturbing elements should be removed from the environment of the patient. Also, comorbidities should be treated effectively if present. Studies considering these suggestions can possibly bring out positive outcomes of melatonin therapy.

Larger trials with higher levels of dosage forms and longer durations should be performed. Several studies suggested that morning bright light therapy with melatonin treatment can be more effective. More studies should thus include bright light therapy along with melatonin to get plausible benefits. Also, the sleep measurements should be done with PSG if possible as the measurement of sleep with actigraphy is not well-recognized. Melatonin receptor agonists such as agomelatine, ramelteon, and tasimelteon can be potential alternatives to melatonin. Only a few studies have been done to explore their efficacies to treat SD in patients with AD with promising results. More studies should be done to a larger extent to evaluate their therapeutic efficacy to treat SD in patients with AD.

CONCLUSIONS

Melatonin is of central importance in the promotion of sleep and regulation of circadian sleep-wake rhythm. Disturbed and irregular secretion of melatonin is found in patients with AD. As a result, many sleep- and circadian-related disorders along with exacerbation of the disease conditions and pathophysiology occur in AD. Melatonin had been found effective in treating various sleep-related disorders both in healthy and diseased individuals. Moreover, it has different potentials to reduce AD

pathophysiological conditions. So, theoretically, melatonin holds great possibilities to treat sleep and circadian rhythm disorders in AD. However, interestingly, large amounts of discrepancies have been observed in the outcomes of the trials that tried to measure the efficacy of exogenous melatonin treatment in SD of AD patients. Though the larger portion of the studies expresses positive effects of melatonin treatment on SD in AD, the studies with negative results keep raised the questions behind its ineffectiveness. The timing, quantity, and form of dosage, duration of the trial, way of sleep assessment, stage, severity, and heterogeneity of the disease, genetic predispositions, expression levels of melatonin receptors, environmental factors, and patients' comorbidities can be responsible for the negative outcomes.

LIST OF ABBREVIATIONS

AB: amyloid beta

AD: Alzheimer's disease

APP: amyloid precursor protein

BBB: blood-brain barrier

BPSD: behavioral and psychological symptoms of dementia

BLT: bright light therapy

CNS: central nervous system

CRSD: circadian rhythm sleep disorder

CSF: cerebrospinal fluid

DMN: default mode network

ECS: extracellular space

EEG: electroencephalogram

ESS: Epworth Sleepiness Scale

FAS: full analysis set

GABA: gamma-aminobutyric acid

ICS: insomnia comorbid subpopulation

IRM: immediate-release melatonin

ISF: interstitial fluid

MDA: malondialdehyde

NREM: non-rapid eye movement

OSAS: obstructive sleep apnea syndrome

PG: pineal gland

PRM: prolonged-release melatonin

PSG: polysomnography

PSQI: Pittsburgh Sleep Quality Index

RBD: rapid eye movement sleep behavior disorder

REM: rapid eye movement

RLS: restless leg syndrome

RNS: reactive nitrogen species

ROS: reactive oxygen species

RP: relative power

SCG: superior cervical ganglion

SCN: suprachiasmatic nucleus

SD: sleep disturbance

SE: sleep efficiency

SOP: sleep onset period

SQ: sleep quality

SRBD: sleep-related breathing disorders

SWS: slow-wave sleep

TST: total sleep time

VLPO: ventrolateral preoptic nucleus

WASO: wake after sleep onset

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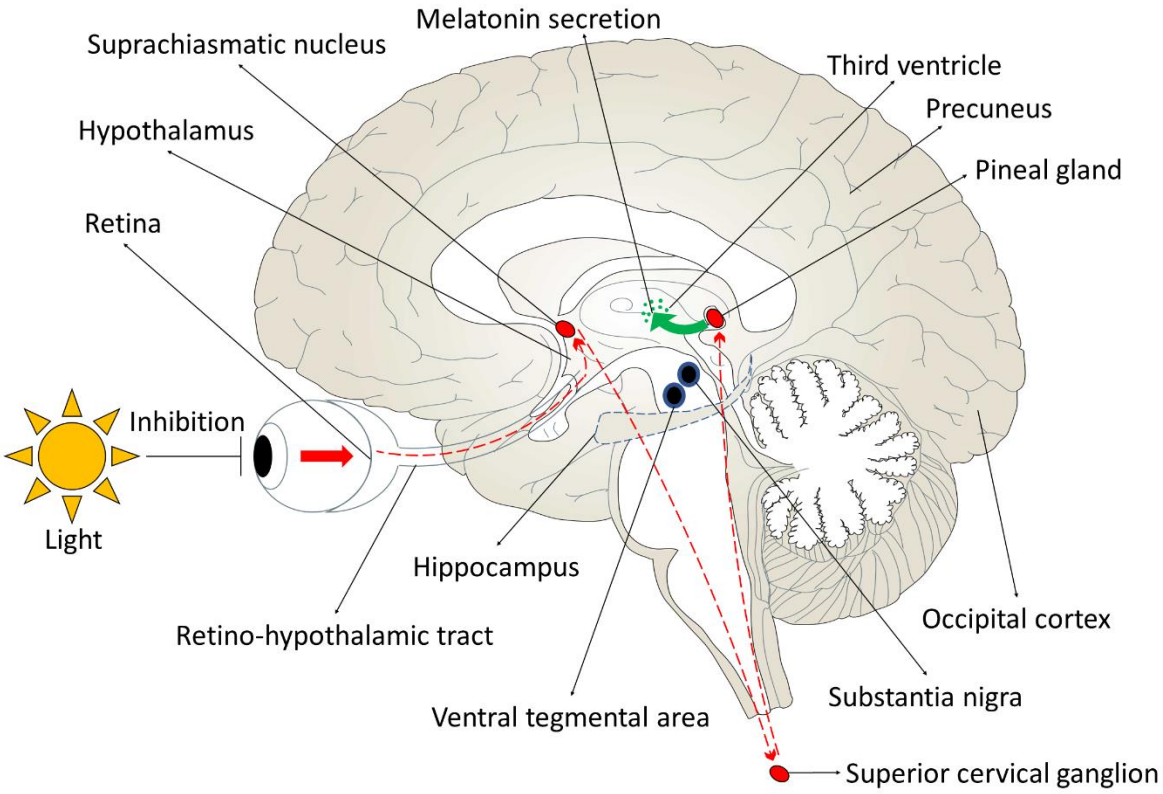

Fig. (1). The retino-hypothalamic pathway (red route) and other brain structures involved in melatonin function.

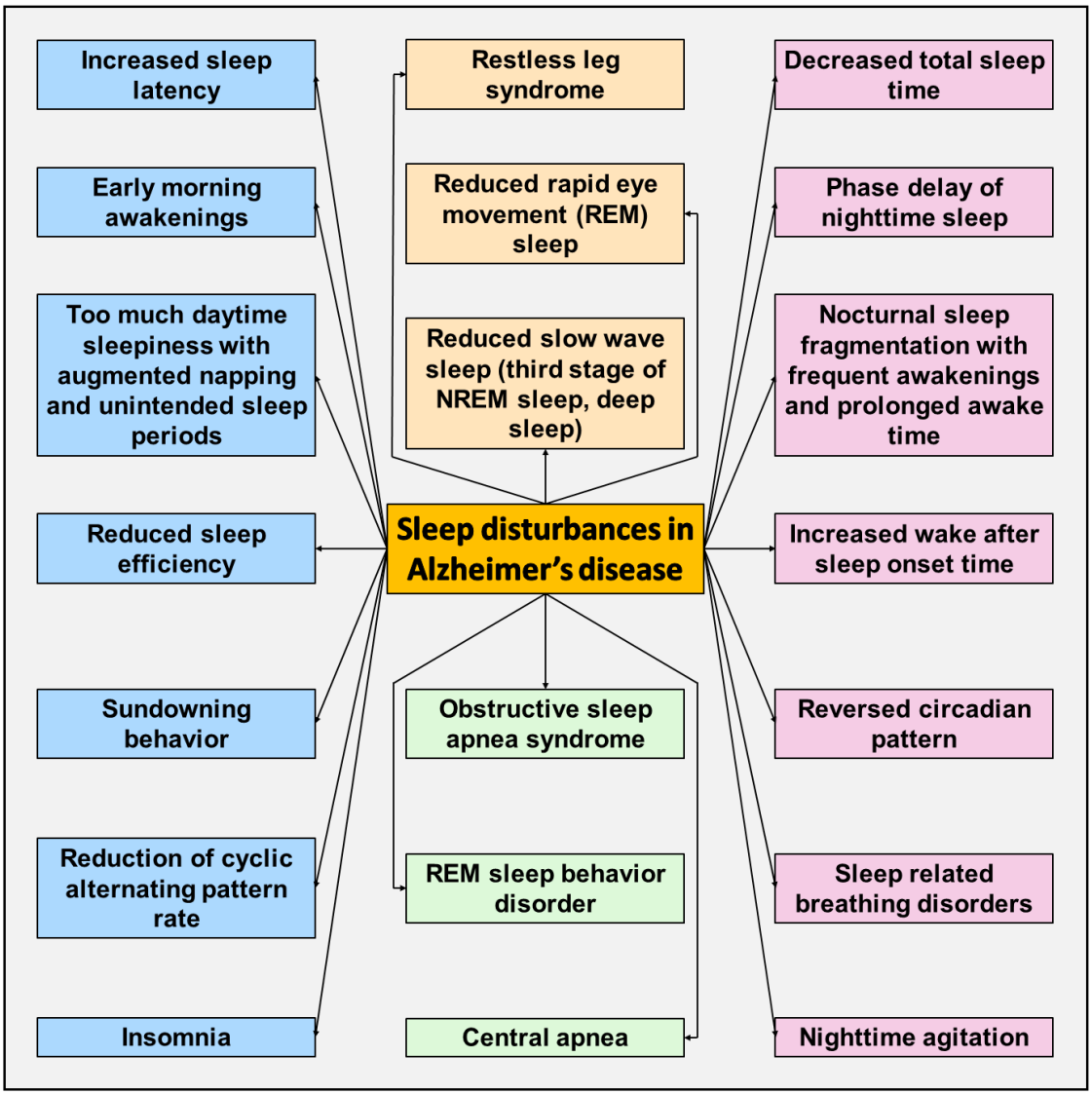

Fig. (2). Different types of sleep disturbances observed in Alzheimer's disease.

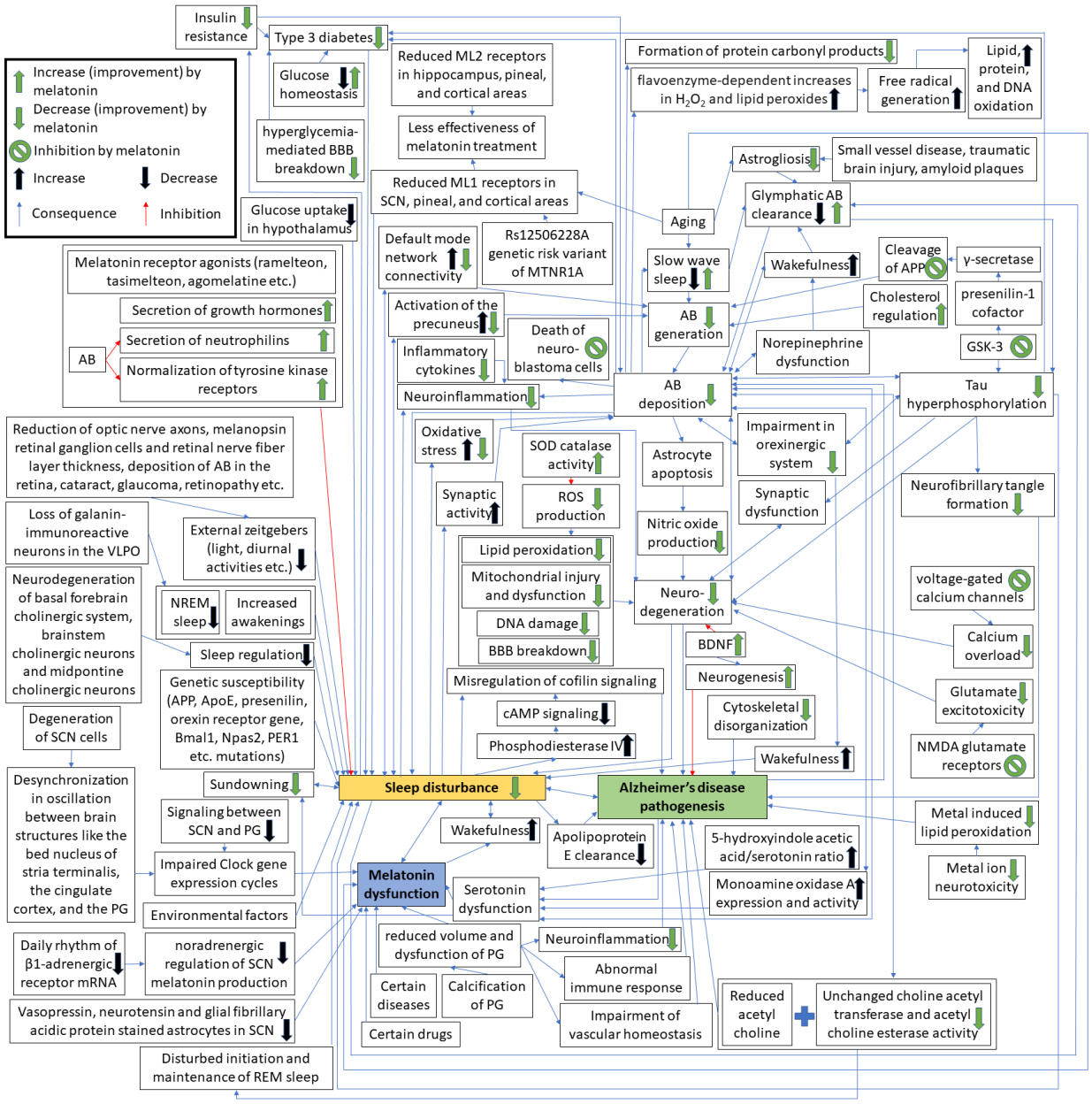

Fig. (3). Possible mechanisms by which melatonin can treat sleep disturbances in Alzheimer's disease.

AB: amyloid beta, APP: amyloid precursor protein, VLPO: ventrolateral preoptic nucleus, SCN: suprachiasmatic nucleus, PG: pineal gland, BBB: blood-brain barrier, ROS: reactive oxygen species, H2O2: hydrogen peroxide, SOD: superoxide dismutase, BDNF: brain-derived neurotrophic factor, NMDA: N-methyl-D-aspartate, GSK-3: glycogen synthase kinase 3.

Table 1. Melatonin and melatonin receptor agonist therapy in AD sleep disturbances.

Study ID [references]	Type of study	Country	Number of AD patients (males)	Age (years) (mean / average / range)	Treatment dosage	Results
Studies regarding melatonin						
Fainstein 1997 [59]	Open-label, short-term pilot study	Argentina	5 (3)	78.0	3 mg MT, 30 minutes before bedtime, for 21 days	MT did not significantly improve SQ, number of awakenings, and daytime alertness in patients with SD + dementia (including AD type).
Jean-Louis 1998 [71]	Case report	USA	2 (0)	72.0-75.0	6 mg MT (or placebo), 2 hours before bedtime, for 10 days	MT significantly improved daytime sleepiness and daytime arousal in one of two AD patients with SD.
Brusco 1998 [72]	Case report	Argentina	2 (2)	79.0	6 mg MT at bedtime (or 50 mg thioridazine) + 800 IU vitamin E, for 36 months	MT substantially improved SQ and reduced sundowning in an AD patient.
Brusco 2000 [78]	Retrospective trial	Argentina	14 (6)	72.0±9.0	9 mg MT at bedtime, for 22 – 35 months	MT significantly improved SQ in AD patients with SD.
Serfaty 2002 [61]	Randomized controlled trial	UK	21	NR	6 mg PRM (or placebo), for 2 weeks	MT did not significantly improve TST, number of awakenings, and SQ in patients with AD-type dementia and SD.
Singer 2003 [62]	Randomized controlled trial	USA	157 (69)	77.4±8.9	2.5 mg PRM or 10 mg IRM (or placebo), 1 hour before bedtime, for 8 weeks	MT did not significantly improve SE, WASO time, sleep disorders inventory, daytime and night-time TST, and their ratio in AD patients with SD. However, SQ improved significantly.
Singer 2002 [73]	Case report	USA	1 (1)	74.0	2.5 mg PRM, for 2 months	MT robustly improved sleep-wake cycle, SE, and TST in an AD patient with a free-running circadian rhythm.
Asayama 2003 [63]	Randomized controlled trial	Japan	20 (3)	79.2±6.4	3 mg MT (or placebo), at 8:30 pm, for 1 week	MT significantly improved TST and reduced activity at night in patients with AD-type dementia.

Mahlberg 2004 [60]	Open-label, uncontrolled pilot study	Germany	7 (4)	75.6±10.6	3 mg MT between 8:45 PM and 9:45 PM + other medications, for 3 weeks	MT significantly reduced night-time activity and was effective to treat CRSD and sundowning in patients with probable AD.
Mahlberg 2007 [64]	Randomized controlled trial	Germany	24 (10)	Treatment: 79.0±9.0, Placebo: 78.2±10.3	3 mg MT (or 2.5 mg dronabinol or placebo) at evening + 1 mg lorazepam, 250 mg clomethiazole, or 40 mg pipamperone, up to 3 times per day for 2 weeks	MT significantly decreased night-time activity in patients with probable AD type dementia and agitated behavior.
Anderson 2008 [74]	Case report	UK	1 (1)	68.0	5-10 mg MT at night	MT was highly effective against RBD and sleep apnea in a patient with AD, RBD, and sleep apnea.
Dowling 2008 [65]	Randomized controlled trial	USA	50 (7)	86.0±8.0	5 mg MT (or placebo) in the evening + morning BLT, from Monday to Friday, for 10 weeks	MT significantly improved daytime TST, daytime activity, day-night sleep ratio, and rest-activity rhythm in AD patients.
Riemersma-van der Lek 2008 [66]	Randomized controlled trial	Netherlands	120 (NR)	NR	2.5 mg medium-fast release MT (or placebo) 1 hour before bedtime + 1000 lux bright light (or 300 lux dim light) from 9 AM to 6 PM, for 15 ± 12 months (up to 3.5 years)	MT significantly improved nocturnal restlessness, SE, duration of awakenings, sleep onset latency, TST, and mean duration of uninterrupted sleep periods in AD patients with dementia.
Gehrman 2009 [67]	Randomized controlled trial	USA	41 (13)	82.9±7.0	8.5 mg IRM + 1.5 mg PRM (or placebo) at 10 pm, for 10 days	MT didn't significantly improve night-time and daytime TST, sleep and wake percentage, daytime sleep percentage, WASO time, and number and mean duration of sleep episodes in probable AD patients.
Lammers 2013 [75]	Case report	Netherlands	1 (1)	81.0	2 mg MT at 8 pm and 3 pm for 2 months	MT improved SQ and significantly improved sundowning behavior in a

						patient with AD, SD, and sundowning behavior.
Cruz-Aguilar 2013 [69]	Non-randomized controlled trial	Mexico	8 (NR)	65.0	Placebo for 1 night and then 5 mg IRM for 2 nights, 1 hour before bedtime (approx. 9 pm)	MT significantly improved the latencies of phase 2, delta wave, and REM sleep in patients with middle to moderate AD.
Wade 2014 [68]	Randomized controlled trial	UK and USA	80 (41)	75.3	2 mg PRM (or placebo) + standard therapy, 1-2 hours before bedtime, for 24 weeks	MT significantly improved PSQI global and component 2, 3, and 4 scores, sleep latency, TST, and SQ in patients with mild-to-moderate AD.
Yin 2015 [79]	5-year outcome study	China	156 (55)	AD-SD: 77.59±3.93, AD+SD: 76.68±4.71	2.55 mg MT (or treatment for other groups) + 5 – 10 mg donepezil, for 5 years	MT didn't significantly improve ESS and PSQI scores in AD patients.
Cruz-Aguilar 2018 [70]	Non-randomized controlled trial	Mexico	8 (8)	65.6±1.0	5 mg IRM (or placebo), 1 hour before PSG for 3 nights	MT significantly reduced SOP in patients with AD.
Studies regarding melatonin receptor agonists						
Asano 2013 [76]	Case report	Japan	1 (1)	79.0	8 mg ramelteon, at 9 pm for 3 months	Ramelteon improved SD, BPSD, night-time awakenings, and daytime sleepiness in a patient with AD.
Altınyazar 2016 [77]	Case report	Turkey	1 (0)	91.0	25 mg agomelatine, for 1 month	Agomelatine improved insomnia, sleep fragmentation, daytime sleepiness, and daily functioning in a patient with AD.

AD: Alzheimer's disease, SD: sleep disturbance, MT: melatonin, NR: not reported, PSG: Polysomnography, EEG: electroencephalogram, SOP: sleep onset period, WASO: wake after sleep onset, FAS: full analysis set, ICS: insomnia comorbid subpopulation, IRM: immediate-release melatonin, PRM: prolonged-release melatonin, RBD: REM sleep behavior disorder, SQ: sleep quality, SE: sleep efficiency.