Review Article

Melatonin Levels in Alzheimer Disease

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Abstract

Introduction: Alzheimer's disease is an age-related neurodegenerative disorder with progressive loss of cognitive function and other manifestations in the central nervous system. It has been found that 45% of patients exhibit sleep disorders.
Purpose: This study aims to describe the role and effects of melatonin levels in Alzheimer's disease.
Methods: In a literature search in the electronic database "PubMed" and "Google Scholar" via search engine. There was a time restriction, the last fourteen years. Exclusion criteria of articles were articles related to the effect of melatonin in other neurodegenerative disorders. Finally, 65 articles were included in the study.
Results: The production of melatonin depends on circadian rhythm and affects the duration and quality of sleep. It is known that the process of aging cause a reduction of melatonin and that endogenous secretion is reduced in people with Alzheimer's disease. Degenerative changes in the pineal gland can cause deregulation in the secretion of melatonin in the early stages of Alzheimer, resulting in the additional presence of disturbances in the sleep cycle. At the same time, lack of sleep can cause chronic accumulation of beta amyloid peptide, which is involved in the pathogenesis of the disease. So, sleep and neurodegenerative disorder exhibit a bidirectional relationship, having a significant impact on the diagnosis and treatment of Alzheimer's disease.
Conclusions: Data from clinical studies suggest that melatonin supplements improve sleep quality and retard the progression of cognitive impairment in patients with Alzheimer.

Key words: Alzheimer disease, melatonin, sleep disorders, Alzheimer's treatment, beta amyloid, exercise in Alzheimer disease

Introduction

Alzheimer's disease (AD) usually occurs in the elder people and is associated with reduced neurogenesis, retraction of dendrites and necrosis of neurons in the hippocampus, via the mechanism of apoptosis. Moreover, free oxygen radicals are increased in neurons and nerve cells, which contain extracellular amyloid plaques and abnormal cytoplasmic fibrous formations. The most characteristic feature of AD is impaired memory associated with atrophy of the hippocampus and difficulty in obtaining and retaining new information. It is needed to be mentioned that the brain injury is not confined to the hippocampus and often involves extensive lesions and in other areas. This progressive neurodegenerative process leads to mental impairment and progressive cognitive decline beyond the field of memory, affecting attention, visuospatial processing and fluency. (Foscolos, 2011; Fox et al, 2001; Mickes et al, 2007).

Regarding genetic background, it has already been found that diverse polymorphisms are associated with the development of AD. Except from theAPOEepsilon4allele, there have been identified over twelve (12) genes associated with the disease: ACE, CHRNB2, CST3, ESR1, GAPDHS, IDE,

MTHFR, NCSTN, PRNP, PSEN1, TF, TFAM and TNF (Bertram et al, 2007).

Contrary to the memory, emotional processing may be maintained in patients with AD, particularly during the early stages of the disease. Specifically, individuals recognize and express their feelings. However this fact is not absolute in all cases (Broster et al, 2012; Kensinger et al, 2002).The differences which are noted in the emotional and mental state of patients are likely to be due to different patterns of neuropathology of the disease and the sleep habits(Guzmán-Vélez et al, 2014).

Another characteristic of AD is the inadequate secretion of melatonin. This deficiency allows hydroxyl radicals damage the mitochondria and thus start a cascade offer oxygen radicals that cause the specific neuropathological changes in AD. Melatonin is a hormone which regulates the circadian rhythms, like the daily sleep schedule, which entails its implication in the observed disorders (Zhou et al, 2003).Sleep disorders, and particularly chronic insomnia is associated with limited reactivity, emotional interpretation in formation and intensity of emotions (Kyle, 2014). Additionally, sleep disorders are an important risk factor for developing anxiety disorders or depression (Neckelmann, 2007).

It has been proposed that chronic sleep deprivation and associated neuronal overactivity may directly confer an increased risk of developing AD (Kang et al, 2009). Sleep disturbance occurs early in the course of disease (Guarnieri et al, 2012) and worsens as disease evolves (Kondratova & Kondratova, 2012). AD is associated with decreased slow-wave sleep and Rapid Eye Movement (REM) sleep, prolonged REM latency, increased proportions of stages I and II sleep, and increased fragmentation of sleep, leading to an overall decrease in sleep duration (Bombois et al, 2010). Even after accounting for the effects of increased sleep fragmentation, AD is also associated with shifts in the normal circadian alertness profile (contributing to ‘sundowning’ in late-stage disease) (Bachman & Rabins, 2006), consistent with a specific impairment of circadian pacemaker function. Moreover, it has been established that 45% of patients suffer from sleep disorders (Cardinali, 2011).

Methods

The literature review was based on the search of data from electronic databases: PubMed and Google Scholar. The articles used in this review included information about the mechanisms by which the production and the secretion of melatonin is reduced, as well as the implications of this reduction. Studies referring to the therapeutic properties of melatonin and studies on non-pharmaceutical agents, which may be used to prevent or treat Alzheimer's disease, were also used. The criteria for the exclusion of articles were languages different from English and Greek, articles for which there was no access to the full text and articles referred to the effect of melatonin in other neurodegenerative disorders. The selection of articles was limited in time from 2000 to 2014, using as key words: Alzheimer disease, melatonin, sleep disorders, Alzheimer's treatment, b amyloid and exercise in the Alzheimer disease. Totally, 88 (eighty-eight) articles were found, 20 (twenty) of them were rejected due to title and 3 (three) articles were excluded because they were not available as full texts. Finally, 65 (sixty-five) articles were studied for this review.

Purpose

The purpose of this study is to describe the role and effects of melatonin levels in AD. The role of melatonin and other non-pharmaceutical methods in the AD treatment (nutrition and physical activity) are also described.

Results

The pineal gland is a central structure in the circadian system, producing melatonin under the control of the central clock, the suprachiasmatic nucleus (SCN). Melatonin, synchronized the 24 hours day by environmental light, which is received by the retina and transmitted to the SCN and broadcast via retinohypothalamic tract. Melatonin not only plays a major role in the regulation of the circadian rhythm, but also acts as antioxidant and neuroprotector, that may be of importance in aging and in AD (Zhou et al, 2003).

Circadian disorders, such as sleep-wake cycle disturbances, are associated with aging and even more pronounced in AD. In many studies it has been found that melatonin production is disturbed, since the level decreases with increasing age and with the occurrence of AD (Zhou et al, 2003). The retinal degeneration-SCN-pineal axis can be the basis for these changes. Recent studies indicate that a dysfunction of the sympathetic regulation of pineal melatonin synthesis by the SCN is responsible for melatonin changes during the early AD stages. The

pineal shows distinct changes related to age (Duffy et al, 2002).

Some studies have linked calcination pineal with disturbed sleep-wake cycle and a reduction in the production of melatonin by increasing age (Duffy et al, 2002). Postmortem human pineal gland was examined and found decreased nocturnal production of melatonin from the early, preclinical stages of AD. Thus, melatonin level could be used as a prognostic indicator (Wu et al, 2003). What is more, the peptides, which are responsible for the synthesis of neurons SCN, such as vasopressin, are decreased in elderly (Hofman, 2000). The total amount of vasopressin mRNA is three times lower in AD patients than in older people who are not suffering from AD. Even daily rhythm of vasopressin mRNA, decrease significantly in patients with AD (Liu et al, 2000).

It has even been found that the beta1-adrenergic receptors of mRNA disappear and simultaneously the expression and activity of the gene of monoamine oxidase (MAO) is increased in patients with AD. This fact suggests that the deregulation of the noradrenergic neuroses and depletion of serotonin, which is a precursor of melatonin, would be responsible for the loss rate and the reduced levels of melatonin in AD (Wu et al, 2007). Changes in other circadian rhythms associated with aging are the regulation of core body temperature, cortisol, blood pressure, testosterone secretion and levels of beta-endorphin (Swaab, 2003). The findings show that the changes observed the rhythm of melatonin may be part of a general effect of aging or SCN and adjustment.

Studies show that older people are exposed to lower light levels in their daily life (Van Someren et al, 2002).The ability of the lens to transmit light, is decreased progressively during the course of aging, which can also contributes to the disorder production of melatonin and circadian disorders in the elderly people (Charman, 2003). The retina and optic nerve present degenerative alterations in AD, but without the appearance of neurofibrillary tangles, neuritic plaques or amyloid angiopathy. Moreover, age-related maculopathy is associated with AD. It has been found that glaucoma is five times more frequent in AD patients compared with other elderly people without AD (Bayer & Ferrari, 2002).A programmed intense light exposure can be used to treat circadian nature of disorders and related disorders sleep in the elderly people (Klerman et al, 2001). In patients with AD, treatment with exposure to intense light increased the secretion of melatonin, improved the disorder of sleep-wake rhythm and behavioral disturbances, such as wandering, stimulation and delirium (Singer et al, 2003; Yamadera et al, 2000). Furthermore, seems to improved cognitive state of patients with AD (Graf et al, 2001), especially in the early stages of the disease (Yamadera et al, 2000).

The disturbed sleep-wake cycle that is presented in the elderly people, it is even more pronounced in patients with AD. Many patients with AD often suffer from circadian disorders associated with behavioral disturbances, such as agitation of the day and night concern (Martin et al, 2000). Furthermore, nocturnal insomnia and wandering in AD patients often pose unbearable problems for caregivers and are the main causes of institutionalization of these individuals. A diachronic eight years term study in adults showed that chronic insomnia associated with AD. Patients who began the study with normal cognition and comorbid insomnia led faster to dementia compared with patients without insomnia (Osorio et al, 2011). This study provides important data for humans, as chronic sleep-wake disorder could increase the risk of developing AD. However, there is no successful pharmaceutical therapy for circadian disturbances in AD until now. Hypnotic or antipsychotic medication is only slightly effective for the alleviation of circadian disorders, while sleep-wake cycle disturbances may even be aggravated by a classic neuroleptic therapy, such as administration of haloperidol (Wirz-Justice et al, 2000).

The patients with AD also report feelings of happiness and sadness, depending on the situations experienced, despite the disruption of declarative memory for the events that initially cause the emotional state (Blessing et al, 2006, 2012; Evans-Roberts & Turnbull, 2011). Specifically, the patients with AD affected emotionally by events in their lives, although not able to remember, actually happening phenomenon "feelings without memory". This likely indicates the relatively conserved function of the amygdale, but further study is necessary for understanding of the neuroanatomical struts (Guzmán-Vélez, 2014).

Amyloid peptide

The accumulation of beta amyloid peptide and its oligomers, may produce sequential inflammatory - oxidative reaction and excitotoxicity, causing neurodegeneration and cognitive dysfunction. The beta amyloid has been shown to act as a pro-

inflammatory agent, by activating further inflammatory processes (Tuppo & Arias, 2005). The deposition of amyloid in the preclinical stage of AD appears to be associated with a worse quality of sleep. Clinically, it has been found that chronic sleep deprivation increases the plaque formation, while the increased hours of sleep reduce that formation (Kang et al, 2009). The beta amyloid is getting increased during wakefulness and decreased during sleep. Therefore, sleep abnormalities could increase the soluble amyloid levels in long term, which entails increased accumulation of amyloid plaques, further disrupting sleep and then symptomatic AD (Huang et al, 2012). In one study, in a transgenic mouse model was reported that the administration of melatonin increased the survival and inhibited the oxidative properties of amyloid (Matsubara et al, 2003).

Melatonin and sleep disorders

Exogenous melatonin administration may improve both quality and sleep duration. In patients suffering from insomnia, melatonin appears to induce the onset of sleep. Despite that fact, its hypnotic action is mild (Cardinali et al, 2011). The benefits of melatonin compared to other sleep-inducing agents are: the lack of headache in the morning, the absence of withdrawal symptoms and addiction (Hardeland et al, 2008; Srinivasan et al, 2008). Melatonin has a short half-life and as mentioned before a mild hypnotic action. Therefore, melatonin's alternative medication, like ramelteon and agomelatine are chosen (Hardeland et al, 2008). The ramelteon has a high affinity for melatonin receptors MT1 and MT2 in the SCN and a longer half life. It has been also used successfully for the insomnia treatment. Agomelatine has high affinity for melatonin receptors MT1 and MT2 in the SCN, acts as an antagonist of serotonin and has hypnotic and antidepressant activity (Kostoglou, 2013).

Melatonin and circadian rhythm

Data from clinical studies indicate that, at therapeutic level, as well as preventive, melatonin supplements may be used for the sleep disorders treatment and resynchronization of circadian rhythms. Melatonin can also be used in blindness or in cyclic working hours (Kostologlou, 2013). Additionally, it may be proved very useful in seasonal emotional disorder (Coogan & Thorne, 2011). It acts on MT1 and MT2 receptors in the SCN of the hypothalamus, the main site of the circadian regulator (Kostoglou, 2013).

Melatonin and antioxidant

Melatonin is a general antioxidant. It effectively protects neuronal cells from the toxicity of beta amyloid through its antioxidant and anti-amyloid properties. Not only inhibits beta amyloid peptide but also interrupts the formation of amyloid fibrils. As an antioxidant, melatonin binds strongly toxic hydroxyl and superoxide radicals (Kostoglou, 2013). It protects the living organisms from oxidative stress even at low concentration (Kostoglou, 2013). Intense oxidative stress results in an acute reduction of circulating levels of melatonin (Galano et al, 2011).

Melatonin and neurodegenerative disorders

In uncontrolled studies, administration of melatonin has been proposed to improve the circadian rhythm in patients with AD, because of the reduction of disruptive behavior and confusion (Cohen-Mansfield et al, 2000; Bruscko et al, 2000) and its beneficial effects on the functioning memory and cognition (Reiter et al, 2002). In patients with AD, have been observed disturbances in melatonin secretion and biological rhythm disorders, changes which may be associated with retinal degeneration -SCN-epiphysis and melatonin secretion disruption by the sympathetic system. Melatonin can be used therapeutically to prevent the histological changes in AD (Olcese et al, 2009).

Other non-pharmacological means

In recent years, there has been particular interest in the potential benefits of physical activity on health, in both healthy elderly and patients with AD. This interest mainly derives from the large integrated studies, which have shown a significant reduction AD risk in physically active individuals. Conversely, sedentary lifestyle is one of the biggest risk factors for age-related disorders (Waldemar & Hasselbalch, 2014). An increased level of physical activity improves circadian rhythm in healthy elderly subjects as found after a three (3) month period of exercising. The low intensity exercise induces the production of melatonin in patients with AD (Kostoglou, 2013). Furthermore, it has been found that individuals with AD could improve memory function through physical exercise. Emotional changes, such as stress reduction, personal stories sharing and positive attitude to exercise and disease, were also observed. Finally, these kinds of patients are better socialized (Wu et al, 2014).

Literature Review of Studies

Melatonin is an essential hormone for the circadian system which improves the cognition and therefore the memory, probably by protecting the organism against the oxidative stress and the neuroprotective capacity (Pappolla, 2000; Reiter et al, 2002). Secretion of melatonin tends to be reduced in elderly patients but even more in patients with AD. In elder people, the level of melatonin is decreased in the pineal gland, plasma and urine, as a 6-hydroxymelatonin, especially during the night (Swaab, 2003). In some studies, age-related differences in the melatonin levels were not statistically significant (Zhou et al, 2003). Some researchers found a linking degeneration and calcification of epiphysis al reducing melatonin (Duffy et al, 2002). However, one study found that the pineal gland of patients with AD has some molecular changes but no changes in weight, total protein content, or calcification (Wu et al, 2003). Circadian melatonin interruption caused by dementia may have physiological effects in the pathology of AD. In some clinical studies which investigated the effects of melatonin on cognitive function, no clear results were found. In another study made in patients with AD, which was performed to investigate the effect of melatonin, showed no improvement in cognition and behavior and had only minor effects on sleep quality (Singer et al, 2003). In another study made in patients with mild cognitive impairment showed improvement in cognitive performance (Peck et al, 2004). Some scholars have linked the severity of mental dysfunction with decreased secretion of melatonin. For this reason, the nocturnal levels of melatonin levels are reduced selectively in patients with AD, depending on the emotional state (Ferrari et al, 2000).

It has been found that the accumulation of amyloid in the preclinical stage of AD can be associated with a worse quality of sleep, certainly not to changes in the amount of sleep (Ju et al, 2013). Chronic lack of sleep increases the plaque formation, while the longer sleep duration by administering an appetite receptor antagonist reduces that formation (Kang et al, 2009). So, further research is needed regarding this topic, as the additional accumulation of beta amyloid peptide hinders cognitive function and therefore the quality of life of these people, aggravating their situation. The beta amyloid, is generally considered to play an important role in promoting neuronal degeneration, making neurons more vulnerable to increases in the levels of oxidative stress and disturbances in cellular energy metabolism occurring with age (Selkoe, 2004). Many studies, carried out both in vivo and in vitro, found a reduction of beta amyloid by administering melatonin. Of course, in an in vivo study, which was given melatonin in the fourteenth month (14) in old mice, not only failed to lift the deposition of existing amyloid plaques but also failed to prevent further deposition (Quinn et al, 2005). This difference between the studies, are probably due to the time of entry administration of melatonin.

In a study, conducted in patients with AD and coexisting sleep disorders, ramelteon, which is a derivative melatonin, was given to nine hundred(209) participants, melatonin ,thirty (30) participants, trazodone and seventy-four (74) participants. Patients who received melatonin and trazodone had moderate to severe AD, patients who received ramelteon had mild to moderate AD. There was no statistically important difference between sleep efficiency, number of nocturnal awakenings, cognitive or performance of activities of daily life and the administetion of melatonin and ramelteon. Nevertheless, there were no serious adverse drug reactions. A small dose of trazodone, improved the overall time and sleep efficiency. Therefore, this study demonstrates that melatonin is beneficial for patients with moderate to severe AD and coexisting sleep problems. There is a lack of evidence, as there are not many randomized trials of drugs made. Benzodiazepines and non-benzodiazepine hypnotics are often administered, although there is considerable uncertainty about the balance of benefits and risks associated with these common treatments (McCleery et al, 2014).Therefore, further study is needed.

Additional exposure to bright light in the morning showed beneficial effects on sleep quality and day time vigilance in the elderly (Yamadera et al, 2000).What is more, the secretion of melatonin was significantly increased in elder people, at levels similar to those in young adults (Mishima et al, 2001) and threat of body temperature was also improved (Klerman et al, 2001).

It has been found that physical activity plays a protective role against psychological symptoms and symptoms of behavior in AD, such as stress and lack of exploration. Exercise and melatonin also play a protective role against cognitive impairment, cerebral oxidative stress and contribute to the reduction of mitochondrial DNA (mtDNA). It has also been found that only the combined treatment of physical activity

and melatonin can effective reduction the mitochondrial complexes (García-Mesa, 2011). Studies have shown a correlation between physical activity and biology of the brain. Specifically physical exercise is positively correlated with cardiac capacity, improving cerebral blood flow and blood volume in the dentate helical, indicating possibly increased neurogenesis (Colcombe, 2003; 2004). Regular physical activity has also been associated with reduced inflammation and increased concentration of various neurotransmitters (Scarmeas, 2009). A study conducted on mice showed that exercise reduces the cortical amyloid burden, possibly through a change in the processing of amyloid precursor protein (Adlard, 2005). In addition to physical activity, crucial is the role of proper nutrition in the disease process. Specifically, it has been suggested that the Mediterranean diet is very effective due to its beneficial ingredients. The combination of fish, fruit and vegetables, which are rich in antioxidants such as vitamin C, vitamin E, flavonoids and products rich in unsaturated fatty acids such as olive oil and olives, help the reduction of the AD risk. The Mediterranean diet substantially reduces oxidative stress and inflammation, characteristics involved in the pathogenesis of the disease (Scarmeas, 2006).

Finally, it is important to be mentioned that patients with AD, usually live in community with their family carers' help. This fact makes necessary the carers' training in supporting patients with dementia. Counselling, physiological support, cognitive and behavioral intervention through occupational therapy play a crucial role for both patient and carer. In other words, not only psychological morbidity is reduced but also general mental health is improved. Controversial are the effects of a short-break in care, as carers are likely to receive it, but its long term results are unclear. In any case, the carers training and support remains essential for three reasons, better quality of life, better mood and health for both patients and carers (Robinson et al, 2010). These family members face distinct challenges concern for patients with AD and may experience compassion fatigue: the combination of helplessness, hopelessness, an inability to be empathic, and a sense of isolation resulting from prolonged exposure to perceived suffering (Day et al, 2014).

Conclusions

Melatonin is a hormone with multiple actions. It is involved in the regulation of biological rhythms, in sleep regulation and it has also strong antioxidant and anti- amyloid activity. It protects the organism from neurodegenerative disorders. In other words it is easy to understand why melatonin can be used therapeutically for the management of insomnia, synchronization of circadian rhythms and the inhibition of AD progression. It is important to mention is that there are no serious side effects caused by this therapeutical measure. Furthermore, measurement of the melatonin levels can be used as a prognostic indicator in AD. Other non-pharmaceutical agents like regular exercise and the adoption of a balanced diet are also essential for the prevention and treatment of disease. Finally, it is worth mentioning the need for further study on the exact pharmaceutical efficacy of melatonin and its derivatives, due to the short half-life in patients with AD and coexisting sleep disorders. The treatment of sleep disorders in these patients is an important part of care. Sleep problems are associated with increased risk of depression and consequently poor quality of life.

References

Adlard PA., Perreau VM., Pop V et al. (2005)Voluntary exercise decreases amyloid load in a transgenic model of AD's disease. Journal of Neuroscience 25(17):4217-4221.

Bachman D & Rabins P. (2006) 'Sundowning' and other temporally associated agitation states in dementia patients. Annual Review of Medicine 57:499–511.

Bayer Au & Ferrari F. (2002) Severe progression of glaucomatous optic neuropathy in patients with AD's disease. Eye (London) 16(2):209-12.

Bertram L., McQueen MB., Mullin K et al. (2007) Systematic meta-analyses of AD disease genetic association studies: the AlzGene database. Nature Genetics 39(1):17-23.

Blessing A., Keil A., Linden DE et al. (2006) Acquisition of affective dispositions in dementia patients. Neuropsychologia 44:2366–2373.

Bombois S., Derambure P., Pasquier F et al. (2010) Sleep disorders in aging and dementia. The Journal of Nutrition Health and Aging 14:212–217.

Broster LS., Blonder LX & Jiang Y. (2012) Does emotional memory enhancement assist the memory-impaired. Frontiers in Aging Neurosciences 4:1–6.

Brusco LI., Marquez M & Cardinali DP. (2000) Melatonin treatment stabilizes chronobiologic and cognitive symptoms in AD's disease. Neuroendocrinology Letters 21: 39–42.

Cardinali D., Pagano E., Scacchi- Bernasconi P et al. (2011) Disrupted chronobiology of sleep and cytoprotection in obesity: possible therapeutic value of melatonin. Neuro endocrinology Letters 32: 588–606.

Charman WN. (2003) Age, lens transmittance, and the possible effects of light on melatonin suppression. Ophthalmic and Physiological Optics 23: 181–187.

Cohen-Mansfield J., Garfinkel D & Lipson S. (2000) Melatonin for treatment of sundowning in elderly persons with dementia – a preliminary study. Archives Gerontology and Geriatrics 31: 65–76.

Colcombe SJ., Erickson KI., Raz N et al. (2003) Aerobic fitness reduces brain tissue loss in aging humans. Journal of Gerontology A Biological Sciences and Medical Sciences 58(2):176-180.

Colcombe SJ., Kramer AF., Erickson KI et al. (2004) Cardiovascular fitness, cortical plasticity, and aging. Proceedings of the National Academy of Sciences 101(9):3316-3321.

Coogan A & Thorne J. (2011) Chronotherapeutics and psychiatry: setting the clock to relieve the symptoms. World Journal of Biological Psychiatry 12 (1): 40–43.

Day JR., Anderson RA & Davis LL. (2014) Compassion fatigue in adult daughter caregivers of a parent with dementia. Issues in Mental Health Nursing 35(10):796-804.

Duffy JF., Zeitzer JM., Rimmer DW et al. (2002) Peak of Circadian Melatonin Rhythm Occurs Later within the Sleep of Older Subjects. American Journal Physioloy Endocrinology Metabolism 282: E297–E303.

Evans-Roberts CE & Turnbull OH. (2011) Remembering relationships: preserved emotion-based learning in AD's disease. Experimental Aging Research 37:1–16.

Fagan AM., Mintun MA., Shah AR et al. (2009) Cerebrospinal fluid tau and ptau (181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of AD's disease. EMBO Molecular Medicine 1(8-9):371–380.

Ferrari E., Arcaini A., Gornati R et al. (2000) Pineal and pituitary- adrenocortical function in physiological aging and in sensile dementia. Experimental Gerontology 35:1239-1250.

Foskolos D. (2011) Stress, Depression and AD: The triangle of oblivion. Εγκέφαλος 48: 131-136.

Fox NC., Crum WR., Scahill RI et al. (2001) Imaging of onset and progression of AD's disease with voxel-compression mapping of serial magnetic resonance images. Lancet 358:201–205.

Galano A., Tan D & Reiter R. (2011) Melatonin as a natural ally against oxidative stress: a physicochemical examination. Journal of Pineal Research 51: 1–16.

García-Mesa Y., Giménez-Llort L, López LC et al. (2012) Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse. Neurobiology of Aging 33(6):1124.

Graf A., Wallner C., Schubert V et al. (2001) The effects of light therapy on mini-mental state examination scores in demented patients. Biological Psychiatry 50: 725–727.

Guarnieri B., Adorni F., Musicco M et al. (2012) Prevalence of sleep disturbances in mild cognitive impairment and dementing disorders: a multicenter Italian clinical cross sectional study on 431 patients. Dementia and Geriatric Cognitive Disorders 33:50–58.

Guzmán-Vélez E., Feinstein JS & Tranel D. (2014) Feelings without memory in AD disease. Cognitive and Behavioral Neurology 27(3):117-29.

Hardeland R., Poeggeler B., Srinivasan V et al. (2008) Melatonergic drugs in clinical practice. Arzneimittelforschung 58: 1–10.

Hofman MA. (2000) The human circadian clock and aging. Chronobiology International 17: 245–259.

Huang Y., Potter R., Sigurdson W et al. (2012) Effects of age and amyloid deposition on Aβ dynamics in the human central nervous system. Archives of Neurology 69(1):51-8.

Kang JE., Lim MM., Bateman RJ et al. (2009) Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 326(5955):1005–1007.

Kensinger EA., Brierly B., Medford N et al. (2002) Effects of normal aging and AD's disease on emotional memory. Emotion 2:118–134.

Kondratova AA & Kondratov RV. (2012) The circadian clock and pathology of the ageing brain. Nature Reviews Neuroscience. 13:325–335.

Kostoglou AI. (2013) Therapeutic applications of melatonin. Therapeutic Advances Endocrinology and Metabolism 4(1):13-24.

Klerman EB., Duffy JF., Dijk DJ et al. (2001) Circadian phase resetting in older people by ocular bright light exposure. Journal of Investigate Medicine 49: 30–40.

Kyle SD., Beattie L., Spiegelhalder K et al. (2014) Altered emotion perception in insomnia disorder. Sleep 1: 37(4):775-83.

Liu RY., Zhou JN., Hoogendijk WJ et al. (2000) Decreased vasopressin gene expression in the biological clock of AD disease patients with and without depression. Journal of Neuropathology Experimental Neurology 59: 314–322.

Martin J., Marler M., Shochat T et al. (2000) Circadian rhythms of agitation in institutionalized patients with AD's disease. Chronobiology International 17: 405–418.

Matsubara E., Bryant T., Pacheco Q et al. (2003) Melatonin increases survival and inhibits oxidative and amyloid pathology in a transgenic model of Alzheimer disease. Journal of Neurochemistry 85 1101:1108.

McCleery J., Cohen DA & Sharpley AL. (2014) Pharmacotherapies for sleep disturbances in AD's disease. Cochrane Database of Systematic Reviwes 21:3:CD009178.

McLeland YE., Toedebusch JS., Xiong C et al. (2013) Sleep quality and preclinical AD disease. JAMA Neurology 70(5):587-93.

Mickes L., Wixted JT., Fennema-Notestine C et al. 2(007) Progressive impairment on neuropsychological tasks in

a longitudinal study of preclinical AD's disease. Neuropsychology 21:696–705.

Mishima K., Okawa M., Shimizu T et al. (2001) Diminished melatonin secretion in the elderly caused by insufficient environmental illumination. Journal of Clinical Endocrinology and Metabolism 86: 129–134.

Neckelmann D., Mykletun A & Dahl AA. (2007) Chronic insomnia as a risk factor for developing anxiety and depression. Sleep 30(7):873-80.

Olcese J., Cao C., Mori T et al. (2009) Protection against cognitive deficits and markers of neurodegeneration by long-term oral administration of melatonin in a transgenic model of AD disease. Journal of Pineal Research 47: 82–96.

Osorio RS., Pirraglia E., Agüera-Ortiz LF (2011) Greater risk of AD's disease in older adults with insomnia. Journal of the American Geriatrics Society 2011, 59:559-562.

Pappolla MA., Chyan YJ., Poeggeler B et al. (2000) An assessment of the antioxidant and the antiamyloidogenic properties of melatonin: implications for AD's disease. Journal of Neural Transmission 107: 203–231.

Peck JS., LeGoff DB., Ahmed et al (2004) Cognitive effects of exogenous melatonin administration in elderly persons: a pilot study. American Journal of Geriatric Psychiatry 12:432-436.

Quinn J., Kulhanek D., Nowlin et al (2005) Chronic melatonin therapy fails to alter amyloid burden or oxidative damage in old Tg2576 mice: Implications for clinical trials. Brain Research 1037:209-213.

Reiter RJ., Tan DX., Manchester LC et al. (2002) Melatonin reduces oxidant damage and promotes mitochondrial respiration: implications for aging. Annals of the New York Academy of Sciences 959: 238–250.

Robinson L., Iliffe S., Brayne Cet al. 2010) Primary care and dementia: 2. Long-term care at home: psychosocial interventions, information provision, carer support and case management. International Journal of Geriatric Psychiatry 25(7):657-64.

Scarmeas N., Luchsinger JA., Schupf N et al. (2009) Physical activity, diet, and risk of AD disease. JAMA 302(6):627-3.

Scarmeas N., Stern Yaakov., Tang M et al. (2006) Mayeux Richard, Luchsinger Jose A. Mediterranean diet and risk for AD's disease. Annals of Neurology 59 (6) :912–921.

Singer C., Tractenberg RE., Kaye J et al. (2003) AD's Disease Cooperative Study: A multicenter, placebo-controlled trial of melatonin for sleep disturbance in AD's disease. Sleep 26:893-901.

Selkoe DJ. (2004) Cell biology of protein misfolding: The examples of AD's and Parkinson's diseases. Nature Cell Biology 6:1054–1061.

Srinivasan V., Spence D., Pandi-Perumal S et al. (2008) Jet lag: therapeutic use of melatonin and possible application of melatonin analogs. Travel Medicine and Infectious Disease 6: 17–28.

Swaab DF. (2003) The human hypothalamus basic and clinical aspects. In: Handbook of clinical neurology 79: 63–123. AminoffMJ, FranpcoisB, SwaabDF series eds. Elsevier, Amsterdam.

Tuppo EE & Arias HR. (2005) The role of inflammation in AD's disease. International Journal of Biochemistry & Cell Biology 7:289–305.

Van Someren EJ., Riemersma RF & Swaab DF.(2002) Functional plasticity of the circadian timing system in old age: light exposure. Progress in Brain Research 138: 205–231.

Waldemar G & Hasselbalch S. (2014) Effect of Physical Exercise on AD's Disease. Neurobiology of Aging 35 (1):24-25.

Wirz-Justice A., Werth E., Savaskan E et al. (2000) Haloperidol disrupts, clozapine reinstates the circadian rest–activity cycle in a patient with early-onset AD disease. AD Disease and Associated Disorders 14: 212–215.

Wu E., Barnes DE., Ackerman SL et al. (2014) Preventing Loss of Independence through Exercise (PLIÉ): qualitative analysis of a clinical trial in older adults with dementia. Aging & Mental Health 14:1-10.

Wu YH., Feenstra MG., Zhou JN et al. (2003) Molecular changes underlying reduced pineal melatonin levels in AD's disease: Alterations in preclinical and clinical stages. Journal of Clinical Endocrinology and Metabolism 88:5898–5906.

Wu YH., Fischer DF & Swaab DF (2007) A promoter polymorphism in the monoamine oxidase A gene is associated with the pineal MAOA activity in AD's disease patients. Brain Research 1167:13–19.

Yamadera H., Ito T, Suzuki H et al. (2001) Effects of bright light on cognitive and sleep-wake (circadian) rhythm disturbances in AD-type dementia. Psychiatry and Clinical Neurosciences 54: 352–353.

Zhou JN., Liu RY., Kamphorst W et al. (2003) Early neuropathological AD's changes in aged individuals are accompanied by decreased cerebrospinal fluid melatonin levels. Journal of Pineal Research 35:125–130.